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XDE-729 Methyl
(Halauxifen-methyl)
Volume 3 – B.8

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Version History

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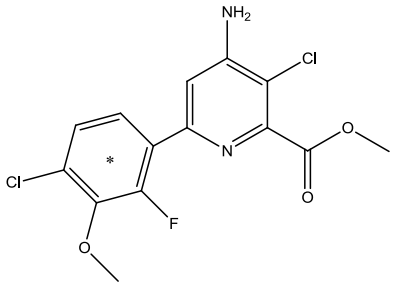
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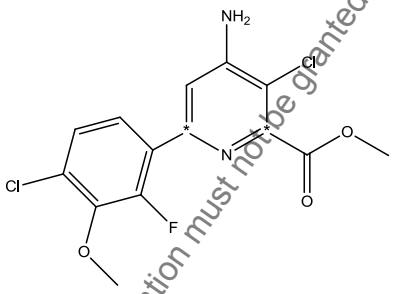
B.8 ENVIRONMENTAL FATE AND BEHAVIOUR

All radiolabel studies used XDE-729 methyl 14C labelling in either the phenyl ring or the pyridine ring. The labelling positions in the molecule are shown below.

Figure B.8.1 Radiolabelling positions for XDE-729 methyl



i) phenyl ring position (Ph)



ii) Pyridine ring position (Py)

The radiochemical purity of both labels of XDE-729 methyl was greater than 97%.

The proposed use of XDE-729 methyl is as a herbicide in winter cereals with an application rate of 7.82 g a.s./ha between GS 10 and 29 in the autumn/winter and a second application of 6.25 g a.s./ha between GS 13 and GS 45 in the spring. This equates to a soil concentration of 0.009 mg/kg using the assumptions in section B.8.3.

B.8.1 Route and rate of degradation in soil (IIA 7.1.1, IIIA 9.1.1)

B.8.1.1 Aerobic route of degradation (II 7.1.1, IIIA 9.1.1)

a) An aerobic soil degradation study was conducted according to OECD 307 guidelines and GLP.

^{14}C-XDE-729 methyl labelled in either the phenyl ring or pyridine ring was added in water to fresh samples (50 g dry weight equivalent) of four different soils at a nominal concentration of 0.1 mg/kg soil; this is approximately an order of magnitude greater than the predicted soil concentrations from the anticipated use of XDE-729 methyl using standard assumptions described in section B.8.3 and is likely to have been determined by analytical considerations given the very low dose of application. Soil properties are shown below. Flasks containing the treated soil were fitted with 2N NaOH traps for CO_2, then incubated at 20°C in the dark for up to 153 days with soil maintained at 50% MHC, which the study author considered to be between pF 2 and 2.5. Data on actual moisture content at pF2 was not provided. It should be noted that 50% MHC was less than FOCUS suggested gravimetric pF2 values in only one soil, RefSol 03-G, thus moisture correction is only required for this soil. Moistened air was drawn through the experimental flasks. It was stated that none of the soils had been treated with pesticides in the previous four years. Soils were used 6-8 weeks following collection and had been stored refrigerated at 4°C prior to use. The soils were allowed to equilibrate at study conditions for approximately 1 week before treatment.

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Table B.8.1 Properties of soils used in aerobic soil degradation study on XDE-729 methyl.

Parameter	Results			
Study Designation	M800	M802	M803	M804
Soil Series	Yolo	RefSol 03-G	Site E	Site I2
Geographic Location	Yolo County, CA, USA	Ebbinghof, Northrhine, Westphalia, Germany	Farditch Farm, Chelmorton, Derbyshire, UK	Longwoods Quarry, Lincolnshire, UK
Taxonomic Classification	a	b	NA	NA
USDA Texture Class	Clay loam	Loam	Silt loam	Sandy loam
% Sand	33	33	27	75
% Silt	34	46	58	12
% Clay	33	21	15	13
International Texture Class	Light clay	Clay loam	Loam	Sandy loam
% Sand	47	51	57	79
% Silt	20	28	28	8
% Clay	33	21	15	13
pH ($CaCl_2$)	7.1	5.0	5.9	7.5
% Organic Carbon	1.3	2.5	3.6	1.4
Initial Biomass (µg/g)	216.6	211.1	146.2	130.0
Final Biomass (µg/g)	199.0	239.5	113.2	13.6
CEC (meq/100g)	21.2	14.8	20.2	9.0
Moisture Holding Capacity	65.6	57.3	62.9	48.5
Bulk Density (g/cm^3)[g]	1.11	1.07	1.03	1.28

a. Fine-silty, mixed, superactive, nonacid, thermic Mollic Xerofluvents
b. Eutric cambisol

It should be noted that only the Yolo soil achieved the OECD 307 recommended microbial biomass of 1% of organic carbon throughout the study. The RMS discusses this in the summary and assessment section at B.8.1.6.

Single soil samples were taken for each radiolabelling position at regular time points for up to 153 days post treatment. The volatile traps were also sampled at the same time points. At each sample time, the soils were extracted as described below. Soils were extracted on the day of sampling. It will be noted that the extraction procedure is relatively novel in comparison with methods employed for a large number of pesticide active substances, particularly the use of accelerated solvent extraction techniques. This is a result of the nature of XDE 729 methyl, particularly the fact that it is unstable under moderately acid and alkaline conditions. Prior experimental work on extraction methodology indicated that moderately acidic extraction using 1N HCl followed by neutralisation of the extract with NaOH to avoid degradation of the analytes resulted in precipitation. In addition, concentration of the acidic extracts prior to analysis (required due to the low doses used in the study, this being a substance intended to be

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applied at low dose in the field) resulted in further loss via precipitation and incomplete elution from solid phase extraction columns. This led to the choice of the Accelerated Solvent Extraction (ASE) methodology as opposed to more usual extraction methodology. Comparison of the extraction procedures on the four soils at 30 DAT indicated that ASE extraction extracted an average of 20.25% AR (12-31% AR) compared to 9.75% AR (5-20% AR) for weak acid and 17.9% (8-27% AR) for a strong acid extraction (total of 27.1% for combined acid extractions, range 14-45% AR). Whilst acid extraction extracted more radioactivity than ASE, ASE gave better recovery of radioactivity through all preparation steps prior to HPLC; average recovery through concentration steps on 30 DAT samples was 87.6% AR for ASE, 53.9% AR for weak acid extraction and 21.2% AR for strong acid extraction. In addition, ASE gave superior characterisation of radioactivity compared to acid extractions; ASE was able to characterise an average of 17.9% AR in 30 DAT samples whilst average characterisation from combined acid extracts was 8.2% AR. The study author suggested that due to the lower levels of characterised radioactivity that would have occurred using the acid extraction method would have been likely to have resulted in artificially faster degradation rates and lower apparent formation of metabolites compared to the ASE methodology. Data presented for the 30 DAT samples indicated that ASE extraction resulted in average recovery of 9.5% AR for metabolite X11393729 compared to 5.3% AR from acid extractions and average 4.2% AR for X11449757 from ASE compared to 0.7% AR from acid extraction. Overall, the RMS considers that the ASE methodology is a reasonable compromise between extraction of radioactivity and ability to characterise individual extracted components.

Details of each step of the extraction procedure are outlined in the sections below:-

$CaCl_2$ Equilibration

Approximately 100 ml of 0.01 M $CaCl_2$ was added to one sample of each radiolabel at 2, 7, 30, 44, 62, 79, 104, 120 and 153 DAT. Samples were placed on a horizontal shaker at low speed overnight. The aqueous and soil layers were separated by centrifugation. Triplicate aliquots were assayed by LSC. An additional aliquot was concentrated by SPE prior to HPLC analysis. The wet soil pellet was freeze-dried immediately after extraction and prior to combustion analysis to determine the amount of radioactivity remaining in the soil pellet. Sub-samples of the freeze-dried samples were also extracted using an Accelerated Solvent Extraction system (ASE). It was noted that in the 2 and 7 DAT $CaCl_2$ extractions that XDE-729 methyl hydrolysed to a metabolite, X11393729. Thus, whilst the radioactivity results from the $CaCl_2$ extractions at these sample points are shown in the mass balance tables, the individual results from this specific extraction at day 2 and 7 are excluded from the distribution and identity of radioactivity tables; please note that identity and distribution data from day 7 are still available because an additional set of extractions were made at day 7 where 80:20 methanol:water was used as the initial extractant. The study author indicated that beyond 30 DAT, the $CaCl_2$ extraction removed little radioactivity (less than 6% AR, but more typically less than 1% AR) and therefore, the $CaCl_2$ extractions are unlikely to significantly influence the results. The $CaCl_2$ extractions were performed in an attempt to obtain information on aged adsorption, but due to hydrolysis of the parent in the $CaCl_2$ solution and the lack of time points where XDE-729 methyl was present, this approach was not pursued.

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Neutral Organic Solvent Extraction

A mixture of 80:20 methanol: water was added to one sample of each radiolabel at 0, 3, 7, and 14 DAT. Samples were extracted twice on a horizontal shaker, centrifuging and combining the extracts. Aliquots were counted by LSC. An additional aliquot was concentrated for HPLC analysis. The extracted soil pellet was air-dried prior to combustion analysis. Sub-samples of the air-dried samples were also extracted using an accelerated solvent extraction. The study authors considered that this organic solvent extract would have effectively halted any biotic degradation processes thus justifying the use of air-drying for at least one week prior to ASE extraction.

Accelerated Solvent Extraction (ASE)

An ASE procedure was developed because initial work on analytical procedures indicated that extraction of the active substance and its metabolites from soil could be challenging, particularly given that the a.s. can be hydrolytically unstable under both moderately acid and alkaline conditions. Soil samples from all sample points except day 0 were subject to the ASE procedure. A 10-g sub-sample was mixed with at least 4 g of diatomaceous earth and transferred to an ASE extraction cell. Each sample was subjected to six discrete ASE extractions, collecting in a separate weighed and labelled vial. Samples were extracted twice at 50°C using 50:50 methanol: water, twice at 80°C using 50:50 methanol: water and finally twice at 100°C using 50:50 methanol: 0.1% phosphoric acid. Triplicate aliquots of each extract were assayed separately by LSC and the remaining extracts were combined prior to concentration and HPLC analysis. ASE extracts were concentrated using a 'Turbovap' to remove the organic solvent and 0.1% phosphoric acid was added prior to SPE concentration/clean-up.

Solid Phase Extraction

Samples were loaded onto an SPE cartridge conditioned with acetonitrile, followed by 0.1% phosphoric acid. The column was then rinsed with 0.1% phosphoric acid, collecting the load and rinse in a single vial. Aliquots of the load/rinse were assayed by LSC. XDE-729 methyl residues were eluted from the cartridge using 95:5 methanol: 0.1% phosphoric acid. A 'keeper' solution containing glycerin was added to the elution vial before concentrating it to near dryness. Samples were reconstituted using 80:20 water:acetonitrile + 0.1% formic acid.

The extracts were analysed using reverse phase HPLC with radiochemical and UV detection. Identification of radiolabelled fractions in the extracts was by co-chromatography with reference standards and with confirmation using LC/MS. The LOQ of the LSC method was stated to be 40 dpm above background (background stated to be 20 dpm) with an LOD of 10 dpm above background. The equivalent %AR in each extract or trap are presented below.

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Table B.8.2 Equivalent % AR at LOD and LOQ in LSC detection equipment for extracts, traps and fractions.

LSC LOD/LOQ				
Applied dpm				
Ph label	1,231,959	dpm	←	total dpm applied to the system
Py label	849,800	dpm	←	total dpm applied to the system
Count Time min	Back-ground dpm	Currie LOD dpm	LOQ dpm	
5	20	10	40	

	Caustic Trap	CaCl2 Extract	Organic RT	ASE extract	Units
Average Total Volume	150	83.8	233.5	19.2	ml
LSC Aliquot Volume	1.0	1.0	1.0	1.0	ml
at LOD % AR					
Ph label	0.12	0.07	0.19	0.02	% AR
Py label	0.18	0.10	0.27	0.02	% AR
at LOQ % AR					
Ph label	0.49	0.27	0.76	0.06	% AR
Py label	0.71	0.39	1.10	0.09	% AR

	Combustion	Units
Average Total Weight	50.76	g
Average weight of Combustion Sample	0.5	g
Average Combustion Efficiency	94.7	%
at LOD % AR		
Ph label	0.09	% AR
Py label	0.13	% AR
at LOQ % AR		
Ph label	0.35	% AR
Py label	0.50	% AR

The LOQ of the HPLC method was stated to be 3% AR and LOD 1% AR. However, it appears that the study authors ascribed identity to peaks of radioactivity at or around the LOD, presumably on the basis of co-incidence of retention time of the peaks with reference standards and from confirmatory LC-MS analysis.

The RMS considers that the analytical method in the study is sufficiently low.

Given the apparent rapid degradation of XDE-729 methyl in this study, the Applicant was questioned further about the sampling and extraction methodology to obtain confidence that the results obtained demonstrated accurate residues of a.s. and metabolites at each sample time. In the revised study report, the study authors described how they investigated whether the ASE and air-drying procedures resulted in degradation of XDE-729 methyl.

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To investigate whether ASE resulted in degradation of XDE-729 methyl, three ASE cells containing diatomaceous earth were dosed with sufficient XDE-729 methyl to allow direct injection of the extract into the HPLC column; it will be noted from the description above that 10 g soil samples were mixed with 4g diatomaceous earth prior to the ASE procedure. Extractions as described were then carried out, although the extracts from each individual temperature/solvent regime were analysed separately. The extract from the 50:50 methanol:water at 80ºC extraction was not analysed immediately and was thus acidified with H_3PO_4 to prevent degradation of XDE-729 methyl. Samples were centrifuged and extracts injected directly onto the HPLC column with no further work-up. Results of the analyses are given below.

Table B.8.3 Distribution of XDE-729 methyl and Metabolite Residues from ASE Extractions as % by HPLC

Sample ID	X11393729	XDE-729 methyl
XDE-729 methyl Py Label at time of application	0.00	99.02
50:50 methanol: water at 50 °C	1.32	97.83
50:50 methanol: water at 80 °C	2.90	97.10
50:50 methanol: 0.1% phosphoric acid at 100 °C	0.00	98.89

The additional work also investigated whether air-drying following extraction with methanol:water allowed significant degradation. Samples of Yolo (showed longest degradation time for XDE-729 methyl) and Site I2 (showed fastest degradation of XDE-729 methyl) soils were initially extracted with the methanol:water extractant and then dosed with XDE-729 methyl at the dose used in the main study. Aliquots were taken before and after dosing and assayed by LSC to confirm the dosing level. The soils were allowed to air dry for 5 days and were then homogenised and subject to combustion to determine gross radioactivity remaining in the soil. Aliquots of soil were then extracted by ASE. An aliquot of Site I2 soil extract was then evaporated to near dryness and then reconstituted in 80:20 water:acetonitrile + 0.1% formic acid and injected onto the HPLC column. To test whether the air-drying and solid phase extraction resulted in degradation of XDE-729 methyl, an aliquot of Yolo soil extract was subject to the same procedure. Results of the analyses are given below.

Table B.8.4 Distribution of XDE-729 methyl and metabolite from ASE Extractions following air-drying as % by HPLC

Sample ID	X11393729	XDE-729 methyl
XDE-729 methyl Py Label at time of application		
Yolo	2.63	96.29
Site I2	1.07	98.93

For both tests, supporting chromatograms were provided which confirmed the very low levels of any other radiolabelled peaks other than parent XDE-729 methyl. The RMS agrees that the additional investigations gives reassurance that the ASE procedure and air-drying of soils following organic extraction does not lead to significant levels of degradation of XDE-729 methyl.

This covers the range of laboratory studies submitted. Statements in some study reports suggested that some soil samples may have been left for up to a week at room

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temperature to dry before extraction took place and that there may have been some delay between extraction and analysis. This raised questions over storage conditions, both in terms of length and temperature, but also exposure to light given the apparent photolabile nature of the a.s. and main metabolites as suggested by the aqueous photolysis study (see section B.8.4.2). The Applicant separately provided the following response:

"Samples from the all e-fate studies were extracted as soon as practical after disconnecting from the incubation apparatus. Typical times before extraction ranged from a few minutes (<10 minutes) in the aerobic soil studies to less than an hour for sediment/water study (centrifugation and decanting of water layer needed prior to extraction). Water samples were stored frozen as soon as practical after sampling. Soil samples extracted with $CaCl_2$ were immediately frozen at -20°C and freeze dried to prevent degradation. Soil samples extracted at room temperature were air dried after extraction and then stored frozen when not in use. Any potential degradation of XDE-729 methyl during air drying of soil prior to ASE extractions is likely to be minimal due to 1) the majority of the available XDE-729 methyl is extracted during the ambient solvent extraction and remains stable in the organic solution. 2) tightly bound XDE-729 methyl residues remaining after room temperature extraction appear to be resistant to hydrolysis based on data from batch equilibrium study where the majority (72-100%, Table 5, page 45) of the remaining residue present in the ASE extracts (after adsorption and desorption steps) is present as XDE-729 methyl (RMS note: in one of the seven soils tested in the adsorption study, one had 41.5% a.s. in the ASE extract). *This suggests that minimal hydrolysis would occur during the 1st two days of air drying where water would have been present.*
DAS does not believe that the acidification of the water samples prior to SPE in the water/sediment resulted in any significant hydrolytic degradation of XDE-729 methyl residues. This acidification step is required to ensure retention of XDE-729 acid and the X-757 metabolites during SPE (30-60 minute procedure max). The slow hydrolytic degradation rate in acidic conditions (DT50 of 81 days at pH 4) also suggests that no significant hydrolysis would occur during the SPE procedure despite the lower pH of the sample.
In almost all cases, samples were analyzed by HPLC the same day as the SPE procedure. Degradation of XDE-729 methyl in samples awaiting HPLC analysis (all studies) was minimized by storing them in a refrigerator or freezer.
XDE-729 methyl and its metabolites are stable during the ASE extraction procedure developed. No GLP data exist as the extraction method development was conducted during a non GLP probe study several years prior to initiating the definitive studies. However, stability of the analytes during the ASE procedure can be demonstrated by examining the procedural recoveries from the XDE-729 methyl and metabolites soil residue method validation. RMS note – as described above, stability of XDE-729 methyl during ASE has been demonstrated.
DAS is confident that photolytic degradation of study samples resulting from exposure to lab lighting is unlikely. The fluorescent lights used in the DAS laboratories have been characterized using a spectroradiometer. Historical measurements indicated that the laboratory lights do not emit light at the wave lengths (no emission below 440 nm) required to induce photolytic decay of XDE-729 methyl or its metabolites (absorbance cut off of 330 nm). This opinion is further supported by the fact that known photo degradates are not observed in aerobic soil and water/sediment studies."

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The RMS considers that the arguments presented are reasonable and considers that the results for a.s. and metabolites in the various studies appropriately reflect the actual concentrations of these substances in the environmental matrices on the dates that they were sampled.

Radioactivity in the NaOH traps was quantified using LSC. Confirmation that radioactivity was from $^{14}CO_2$ was by precipitation of $BaCO_3$ following addition of $BaCl_2$ to the NaOH trapping solution.

Following extraction, sub-samples of the extracted soils were combusted to determine unextracted residues and thus allow determination of mass balance. Characterisation of the unextracted residue was performed by partitioning into fulvic acid, humic acid and humin fractions. Extracted soil samples were extracted with NaOH overnight at room temperature; this was considered to represent the humin fraction. The resulting soil sample was then acidified to pH 2 and allowed to stand overnight. The supernatant (considered to represent the fulvic acid fraction) was decanted. The precipitate (considered to represent the humic acid fraction) was re-dissolved in NaOH. Each separate fraction was subject to LSC to quantify the amount of radioactivity.

Results of mass balance in the four tested soils are given in the following tables. Rows relating to results using the phenyl labelled material are shaded to aid differentiation of results between labels.

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Table B.8.5 Mass balance from XDE-729 route and rate of degradation study on Yolo soil (% AR)

label	DAT	NaOH trap	Room Temp extract	ASE extract	NER	Total
Ph*	0	NA	99.6	NA	6.0	105.6
Py*	0	NA	99.4	NA	6.3	105.7
Ph*	1	0.1	84.1	13.0	4.7	101.8
Py*	1	0.2	87.0	14.8	3.6	105.7
Ph	2	0.1	16.9	69.9	4.0	90.9
Py	2	0.2	18.0	71.8	9.0	99.1
Ph*	3	0.3	70.7	19.1	7.2	97.3
Py*	3	0.3	73.4	24.2	4.7	102.5
Ph	7	1.1	14.4	54.0	19.8	89.3
Py	7	0.6	14.8	64.3	24.3	103.9
Ph*	7	1.0	52.5	23.4	18.6	95.5
Py*	7	0.2	55.9	26.1	20.3	102.5
Ph*	14	0.7	36.4	27.6	31.7	96.4
Py*	14	4.4	37.5	26.4	38.3	106.6
Ph	30	6.7	5.9	26.9	53.6	93.1
Py	30	2.5	6.0	31.1	62.2	101.9
Ph	44	9.9	4.3	29.9	53.6	97.7
Py	44	3.7	4.9	36.1	61.4	105.9
Ph	62	12.7	3.1	23.9	57.9	97.5
Py	62	5.0	3.4	30.1	67.2	105.7
Ph	79	14.8	2.5	17.3	60.3	94.9
Py	79	6.4	3.2	21.4	66.7	97.7
Ph	104	14.8	2.3	16.1	59.5	92.7
Py	104	6.7	2.8	15.9	67.8	93.2
Ph	120	19.9	1.9	13.8	62.2	97.8
Ph	153	22.2	1.6	9.2	59.4	92.4
Py	153	11.5	2.3	11.2	78.4	103.3
					average	99.1
					standard deviation	5.3
					minimum	89.3
					maximum	106.6

*At 0, 1, 3, 7 and 14 DAT, samples were initially extracted with 80:20 methanol:water. All other samples initially extracted overnight with $CaCl_2$.

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Table B.8.6 Mass balance from XDE-729 route and rate of degradation study on RefSol 03-G soil (% AR)

label	DAT	NaOH trap	Room Temp extract	ASE extract	NER	Total
Ph*	0	NA	99.8	NA	6.0	105.8
Py*	0	NA	98.6	NA	5.9	104.5
Ph*	1	0.1	84.3	11.4	6.6	102.3
Py*	1	0.2	85.3	13.0	5.0	103.5
Ph	2	0.3	6.6	56.5	31.9	95.3
Ph*	3	0.7	58.3	19.6	18.8	97.3
Py	3	0.4	56.9	21.1	21.8	100.2
Ph	7	3.3	2.7	35.0	48.3	89.3
Py	7	0.7	2.9	35.5	59.3	98.4
Ph*	7	3.3	26.5	18.9	54.0	102.7
Py*	7	0.6	24.5	22.1	59.2	106.3
Py*	14	1.1	10.5	21.7	69.3	102.6
Ph	30	9.0	0.9	20.1	66.6	96.6
Py	30	1.9	0.9	17.8	80.0	100.6
Ph	44	14.7	0.7	17.2	57.6	90.1
Py	44	2.3	0.8	18.9	86.2	108.2
Ph	62	17.5	0.6	15.0	60.3	93.4
Py	62	2.7	0.7	19.7	87.0	110.1
Ph	79	19.3	0.6	6.5	73.8	100.3
Py	79	3.2	0.8	13.2	83.7	100.9
Ph	104	17.0	0.7	8.7	62.5	88.9
Py	104	3.3	0.8	12.6	73.8	90.5
Ph	120	22.8	0.5	7.5	61.5	92.3
Py	120	2.6	0.6	13.3	78.7	95.3
Ph	153	23.9	0.6	7.2	61.8	93.5
Py	153	4.6	0.7	12.3	82.1	99.8
					average	98.8
					standard deviation	6.0
					minimum	88.9
					maximum	110.1

*At 0, 1, 3, 7 and 14 DAT, samples were initially extracted with 80:20 methanol:water. All other samples initially extracted overnight with $CaCl_2$.

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Table B.8.7 Mass balance from XDE-729 route and rate of degradation study on Site E soil (% AR)

label	DAT	NaOH trap	Room Temp extract	ASE extract	NER	Total
Ph*	0	NA	98.2	NA	7.7	105.9
Py*	0	NA	98.8	NA	5.6	104.4
Ph*	1	0.1	81.8	13.0	7.6	102.5
Py*	1	0.1	77.3	17.7	6.0	101.1
Ph	2	0.1	6.9	63.0	19.0	89.0
Py	2	0.3	7.2	63.3	20.8	91.5
Ph*	3	0.5	57.1	22.3	14.4	94.2
Py*	3	0.4	55.4	24.3	17.7	97.9
Ph	7	2.0	4.3	48.4	44.8	99.5
Py	7	0.6	4.3	48.9	49.5	103.3
Ph*	7	1.8	31.5	21.4	42.1	96.8
Py*	7	0.7	29.4	24.7	41.5	96.3
Ph*	14	5.4	15.9	20.7	54.7	96.7
Py*	14	0.1	15.9	19.6	59.3	94.9
Ph	30	11.6	0.8	12.0	70.9	95.4
Py	30	3.2	0.8	18.6	69.1	91.7
Ph	44	14.4	0.5	15.7	63.3	94.0
Py	44	4.8	0.5	18.4	67.2	90.9
Ph	62	17.8	0.5	11.7	71.9	102.0
Py	62	6.1	0.5	14.0	81.5	102.0
Ph	79	20.0	0.4	6.5	69.5	96.4
Py	79	7.8	0.4	10.9	83.4	102.5
Ph	104	17.3	0.5	6.6	64.4	88.8
Py	104	7.6	0.6	8.3	82.5	99.1
Ph	120	23.9	0.3	6.7	66.4	97.4
Py	120	10.5	0.4	7.7	77.9	96.4
Ph	153	26.3	0.3	7.1	60.8	94.5
Py	153	12.9	0.4	7.8	74.9	96.0
					average	97.2
					standard deviation	4.6
					minimum	88.8
					maximum	105.9

*At 0, 1, 3, 7 and 14 DAT, samples were initially extracted with 80:20 methanol:water. All other samples initially extracted overnight with $CaCl_2$.

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Table B.8.8 Mass balance from XDE-729 route and rate of degradation study on Site I2 soil (% AR)

label	DAT	NaOH trap	Room Temp extract	ASE extract	NER	Total
Ph*	0	NA	103.2	NA	2.5	105.7
Py*	0	NA	103.2	NA	2.6	105.8
Ph*	1	0.1	90.5	5.6	4.3	100.6
Py*	1	0.2	90.9	7.5	3.3	101.9
Ph	2	0.4	38.3	42.6	23.3	104.5
Py	2	0.3	39.9	40.7	21.8	102.7
Ph*	3	0.7	75.9	12.9	4.9	94.5
Py*	3	0.5	78.0	11.8	5.0	95.3
Ph	7	4.2	27.1	36.7	27.5	95.6
Py	7	2.3	28.6	34.5	34.2	99.6
Ph*	7	4.5	48.5	12.0	28.0	92.9
Py*	7	2.5	49.8	12.7	32.0	96.9
Ph*	14	10.0	29.5	13.5	37.4	90.4
Py*	14	6.1	30.7	15.0	38.3	90.2
Ph	30	20.5	5.8	16.3	48.8	91.4
Py	30	14.7	6.7	19.1	47.3	87.8
Ph	44	25.6	3.3	13.4	58.2	100.5
Py	44	18.7	4.1	14.8	53.7	91.3
Ph	62	30.0	2.1	9.7	52.7	94.5
Py	62	24.0	2.5	11.8	56.2	94.6
Ph	79	32.5	1.8	8.5	59.1	101.8
Py	79	24.7	2.1	10.2	57.2	94.3
Py	104	21.0	2.1	7.0	62.5	92.5
Ph	120	37.9	1.3	6.0	47.7	92.9
Py	120	30.5	1.7	7.5	55.0	94.7
					average	96.5
					standard deviation	5.2
					minimum	87.8
					maximum	105.8

*At 0, 1, 3, 7 and 14 DAT, samples were initially extracted with 80:20 methanol:water. All other samples initially extracted overnight with $CaCl_2$.

Results of concentrations of active substance and metabolites are given below. Rows relating to results using the phenyl labelled material are shaded to aid differentiation of results between labels.

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Table B.8.9 Distribution of XDE-729 methyl and metabolite residues (% AR) in Yolo soil

label	DAT	XDE-729 methyl	X11393729	X11449757	X11406790	Polar	other
Ph	0	98.1	1.0	0.0	0.0	0.0	0.6
Py	0	97.2	1.6	0.0	0.0	0.0	0.6
Ph	1	69.1	24.8	1.1	1.4	0.0	0.7
Py	1	70.6	27.7	1.1	1.3	0.0	1.1
Ph	3	37.0	47.5	3.4	1.4	0.0	0.5
Py	3	40.6	50.9	3.8	1.1	0.3	0.9
Ph	7	19.8	50.2	4.3	0.9	0.3	0.5
Py	7	22.3	53.1	4.8	0.9	0.4	0.5
Ph	14	12.6	43.5	4.7	0.9	0.6	1.6
Py	14	12.1	43.6	5.0	0.7	1.5	1.0
Ph	30	4.7	21.6	4.3	0.4	0.6	1.2
Py	30	5.4	24.6	4.3	0.3	1.9	0.6
Ph	44	5.2	22.0	4.2	0.0	0.9	1.9
Py	44	5.3	23.2	4.2	0.0	3.2	5.0
Ph	62	3.8	15.7	3.0	0.0	0.9	3.6
Py	62	3.7	16.6	3.3	0.0	4.3	5.6
Ph	79	2.5	12.0	2.8	0.3	0.7	1.3
Py	79	3.2	13.3	2.6	0.1	3.0	2.4
Ph	104	2.8	9.5	2.3	0.2	0.7	2.9
Py	104	2.4	9.4	2.3	0.2	2.2	2.2
Ph	120	2.8	7.8	2.2	0.2	0.6	2.3
Ph	153	2.0	5.4	1.1	0.2	0.2	1.8
Py	153	2.0	6.0	1.2	0.1	1.6	2.5

Note that initial extraction on days 0, 1, 3, 7 and 14 performed with 80:20 methanol:water. Initial extraction at all other sample times performed with overnight extraction with $CaCl_2$ and excluded the 80:20 methanol:water extraction. At 7 DAT, separate initial extractions were made with $CaCl_2$ and 80:20 methanol:water. Results at day 7 exclude results with initial $CaCl_2$ extraction.

Other includes the sum of several small metabolites, none of which individually accounted for more than 5% AR.

Polar represents a peak poorly retained on HPLC, eluting near the solvent front. Values represent the highest occurring component in the analysis.

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Table B.810 Distribution of XDE-729 methyl and metabolite residues (% AR) in RefSol 03-G soil

label	DAT	XDE-729 methyl	X11393729	X11449757	X11406790	Polar	other
Ph	0	97.8	1.7	0.0	0.0	0.0	0.3
Py	0	96.4	1.8	0.0	0.0	0.0	0.4
Ph	1	63.2	27.1	3.9	0.9	0.0	0.6
Py	1	60.4	32.0	4.1	0.8	0.1	0.8
Ph	3	23.7	38.2	14.2	0.7	0.3	0.8
Py	3	19.8	41.3	15.2	0.3	0.5	0.8
Ph	7	8.0	16.0	17.2	0.5	0.6	3.1
Py	7	6.4	16.2	17.4	0.5	1.8	4.3
Py	14	3.8	6.4	12.3	0.5	3.9	5.2
Ph	30	1.9	3.6	8.7	0.0	1.9	4.8
Py	30	1.5	3.8	6.7	0.0	3.9	2.8
Ph	44	1.6	2.9	4.5	0.2	1.3	7.4
Py	44	0.9	2.4	4.5	0.0	4.0	6.3
Ph	62	1.1	1.9	4.6	0.0	1.3	6.6
Py	62	0.8	2.2	3.4	0.2	4.4	7.2
Ph	79	0.5	1.1	1.5	0.0	0.9	3.1
Py	79	0.7	1.5	3.5	0.0	3.7	4.0
Ph	104	0.7	1.0	2.7	0.0	1.1	3.9
Py	104	0.7	1.0	2.8	0.0	4.8	3.5
Ph	120	0.7	1.1	2.4	0.0	1.2	2.7
Py	120	0.6	1.3	3.2	0.0	4.5	3.3
Ph	153	0.8	0.4	1.5	0.0	1.3	3.8
Py	153	0.6	0.8	1.5	0.0	4.2	4.8

Note that initial extraction on days 0, 1, 3, 7 and 14 performed with 80:20 methanol:water. Initial extraction on at all other sample times performed with overnight extraction with $CaCl_2$ and excluded the 80:20 methanol:water extraction. At 7 DAT, separate initial extractions were made with $CaCl_2$ and 80:20 methanol:water. Results at day 7 exclude results with initial $CaCl_2$ extraction.
Other includes the sum of several small metabolites, none of which individually accounted for more than 5% AR or were still increasing at study termination.
Polar represents a peak poorly retained on HPLC, eluting near the solvent front. Values represent the highest occurring component in the analysis.

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Table B.8.11 Distribution of XDE-729 methyl and metabolite residues (% AR) in Site E soil

label	DAT	XDE-729 methyl	X11393729	X11449757	X11406790	Polar	other
Ph	0	94.7	3.0	0.0	0.0	0.0	0.4
Py	0	94.7	3.4	0.0	0.0	0.0	0.7
Ph	1	58.9	32.5	1.6	0.9	0.0	0.9
Py	1	51.3	40.2	1.8	0.8	0.0	0.8
Ph	3	25.0	48.2	4.6	1.1	0.0	0.4
Py	3	20.9	51.5	4.9	1.1	0.3	1.1
Ph	7	7.9	32.7	10.1	0.9	0.3	1.0
Py	7	7.3	33.9	10.8	0.8	0.7	0.7
Ph	14	4.8	17.0	9.8	1.0	0.6	3.3
Py	14	4.2	16.6	10.2	0.5	1.3	2.8
Ph	30	1.7	4.8	4.7	0.3	0.4	1.0
Py	30	1.8	6.4	5.8	0.3	2.3	2.9
Ph	44	1.6	3.9	3.9	0.4	0.8	5.7
Py	44	1.7	4.8	4.0	0.0	2.8	5.5
Ph	62	1.3	3.0	3.2	0.2	0.7	3.8
Py	62	1.4	3.3	3.2	0.1	2.2	4.1
Ph	79	0.9	1.8	1.7	0.1	0.6	1.8
Py	79	1.1	3.1	2.7	0.1	2.3	2.1
Ph	104	1.0	1.8	1.8	0.1	0.7	1.7
Py	104	1.1	2.1	1.4	0.0	1.9	2.5
Ph	120	1.1	1.7	1.9	0.1	0.7	1.5
Py	120	1.0	1.7	1.9	0.1	1.6	1.7
Ph	153	0.9	1.7	1.7	0.2	0.6	2.3
Py	153	1.0	1.9	1.6	0.0	2.3	1.3

Note that initial extraction on days 0, 1, 3, 7 and 14 performed with 80:20 methanol:water. Initial extraction on at all other sample times performed with overnight extraction with $CaCl_2$ and excluded the 80:20 methanol:water extraction. At 7 DAT, separate initial extractions were made with $CaCl_2$ and 80:20 methanol:water. Results at day 7 exclude results with initial $CaCl_2$ extraction.
Other includes the sum of several small metabolites, none of which individually accounted for more than 5% AR.
Polar represents a peak poorly retained on HPLC, eluting near the solvent front. Values represent the highest occurring component in the analysis.

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Table B.8.12 Distribution of XDE-729 methyl and metabolite residues (% AR) in Site I2 soil

label	DAT	XDE-729 methyl	X11393729	X11449757	X11406790	Polar	other
Ph	0	98.5	4.2	0.0	0.0	0.0	0.6
Py	0	97.1	5.1	0.0	0.0	0.0	1.0
Ph	1	55.1	39.3	0.6	0.8	0.0	0.4
Py	1	48.2	47.9	0.6	0.7	0.0	0.9
Ph	3	13.8	70.9	3.1	0.7	0.2	0.0
Py	3	13.1	72.7	2.7	0.0	0.7	0.7
Ph	7	4.6	52.0	2.1	0.3	0.5	1.0
Py	7	5.0	53.2	2.0	0.0	1.7	0.7
Ph	14	2.7	35.7	2.2	0.2	0.9	1.3
Py	14	3.2	36.5	2.0	0.0	2.9	1.2
Ph	30	1.4	16.5	1.6	0.0	0.7	1.9
Py	30	1.7	16.8	2.1	0.0	2.1	3.0
Ph	44	1.3	10.0	1.3	0.1	0.7	3.3
Py	44	1.5	10.8	1.0	0.0	1.9	3.6
Ph	62	1.0	6.6	0.8	0.0	0.5	2.9
Py	62	1.5	7.8	0.8	0.0	2.0	2.2
Ph	79	0.8	5.7	1.0	0.0	0.5	2.4
Py	79	1.0	7.1	1.0	0.0	1.4	1.9
Py	104	0.6	4.7	0.5	0.0	1.0	2.2
Ph	120	0.9	3.5	0.9	0.0	0.7	1.4
Py	120	1.1	4.4	0.6	0.0	1.2	1.8

Note that initial extraction on days 0, 1, 3, 7 and 14 performed with 80:20 methanol:water. Initial extraction on at all other sample times performed with overnight extraction with $CaCl_2$ and excluded the 80:20 methanol:water extraction. At 7 DAT, separate initial extractions were made with $CaCl_2$ and 80:20 methanol:water. Results at day 7 exclude results with initial $CaCl_2$ extraction.
Other includes the sum of several small metabolites, none of which individually accounted for more than 5% AR.
Polar represents a peak poorly retained on HPLC, eluting near the solvent front. Values represent the highest occurring component in the analysis.

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Characterisation of unextracted residues was performed on all four soils at sample times of 14, 30, 62 and 120 DAT for both radio labels. As an example, the results of the 120 DAT determination are presented here given their proximity to the 100 day incubation time mentioned in the Uniform Principles with respect to the unextracted residues/mineralisation clause.

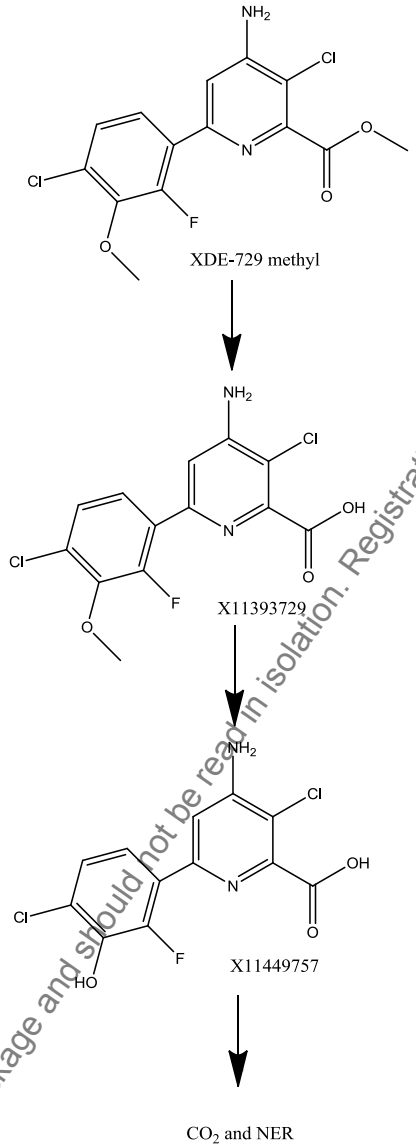
Table B.8.13 Characterisation of unextracted residues at 120 DAT in XDE-729 methyl aerobic route of degradation in soil study

		Proportion (%) in fraction			% AR in fraction			
Label	DAT	Fulvic acid	Humic acid	Humin	Fulvic acid	Humic acid	Humin	Total
Yolo								
Ph	120	26.1	34.0	39.9	16.2	21.2	24.8	62.2
RefSol 03-G								
Ph	120	38.7	38.1	23.3	23.8	23.4	14.3	61.5
Py	120	42.4	32.0	25.6	33.4	25.2	20.1	78.7
Site E								
Ph	120	29.4	30.5	40.1	19.5	20.3	26.6	66.4
Py	120	34.8	30.8	34.4	27.1	24.0	26.8	77.9
Site I2								
Ph	120	28.8	20.8	50.5	13.7	9.9	24.1	47.7
Py	120	38.7	27.6	33.7	21.3	15.2	18.5	55.0

Rates of degradation are described in section B.8.1.4 a). The proposed degradation pathway for dark, aerobic soil is shown below.

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Figure B.8.2 Proposed degradation pathway of XDE-729 methyl in dark, aerobic soils



(Yoder *et al* 2011a, amended 2012)

b) A further aerobic soil degradation study was conducted according to OECD 307 guidelines and GLP.

The study was very similar to that described in B.8.1.1a) above with the exception that the same four soils were gamma-irradiated in order to investigate degradation in sterile soils. These sterile incubations were conducted for 62 days. In addition, a sample of microbially active Site E soil was subject to incubation at 10ºC for 125 days to investigate degradation at lower temperature. In contrast to the study above, no $CaCl_2$ extraction was performed.

Results of mass balance in the four tested sterile soils and the single soil at 10ºC are given in the following tables. Rows relating to results using the phenyl labelled material are shaded to aid differentiation of results between labels.

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Table B.8.14 Radioactive mass balance (% AR) from Yolo sterile soil

Label	DAT	NaOH trap	initial extract	ASE extract	NER	Total
Ph	0	NA	106.0	NA	6.2	112.2
Py	0	NA	97.1	NA	4.6	101.7
Ph	7	0.4	80.7	21.7	6.3	109.1
Py	7	0.6	76.7	25.0	0.0	102.4
Ph	14	NA	71.3	33.8	0.0	105.0
Py	14	NA	68.6	26.8	3.3	98.7
Ph	31	0.4	58.6	34.6	5.1	98.7
Py	31	0.6	56.5	35.1	5.8	97.9
Ph	62	0.4	54.3	37.4	0.0	92.2
Py	62	1.0	52.2	35.9	0.0	89.2
					Average	100.7
					Standard Deviation	7.0
					Maximum	112.2
					Minimum	89.2

No trap data is available for 14 DAT samples

Table B.8.15 Radioactive mass balance (% AR) from RefSol 03-G sterile soil

Label	DAT	NaOH trap	initial extract	ASE extract	NER	Total
Ph	0	NA	105.6	NA	6.6	112.1
Py	0	NA	97.9	NA	5.2	103.1
Ph	7	0.3	92.9	13.0	2.0	108.1
Py	7	0.5	90.1	13.7	0.0	104.2
Ph	14	NA	83.7	19.0	1.6	104.2
Py	14	NA	79.5	18.9	1.4	99.9
Ph	31	0.3	70.6	28.7	2.7	102.2
Py	31	0.5	66.4	27.0	3.4	97.4
Ph	62	0.3	62.8	31.0	1.4	95.5
Py	62	0.6	59.5	32.0	0.7	92.9
					Average	102.0
					Standard Deviation	5.8
					Maximum	112.1
					Minimum	92.9

No trap data is available for 14 DAT samples

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Table B.8.16 Radioactive mass balance (%AR) from Site E sterile soil

Label	DAT	NaOH trap	initial extract	ASE extract	NER	Total
Ph	0	NA	104.5	NA	7.0	111.4
Py	0	NA	95.1	NA	6.3	101.3
Ph	7	0.7	86.2	18.8	2.2	108.0
Py	7	1.1	81.5	19.6	1.4	103.5
Ph	14	NA	76.8	24.9	2.6	104.4
Py	14	NA	71.2	27.2	0.0	98.4
Ph	31	0.4	62.7	31.2	4.4	98.6
Py	31	0.7	59.8	35.5	0.0	96.0
Ph	62	0.5	59.9	33.6	4.5	98.6
Py	62	0.8	56.8	27.6	11.9	97.1
					Average	101.7
					Standard Deviation	5.0
					Maximum	111.4
					Minimum	96.0

No trap data is available for 14 DAT samples

Table B.8.17 Radioactive mass balance (% AR) from Site I2 sterile soil

Label	DAT	NaOH trap	initial extract	ASE extract	NER	Total
Ph	0	NA	98.3	NA	2.1	100.5
Py	0	NA	100.3	NA	2.3	102.6
Ph	7	1.0	97.4	11.1	0.8	110.4
Py	7	0.7	93.8	10.9	1.2	106.7
Ph	14	NA	80.0	12.8	1.0	93.9
Py	14	NA	84.7	22.1	0.0	106.8
Ph	62	0.7	72.3	22.4	6.7	102.2
Py	62	1.0	70.3	20.8	1.8	93.9
					Average	102.1
					Standard Deviation	6.0
					Maximum	110.4
					Minimum	93.9

No trap data is available for 14 DAT samples

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Table B.8.18 Radioactive mass balance (% AR) from Site E 10 °C incubation

Label	DAT	NaOH trap	initial extract	ASE extract	NER	Total
Ph	0	NA	104.5	NA	7.0	111.4
Py	0	NA	95.1	NA	6.3	101.3
Ph	2	0.2	84.9	13.2	4.4	102.8
Py	2	0.5	78.5	13.1	6.6	98.6
Ph	7	0.6	66.5	19.1	16.4	102.5
Py	7	0.6	59.6	23.5	19.2	102.8
Ph	14	1.2	45.8	23.5	30.1	100.5
Py	14	0.7	39.2	23.7	34.9	98.5
Ph	30	4.5	23.7	17.3	60.3	105.8
Py	30	1.5	20.8	18.1	55.2	95.6
Ph	45	7.2	13.5	14.5	57.9	93.1
Py	45	2.0	11.3	13.8	70.7	97.8
Ph	62	9.0	9.6	12.5	75.1	106.3
Py	62	2.7	8.6	11.7	76.6	99.6
Ph	80	11.4	7.1	12.2	73.9	104.7
Py	80	3.8	6.3	11.6	79.3	101.0
Ph	99	11.7	6.5	9.2	69.8	97.2
Py	99	0.9	5.0	10.2	82.2	98.4
Ph	125	14.5	4.7	12.1	67.5	98.8
Py	125	2.4	4.0	12.1	74.9	93.4
					Average	100.5
					Standard Deviation	4.5
					Maximum	111.4
					Minimum	93.1

No trap data are available for 14 DAT samples

Results of concentrations of active substance and metabolites are given below. Rows relating to results using the phenyl labelled material are shaded to aid differentiation of results between labels.

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Table B.8.19 Distribution of XDE-729 methyl and metabolite residues (% AR) in Yolo sterile soil

Label	DAT	XDE-729 methyl	X11393729	other
Ph	0	103.9	2.2	0.0
Py	0	93.1	2.4	1.5
Ph	7	61.6	39.9	0.9
Py	7	57.5	43.1	1.1
Ph	14	39.0	66.0	0.0
Py	14	37.3	57.6	0.5
Ph	31	22.1	71.2	0.0
Py	31	22.6	68.6	0.4
Ph	62	14.5	75.9	1.3
Py	62	13.3	73.9	0.9

Other includes the sum of several small metabolites, none of which individually accounted for more than 2% of the applied radiocarbon

Table B.8.20 Distribution of XDE-729 methyl and metabolite residues (% AR) in RefSol 03-G sterile soil

Label	DAT	XDE-729 methyl	X11393729	other
Ph	0	103.5	2.1	0.0
Py	0	94.6	2.6	0.8
Ph	7	76.4	28.9	0.5
Py	7	70.1	32.9	0.9
Ph	14	55.8	46.6	0.2
Py	14	47.2	50.7	0.5
Ph	31	18.5	80.8	0.0
Py	31	13.7	79.5	0.3
Ph	62	5.9	87.2	0.6
Py	62	6.6	83.3	1.6

Other includes the sum of several small metabolites, none of which individually accounted for more than 2% of the applied radiocarbon

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Table B.8.21 Distribution of XDE-729 methyl and metabolite residues (% AR) in Site E sterile soil

Label	DAT	XDE-729 methyl	X11393729	other
Ph	0	100.7	3.2	0.5
Py	0	90.4	3.5	1.2
Ph	7	53.5	51.5	0.5
Py	7	43.8	56.7	0.6
Ph	14	31.3	69.9	0.4
Py	14	21.9	76.0	0.5
Ph	31	5.9	88.0	0.0
Py	31	5.0	89.9	0.4
Ph	62	3.7	89.0	0.9
Py	62	3.1	78.7	2.6

Other includes the sum of several small metabolites, none of which individually accounted for more than 3% of the applied radiocarbon

Table B.8.22 Distribution of XDE-729 methyl and metabolite residues (% AR) in Site I2 sterile soil

Label	DAT	XDE-729 methyl	X11393729	other
Ph	0	93.5	4.9	0.0
Py	0	94.7	5.0	0.7
Ph	7	56.1	51.7	0.8
Py	7	52.9	51.0	0.8
Ph	14	27.4	65.2	0.2
Py	14	33.6	72.0	1.2
Ph	62	6.7	87.5	0.6
Py	62	6.1	84.1	1.0

Other includes the sum of several small metabolites, none of which individually accounted for more than 2% of the applied radiocarbon

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Table B.8.23 Distribution of XDE-729 methyl and metabolite residues (% AR) in Site E 10 °C incubation

Label	DAT	XDE-729 methyl	X11393729	X11449757	X11406790	Polar	other
Ph	0	101.5	3.0	0.0	0.0	0.0	0.0
Py	0	92.0	3.1	0.0	0.0	0.0	0.0
Ph	2	62.7	34.9	0.4	0.1	0.0	0.0
Py	2	52.6	36.9	0.3	0.9	0.0	0.9
Ph	7	21.3	60.4	3.1	0.7	0.0	0.2
Py	7	17.9	59.7	3.8	0.7	0.2	0.8
Ph	14	8.0	51.8	8.4	0.5	0.1	0.4
Py	14	7.1	43.7	9.6	0.5	1.2	0.9
Ph	30	4.1	25.8	7.8	0.4	0.3	2.7
Py	30	3.8	23.7	8.3	0.3	1.1	1.7
Ph	45	2.9	15.6	7.0	0.2	0.4	1.9
Py	45	2.8	13.2	6.2	0.3	1.2	1.6
Ph	62	2.5	11.8	5.3	0.2	0.7	1.6
Py	62	2.4	9.8	4.9	0.2	1.5	1.4
Ph	80	2.1	9.3	5.4	0.2	0.8	1.5
Py	80	1.9	7.7	4.3	0.2	1.7	2.1
Ph	99	2.0	7.6	3.9	0.0	0.7	1.5
Py	99	2.0	5.7	3.9	0.0	1.7	2.0
Ph	125	1.7	6.4	4.1	0.1	1.0	3.6

Other includes the sum of several small metabolites, none of which individually accounted for more than 4% of the applied radiocarbon
The 125 DAT Py-labelled sample was lost during HPLC analysis and could not be re-generated

Kinetics from this study are described in section B.8.1.4b) below.

(Yoder and Boulton 2011)

c) The Applicant undertook a specific laboratory study on development of unextracted residues to support an earthwork toxicity study (described in Section B.9.8.4 of the DAR). The study was conducted to OECD 307 and US EPA OPPTS 835.4100 guidelines and to GLP.

The study was conducted on Site E1 and RefSol 03-G soils. These soils appear to be similar to the Site E and RefSol 03-G soils used in the test at B.8.1.1a) described above. It is noted that the soil textural details under USDA and International textural classification schemes may have been transposed compared to those in Table B.8.1.

Samples of these soils were incubated in the dark under aerobic conditions at 20ºC and 50% MHC for 89 days following dosing with ^{14}C-XDE-729 methyl radiolabelled in the Py position. Three different doses were used, 0.1, 1.0 and 10 mg a.s./kg. Incubation vessels were supplied with humidified air and were connected to a 2N NaOH trap for collection of volatiles. At each sample time, duplicate complete incubation vessels and associated volatile trap were sacrificed. Soils were extracted

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twice with methanol water followed by ASE extraction for all sample times except 0 DAT. The ASE procedure is described in B.8.1.1a). Extracted soils were subjected to combustion analysis to determine unextracted residues. Soil extracts were stated to be analysed by HPLC with UV and radiochemical detection. Substance identification was by co-chromatography with reference standards. However, the study gave no results of quantification of active substance or metabolites, only gross radioactivity in extracts, unextracted residue and volatiles.

Given that the study was used in support of an earthworm study to ascertain unextracted residues, only these details have been given below.

Table B.8.24 Unextracted residues and mass balance (mean of two replicates) in Site E1 soil

	0.1 mg a.i./kg		1.0 mg a.i./kg		10.0 mg a.i./kg	
DAT	NER%	Mass Balance%	NER%	Mass Balance%	NER%	Mass Balance%
0	7.1	99.8	6.9	101.0	7.3	101.6
32	64.5	99.9	68.0	99.5	28.3	98.2
59	65.3	94.3	71.1	94.4	48.6	98.9
89	74.6	103.6	81.7[a]	105.5[a]	68.8	99.7

NER = unextracted residue. [a] = single replicate value only available

Table B.8.25 Unextracted residues and mass balance (mean of two replicates) in RefSol 03-G soil

	0.1 mg a.i./kg		1.0 mg a.i./kg		10.0 mg a.i./kg	
DAT	NER%	Mass Balance%	NER%	Mass Balance%	NER%	Mass Balance%
0	8.3	103.2	7.5	103.3	6.9	102.2
32	74.6	102.9	78.4[a]	102.2[a]	71.0	102.5
59	69.8	102.3	72.8	100.9	73.4	105.4
89	67.8	99.3	71.2	103.7	68.7[a]	99.1[a]

NER = unextracted residue. [a] = single replicate value only available

(Liu and Croffie, 2012)

B.8.1.2 Anaerobic route of degradation

The study described above at B.8.1.1b) on sterile and low temperature aerobic degradation in soils also incorporated anaerobic incubations. The same four soils as described above were used. The study methodology for the anaerobic incubations was essentially similar to that for the sterile and low temperature incubations described above, although there were important changes to the incubation of the soil. Following treatment of the soils with a.s., the soils were incubated at 20ºC and 50% MHC for two days. No trapping of volatile substances was attempted in this initial phase of the study as the study at B.8.1.1a) suggested negligible mineralisation in the first two days. After this two day period, the soils were flooded with HPLC-grade water, connected to NaOH traps and also to a supply of nitrogen to encourage the development of anaerobic conditions. Whilst the volume of water was observed to decrease over time, the authors did not open the containers to add more water in order to avoid introducing oxygen into the system. Untreated flooded soil samples incubated under the same conditions were monitored for water phase pH, water phase dissolved oxygen and

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redox potential of water and soil phases. Sampling occurred at regular intervals up to 121 days post-flooding. The aqueous phase of each sample was removed following centrifugation and concentrated by solid phase extraction prior to HPLC analysis. The remaining soil was then extracted using the Accelerated Solvent Extraction methodology described previously in B.8.1.1a).

Results of the pH, dissolved oxygen and redox potential in the four soils are given below.

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Table B.8.26 Measurements of pH, dissolved oxygen, redox potential, and redox potential corrected to pH 7 for all anaerobic systems

Yolo light clay

DAF	pH	O_2 (ppm)	Aqueous Potential (mV)	Aqueous Eh7[a] (mV)	Sediment Potential (mV)	Sediment Eh7[a] (mV)
0	6.67	7.20	218	238	261	280
2	8.03	0.74	231	170	148	87
6	7.63	0.44	204	166	203	166
14	8.39	1.34	162	80	119	36
30	9.13	1.38	151	25	-45	-171
44	8.66	0.74	138	40	-49	-147
69	8.11	3.92	175	109	-209	-274
100	8.42	0.22	171	87	-185	-269
121	8.61	1.95	159	64	-187	-282

RefSol 03-G clay loam

DAF	pH	O_2 (ppm)	Aqueous Potential (mV)	Aqueous Eh7[a] (mV)	Sediment Potential (mV)	Sediment Eh7[a] (mV)
0	6.50	7.07	262	292	370	399
2	6.38	0.51	274	311	240	276
6	7.03	0.28	277	275	247	245
14	7.50	1.17	221	191	127	98
30	7.77	0.92	214	168	-36	-82
44	7.07	0.85	166	162	-27	-32
69	7.46	2.77	7	-34	-324	-351
100	7.33	0.18	78	58	-214	-234
121	7.31	1.00	105	87	-172	-190

Site E loam

DAF	pH	O_2 (ppm)	Aqueous Potential (mV)	Aqueous Eh7[a] (mV)	Sediment Potential (mV)	Sediment Eh7[a] (mV)
0	6.29	7.41	251	293	362	404
2	6.53	0.51	318	346	267	295
6	6.92	0.35	296	301	235	240
14	7.07	2.12	205	201	140	136
30	7.46	1.68	211	184	-20	-47
44	7.35	1.02	199	178	-183	-203
69	7.43	3.62	61	36	-356	-382
100	7.63	0.19	76	39	-437	-475
121	7.44	0.25	100	74	-450	-476

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Site I2 sandy loam

DAF	pH	O_2 (ppm)	Aqueous Potential (mV)	Aqueous Eh7[a] (mV)	Sediment Potential (mV)	Sediment Eh7[a] (mV)
0	7.27	7.00	209	193	232	216
2	7.52	0.98	194	163	140	109
6	8.31	0.31	228	150	201	123
14	8.61	1.42	185	90	94	-2
30	8.86	1.28	169	59	-142	-252
44	8.73	0.83	170	68	-242	-345
69	8.90	4.27	80	-32	-413	-526
100	9.59	0.17	65	-88	-456	-609
121	9.04	2.48	80	-41	-363	-484

[a] E_h7 = redox potential corrected to pH 7 = measured redox potential - (59.2 mV x (measured pH – 7))
DAF = days after flooding

Results of mass balance in the four tested soils are given in the following tables. Rows relating to results using the phenyl labelled material are shaded to aid differentiation of results between labels.

Table B.8.27 Radioactive mass balance (% AR) at 0 DAT (-2 DAF), Anaerobic Soil

Soil ID	Label	Organic Extract	NER	total
Yolo	Ph	94.0	5.6	99.6
	Py	95.1	4.9	100.0
RefSol 03-G	Ph	94.0	5.6	99.7
	Py	93.9	5.7	99.6
Site E	Ph	94.0	6.8	100.8
	Py	91.9	6.7	98.7
Site I2	Ph	97.3	2.5	99.7
	Py	96.8	2.5	99.3

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Table B.8.28 Radioactive mass balance (% AR) from Yolo anaerobic soil

Label	DAF	NaOH trap	aqueous	ASE extract	NER	total
Ph	0	NA	9.1	77.2	22.9	109.3
Py	0	NA	8.8	84.3	5.0	98.1
Ph	2	0.4	28.3	67.4	8.9	104.9
Py	2	0.5	27.4	65.4	11.9	105.2
Ph	6	0.0	36.0	47.0	20.4	103.5
Py	6	0.0	38.2	49.5	15.3	103.0
Ph	14	0.1	38.1	46.8	14.1	99.1
Py	14	0.2	41.0	46.6	13.2	101.0
Ph	30	0.1	30.6	52.7	18.9	102.3
Py	30	0.1	29.1	53.5	20.7	103.4
Ph	44	0.8	20.3	54.4	28.9	104.5
Py	44	0.8	22.8	56.1	21.7	101.4
Ph	69	0.3	16.9	53.0	28.9	99.1
Py	69	0.2	17.8	56.7	22.9	97.5
Ph	100	0.3	13.1	53.5	33.9	100.8
Py	100	0.3	10.7	53.2	33.4	97.7
Ph	121	0.4	9.5	36.5	48.4	94.9
Py	121	0.4	20.5	69.7	15.7	106.2
					Average	101.6
					Standard Deviation	3.5
					Minimum	94.9
					Maximum	109.3

DAF = Days after flooding

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Table B.8.29 Radioactive mass balance (% AR) from RefSol 03-G anaerobic soil

Label	DAF	NaOH trap	aqueous	ASE extract	NER	total
Ph	0	NA	6.2	79.7	16.5	102.5
Py	0	NA	7.4	74.3	20.4	102.0
Ph	2	0.3	25.0	53.3	8.2	86.9
Py	2	0.5	24.0	55.6	25.9	106.0
Ph	6	0.3	28.9	46.8	25.4	101.4
Py	6	0.2	27.7	46.2	37.0	111.2
Ph	14	0.2	28.3	53.0	16.1	97.6
Py	14	0.8	25.4	50.9	20.9	98.0
Ph	30	0.5	19.3	45.4	42.2	107.4
Py	30	0.1	19.5	39.9	45.3	104.8
Ph	44	0.8	15.8	45.2	41.4	103.3
Py	44	0.6	13.9	44.9	39.0	98.4
Ph	69	0.6	11.8	41.7	43.8	98.0
Py	69	0.2	11.1	34.8	50.9	97.0
Ph	100	0.8	9.7	39.7	48.3	98.5
Py	100	0.5	4.4	44.5	46.0	95.4
Ph	121	0.7	10.6	46.2	40.0	97.5
Py	121	0.4	8.7	33.8	57.2	100.0
					Average	102.4
					Standard Deviation	32.8
					Minimum	96.9
					Maximum	111.7

DAF = Days after flooding

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Table B.8.30 Radioactive mass balance (% AR) from Site E anaerobic soil

Label	DAF	NaOH trap	aqueous	ASE extract	NER	total
Ph	0	NA	11.8	74.3	15.3	101.4
Py	0	NA	5.1	85.0	10.2	100.4
Ph	2	0.3	27.6	61.1	8.0	97.1
Py	2	0.6	30.9	56.8	13.7	102.1
Ph	6	0.2	33.4	44.5	22.1	100.1
Py	6	0.2	33.3	44.2	25.0	102.6
Ph	14	0.2	27.9	56.9	15.8	100.9
Py	14	0.2	20.8	61.2	16.0	98.1
Ph	30	0.3	16.8	48.2	35.9	101.1
Py	30	0.2	16.2	46.8	37.9	101.1
Ph	44	0.4	11.3	37.7	53.2	102.6
Py	44	0.5	12.4	39.0	51.0	102.8
Ph	69	0.3	8.0	38.7	50.3	97.2
Py	69	0.3	7.5	33.2	57.2	98.2
Ph	100	0.5	6.1	37.9	48.6	93.1
Py	100	0.4	5.6	44.0	47.4	97.4
Ph	121	0.4	6.1	35.8	59.0	101.2
Py	121	0.4	5.2	27.9	64.8	98.2
					Average	99.8
					Standard Deviation	2.5
					Minimum	93.1
					Maximum	102.8

DAF = Days after flooding

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Table B.8.31 Radioactive Mass Balance (Expressed as Percent of Applied Radiocarbon) from Site I2 sandy loam—Anaerobic Soil

Label	DAF	NaOH trap	aqueous	ASE extract	NER	total
Ph	0	NA	28.7	55.5	12.7	96.9
Py	0	NA	30.0	55.5	12.3	97.8
Ph	2	0.4	50.2	40.1	18.8	109.6
Py	2	0.5	53.8	36.0	21.4	111.7
Ph	6	0.1	53.0	36.5	11.7	101.4
Py	6	0.1	52.9	36.3	12.0	101.2
Ph	14	0.3	56.5	35.3	13.6	105.7
Py	14	0.3	53.7	36.4	13.2	103.6
Ph	30	0.3	42.9	36.2	27.5	106.9
Py	30	0.3	45.6	34.7	22.4	102.9
Ph	44	0.4	34.3	46.7	23.1	104.4
Py	44	0.5	38.7	40.5	28.3	108.0
Ph	69	0.5	32.5	46.4	20.7	100.2
Py	69	0.3	28.4	48.1	23.5	100.4
Ph	100	0.8	31.3	45.1	21.9	99.1
Py	100	0.7	30.2	48.5	19.1	98.4
Ph	121	0.9	40.8	37.9	20.4	100.0
Py	121	1.0	38.7	38.1	23.8	101.6
					Average	102.4
					Standard Deviation	32.8
					Minimum	96.9
					Maximum	111.7

DAF = Days after flooding

Results of concentrations of active substance and metabolites are given below. Rows relating to results using the phenyl labelled material are shaded to aid differentiation of results between labels.

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Table B.8.32 Distribution of XDE-729 methyl and metabolite residues (% AR) in Yolo anaerobic soil

Label	DAF	XDE-729 methyl	X11393729	X11449757	X11406790	other
Ph	-2	93.2	0.8	0.0	0.0	0.0
Py	-2	93.8	1.3	0.0	0.0	0.0
Ph	0	42.4	40.2	2.3	1.5	0.0
Py	0	52.1	37.8	2.1	1.2	0.0
Ph	2	29.3	60.3	4.9	1.1	0.0
Py	2	28.7	56.7	5.4	1.2	0.8
Ph	6	11.6	64.4	6.4	0.7	0.0
Py	6	13.4	66.2	7.2	0.8	0.0
Ph	14	8.0	67.5	8.9	0.5	0.0
Py	14	8.7	69.2	8.9	0.3	0.4
Ph	30	3.4	66.8	12.9	0.2	0.0
Py	30	3.5	65.7	13.4	0.0	0.0
Ph	44	3.2	55.6	15.0	0.5	0.4
Py	44	3.3	58.9	16.7	0.0	0.0
Ph	69	2.3	47.2	20.5	0.0	0.0
Py	69	2.2	50.9	21.3	0.0	0.0
Ph	100	1.3	38.2	25.7	0.3	1.0
Py	100	1.4	39.4	22.0	0.0	1.1
Ph	121	1.0	22.7	22.2	0.0	0.1
Py	121	2.0	44.6	41.4	0.0	2.1

Other includes the sum of several small metabolites, none of which individually accounted for more than 3% of the applied radiocarbon
DAF = days after flooding

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Table B.8.33 Distribution of XDE-729 methyl and metabolite residues (% AR) in RefSol 03-G anaerobic soil

Label	DAF	XDE-729 methyl	X11393729	X11449757	X11406790	other
Ph	-2	92.4	1.6	0.0	0.0	0.0
Py	-2	91.7	2.3	0.0	0.0	0.0
Ph	0	26.4	47.4	11.2	0.9	0.0
Py	0	23.6	45.5	11.8	0.8	0.0
Ph	2	10.3	41.4	25.2	0.5	0.9
Py	2	9.2	41.8	27.1	0.5	0.9
Ph	6	3.5	37.0	35.2	0.0	0.0
Py	6	3.4	36.5	34.0	0.0	0.0
Ph	14	2.0	27.5	50.9	0.0	0.9
Py	14	1.8	25.1	48.3	0.0	1.1
Ph	30	0.5	17.0	47.1	0.0	0.0
Py	30	0.7	14.9	43.6	0.0	0.2
Ph	44	3.0	13.8	43.4	0.0	0.8
Py	44	0.5	10.9	47.3	0.0	0.0
Ph	69	0.4	6.5	45.9	0.0	0.7
Py	69	0.3	4.4	40.6	0.0	0.5
Ph	100	0.2	1.8	46.1	0.0	1.3
Py	100	0.2	1.6	46.5	0.0	0.7
Ph	121	0.6	1.6	54.3	0.0	0.3
Py	121	0.2	1.7	38.2	0.0	2.3

Other includes the sum of several small metabolites, none of which individually accounted for more than 3% of the applied radiocarbon
DAF = days after flooding

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Table B.8.34 Distribution of XDE-729 methyl and metabolite residues (% AR) in Site E anaerobic soil

Label	DAF	XDE-729 methyl	X11393729	X11449757	X11406790	other
Ph	-2	91.3	2.7	0.0	0.0	0.0
Py	-2	89.0	3.0	0.0	0.0	0.0
Ph	0	66.6	16.1	0.7	2.7	0.0
Py	0	25.3	57.2	6.4	1.2	0.1
Ph	2	10.6	63.6	13.3	1.3	0.0
Py	2	9.4	63.6	13.0	1.1	0.6
Ph	6	3.4	52.8	21.0	0.6	0.1
Py	6	3.0	53.3	20.7	0.5	0.0
Ph	14	2.4	44.1	37.6	0.0	0.8
Py	14	2.3	36.6	43.0	0.0	0.0
Ph	30	0.9	18.9	45.2	0.0	0.0
Py	30	1.0	18.2	43.8	0.0	0.0
Ph	44	0.7	6.6	41.6	0.0	0.0
Py	44	0.6	4.9	45.3	0.0	0.6
Ph	69	0.6	2.6	42.9	0.0	0.5
Py	69	0.6	2.2	37.2	0.0	0.7
Ph	100	0.4	1.9	40.8	0.0	0.9
Py	100	0.5	1.9	46.1	0.0	1.1
Ph	121	0.4	1.5	39.3	0.0	0.6
Py	121	0.3	1.7	29.8	0.0	1.3

Other includes the sum of several small metabolites, none of which individually accounted for more than 3% of the applied radiocarbon
DAF = days after flooding

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Table B.8.35 Distribution of XDE-729 methyl and metabolite residues (% AR) in Site I2 anaerobic soil

Label	DAF	XDE-729 methyl	X11393729	X11449757	X11406790	other
Ph	-2	93.5	3.7	0.0	0.0	0.0
Py	-2	92.5	4.3	0.0	0.0	0.0
Ph	0	20.2	61.2	2.6	0.0	0.1
Py	0	17.8	63.6	2.8	0.5	0.9
Ph	2	9.1	74.6	6.0	0.4	0.2
Py	2	7.3	75.4	5.8	0.3	0.9
Ph	6	3.1	78.9	7.5	0.0	0.0
Py	6	3.3	77.3	8.2	0.0	0.4
Ph	14	2.0	79.6	9.6	0.0	0.6
Py	14	2.2	77.0	10.0	0.0	0.9
Ph	30	0.9	66.6	11.0	0.0	0.6
Py	30	0.7	68.2	11.4	0.0	0.0
Ph	44	0.8	65.5	13.4	0.0	1.1
Py	44	0.7	65.4	13.1	0.0	0.0
Ph	69	0.6	60.1	17.3	0.0	0.9
Py	69	0.7	56.9	19.0	0.0	0.0
Ph	100	0.5	43.5	31.1	0.0	1.3
Py	100	0.4	44.3	33.2	0.0	0.7
Ph	121	0.5	39.0	37.9	0.0	1.3
Py	121	0.4	28.9	46.8	0.0	0.6

Other includes the sum of several small metabolites, none of which individually accounted for more than 2% of the applied radiocarbon
DAF = days after flooding

(Yoder and Boulton 2011)

B.8.1.3 Photolysis in soil

A photolysis study was conducted according to US EPA guidelines (OPPTS 835.2410) and GLP.

Samples of moist Site E soil used in the aerobic soil degradation study (soil properties shown in Table B.8.1, 4 g dry weight) were added to quartz vials and evenly distributed over the surface of the vials. Dark control soil samples were added to glass vials. ^{14}C-XDE-729 methyl labelled in either the phenyl ring or pyridine ring was added to the soil samples in the vials to give a nominal concentration of 6 µg/g of dry soil. The addition of the dosing solution was calculated to have adjusted soil moisture to approximately 50% of MHC. The vials were connected to a gas trapping system containing NaOH for trapping of CO_2. Temperature of the incubation was adjusted to 28ºC; dark controls were housed in an incubator equipped with a humidifier to keep the airflow over the soil sample moist, but this was not specified to have been the case in the irradiated samples. The light source for the irradiated samples was a xenon lamp equipped with a filter removing wavelengths <290 nm. The light energy output was determined to be 303 W/(m^{2}nm), compared to 403 W/(m^{2}nm) measured on the

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summer solstice at 40ºN. Total energy output was quantified using a PNAP/pyr actinometer. Illumination was constant for 15 days. Based on the actinometer results, the period of illumination was calculated to be equivalent to 28 days of summer sunlight at 40ºN.

Duplicate samples were taken for each radiolabel treatment at day 0 and five further representative time points up to 15 DAT. Radioactivity from soil samples was extracted using the accelerated solvent extraction technique previously described in B.8.1.1. Analysis was by HPLC with UV and radiochemical detection with identification by co-chromatography with reference standards. Confirmation of metabolite identification was by LC/MS. Unextracted radioactivity was quantified by combustion and LSC. Radioactivity in trapping solutions was quantified by LSC. There appeared to be no confirmation that radioactivity in the NaOH trapping solution was CO_2. However, previous studies had confirmed that radioactivity in NaOH solutions was CO2, and thus it seems reasonable for the study authors to have made this assumption.

Results of the irradiated and dark control incubations are shown below. Results of the phenyl labelled material are shaded to aid differentiation of results.

Table B.8.36 Results of soil photolysis irradiated study with XDE-729 methyl (% AR)

DAT[a] Label	Soil Extract	Caustic trap	XDE-729 methyl[b]	X11393729 [b]	X11449757 [b]	Other[b,c]	NER [d]	Total
0 PH-A	95.2		95.2				NA	95.2
0 PH-B	97.9		97.9				NA	97.9
0 PY-A	97.3		97.3				NA	97.3
0 PY-B	97.2		97.2				NA	97.2
1 PH-A	96.0	0.1	89.8	6.1			NA	96.0
1 PH-B	96.9	0.4	86.4	8.1		2.3	NA	97.2
1 PY-A	99.1	2.1	92.0	7.1			NA	101.2
1 PY-B	95.9	0.3	88.8	7.1			NA	96.2
4 PH-A	85.8	0.4	57.6	28.2			NA	86.1
4 PH-B	93.4	1.6	68.0	25.4			NA	95.0
4 PY-A	88.7	0.7	64.7	22.1		1.9	NA	89.4
4 PY-B	90.5	0.5	58.3	32.3			NA	91.0
7 PH-A	97.2	5.5	66.1	31.1			NA	102.7
7 PH-B	91.6	0.8	53.5	38.2			NA	92.4
7 PY-A	90.5	0.6	61.7	28.8			NA	91.1
7 PY-B	94.4	1.5	69.4	25.0			NA	95.9
12 PH-A	81.7	2.2	27.4	48.7	4.6	1.0	13.1	96.9
12 PH-B	77.1	4.5	27.1	43.3	5.6	1.2	19.0	100.6
12 PY-A	83.1	2.0	28.2	48.7	6.2		13.1	98.1
12 PY-B	83.9	1.9	37.2	41.0	5.6		11.6	97.4
15 PH-A	84.2	4.6	31.4	47.2	5.5		12.9	101.6
15 PH-B	78.9	4.9	30.9	43.7	4.4		15.9	99.7
15 PY-A	84.7	1.8	28.8	49.1	6.8	0.01	12.3	98.8
15 PY-B	85.6	1.4	41.0	40.7	3.9	0.01	10.4	97.4
						Average:		96.4
						Std Dev:		4.0

[a] DAT = Days after treatment (uncorrected for light-energy received by samples)
[b] Values based on HPLC results of soil extracts
[c] Other = % Soil extract - % XDE-729 methyl – % X11449757 – %X11393729
[d] NER = Non-extractable residues recovered by combustion of extracted soil pellet

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Table B.8.37 Results of soil photolysis dark control study with XDE-729 methyl (% AR)

DAT[a] Label	Soil Extract	Caustic trap	XDE-729 methyl[b]	X11393729 [b]	X11449757 [b]	Other[b,c]	NER [d]	Total
0 PH-A	95.2		95.2				NA	95.2
0 PH-B	97.9		97.9				NA	97.9
0 PY-A	97.3		97.3				NA	97.3
0 PY-B	97.2		97.2				NA	97.2
1 PH-A	95.7	0.04	88.1	7.6		1.7	NA	95.7
1 PH-B	99.1	0.1	90.7	8.4			NA	99.1
1 PY-A	95.7	0.3	87.4	8.3			NA	96.0
1 PY-B	97.4	0.3	89.1	8.2			NA	97.7
4 PH-A	90.4	0.3	53.9	34.8		2.2	NA	90.7
4 PH-B	90.2	0.4	54.3	34.1	1.9	1.2	NA	90.6
4 PY-A	93.3	0.6	47.1	46.2			NA	93.9
4 PY-B	93.3	0.6	43.6	49.7			NA	93.8
7 PH-A	82.4	1.2	12.8	62.5	5.0		13.9	97.5
7 PH-B	87.9	0.5	54.8	30.3	1.5		9.7	98.1
7 PY-A	86.4	0.7	9.9	72.5	4.1		11.1	98.3
7 PY-B	86.5	0.7	8.4	71.7	6.4		11.6	98.8
12 PH-A	67.7	2.8	4.7	49.2	13.7		25.9	96.3
12 PH-B	67.0	2.9	8.6	46.2	12.3		26.9	96.9
12 PY-A	77.0	0.9	5.9	66.1	5.0		19.9	97.8
12 PY-B	65.6	0.8	4.6	54.2	6.8		20.5	86.9
15 PH-A	60.3	4.0	3.9	44.8	11.7		34.3	98.6
15 PH-B	58.5	3.6	4.6	41.3	12.6		34.8	96.8
15 PY-A	60.3	0.9	4.0	47.1	9.3		24.4	85.7
15 PY-B	59.0	1.0	3.0	46.6	9.5		25.9	86.0
						Average:		95.1
						Std Dev:		4.1

[a] DAT = Days after treatment (uncorrected for light-energy received by samples)
[b] Values based on HPLC results of soil extracts
[c] Other = % Soil extract - % XDE-729 methyl – % X11449757 – %X11393729
[d] NER = Non-extractable residues recovered by combustion of extracted soil pellet

It was noted that the rate of degradation of XDE-729 methyl under illuminated conditions was slower than under dark conditions. Higher formation of X11393729 was also seen in the dark control falling to similar levels at the study end as in the illuminated samples, suggesting either slower degradation of X11393729 under illuminated conditions or that it was still in its formation phase. The study author kinetic calculations confirmed this, results of which are shown in the following table. The RMS confirms that the kinetic analysis was reasonable and that visual and residual fits were acceptable. The values for the metabolite represent DegT50 values from sequential fitting.

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Table B.8.38 Results of kinetic assessment (SFO) of XDE-729 methyl and X11393729 in soil photolysis study

	Illuminated DT50 (days)	χ^2	Dark control DT50 (days)	χ^2
XDE-729 methyl	8.6 (16.1)	7.0	3.5	7.4
X11393729	16.4 (30.6)	7.0	12.6	6.9

Note: values in parentheses are DT50 values corrected to natural sunlight conditions equivalent to summer sunlight days at 40ºN. Results in not parentheses are actual values recorded in the study.

(Ma and Adelfinskaya 2011)

B.8.1.4 Rate of degradation – laboratory studies

It should be noted at the outset that in general, the Applicant has chosen soil degradation parameters from field dissipation studies rather than those from the laboratory.

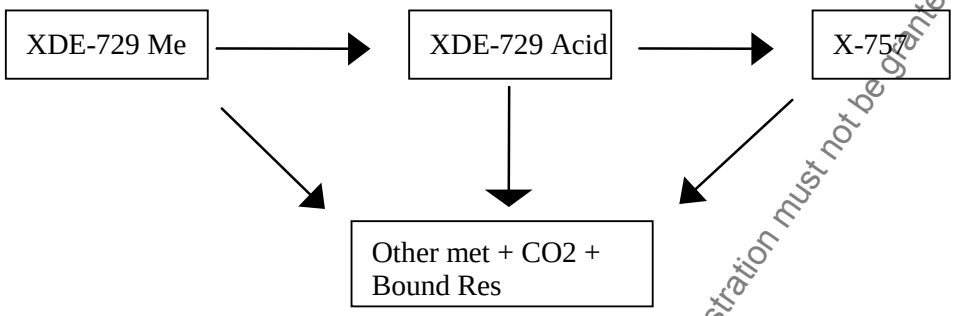
a) The degradation kinetics of XDE-729 methyl and its major metabolites under dark, aerobic conditions were investigated as part of the route of degradation study described at section B.8.1.1a) above. The study author stated that FOCUS Degradation Kinetics guidance had been followed in determining kinetic endpoints. It is noted that this exercise was to determine **persistence endpoints** for use against regulatory triggers and thus the objective of the exercise was to obtain 'best fit' kinetics. However, the RMS noted that in this kinetic assessment, the study author consistently failed to add the values of unextracted residue and metabolites to the day 0 total for parent. This is an important aspect specifically addressed in the FOCUS degradation kinetics guidance. However, the RMS also notes that as this approach tends to increase day 0 parent residues, it often has the effect of slightly decreasing the magnitude of the DT50/DT90 values. However, with this departure from FOCUS guidance in mind, the RMS has not described the kinetic assessment in the report of Yoder *et al* 2011a, but rather has used the report of Jackson 2012 (GHE-P-12651R) which calculates **modelling endpoints**. As this report more closely follows FOCUS kinetics principles, including adding day 0 metabolite and unextracted residues to parent residues, the RMS considers this to be appropriate. In any case, the procedures for deriving persistence and modelling endpoints are similar, and it is considered possible to obtain persistence endpoints from the Jackson 2012 study.

The study author used the software KinGUI v 1.1. for the determination of kinetics, initially using unweighted, ordinary least-square fitting procedures with free-fitting and un-modified data sets; data sets were modified, for example by removal of 'outliers', on a case-by-case basis. The applicant adopted the standard approach of initially considering SFO and FOMC kinetics; if FOMC kinetics gave a better fit, DFOP kinetics were additionally investigated. It appears that the study authors did not consider the use of HS kinetics. The study authors also used a 'top-down' approach for the metabolites where fitting metabolite kinetics in series with parent kinetics was problematic. Parent and metabolite kinetics was performed in a step-wise approach as recommended by FOCUS Kinetics guidance, i.e. fit metabolite with fixed best fit parent parameter, then re-fit allowing free-fitting of all parameters. The data sets for

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the individual radiolabels were used as replicates, which is considered acceptable as parent and the major metabolites both contained both radiolabelled positions. The following conceptual model was used in the kinetic modelling.

Figure B.8.3 Conceptual model used in kinetic modelling of XDE-729 methyl and its metabolites in soil.



It is noted in some parts of the kinetic analysis that one or more data points have been omitted either as outliers or where these is a large 'tail' of data at very low concentrations. Generally, the Applicant considered that it was acceptable to exclude certain sample points on the basis of FOCUS Kinetic guidance which states:

"Statistical tests for identifying outliers in an objective manner may not be appropriate given the limited number of data available. Therefore, all measurements should initially be included in the optimisation. Samples that clearly differ from others can then be eliminated based on expert judgement and the fitting procedure repeated. The removal of any data points as outliers must be clearly documented and justified in the report. Experimental errors should be identified wherever possible." (FOCUS Degradation Kinetics, Section 6.1.5).

The Applicant conducted fits including and excluding the results from this sample, and thus the RMS considers that the approach taken to be acceptable given the significant deviation of this sample from the overall results obtained.

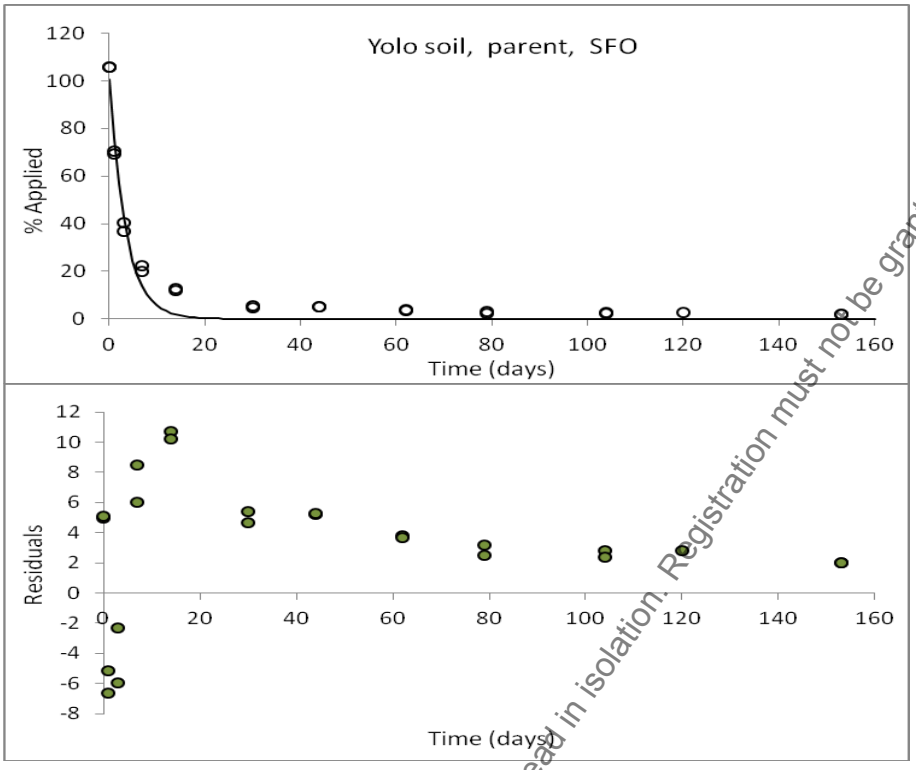
Yolo soil

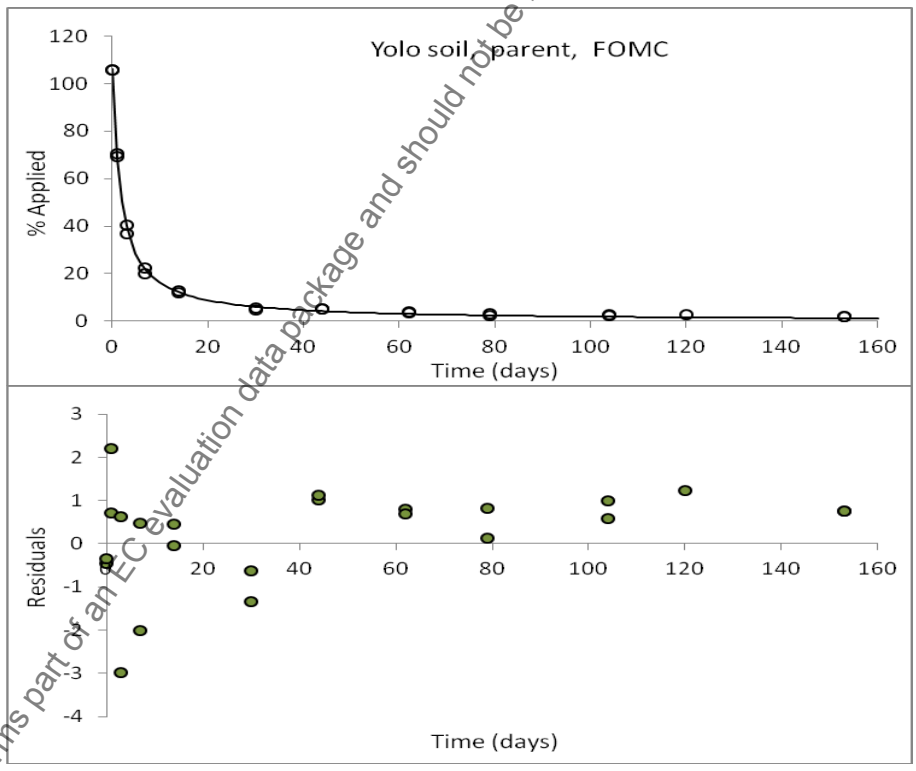
<u>Yolo soil - parent</u>

In view of the relatively better FOMC fit compared to SFO, the study authors also fitted DFOP kinetics. The visual and residual fits are shown below as are the statistical parameters.

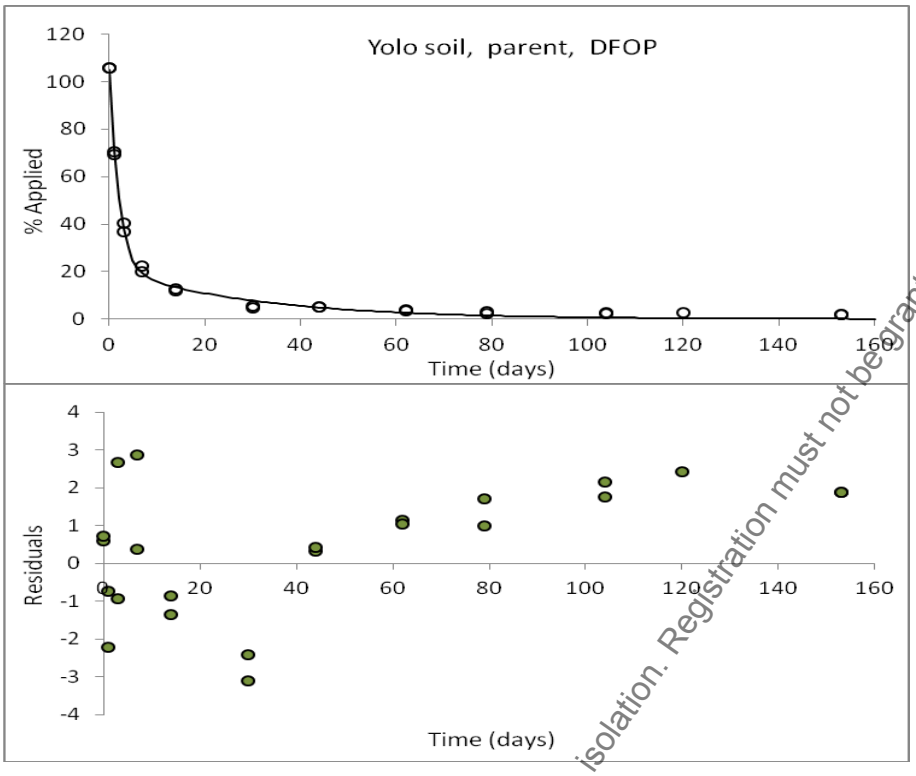
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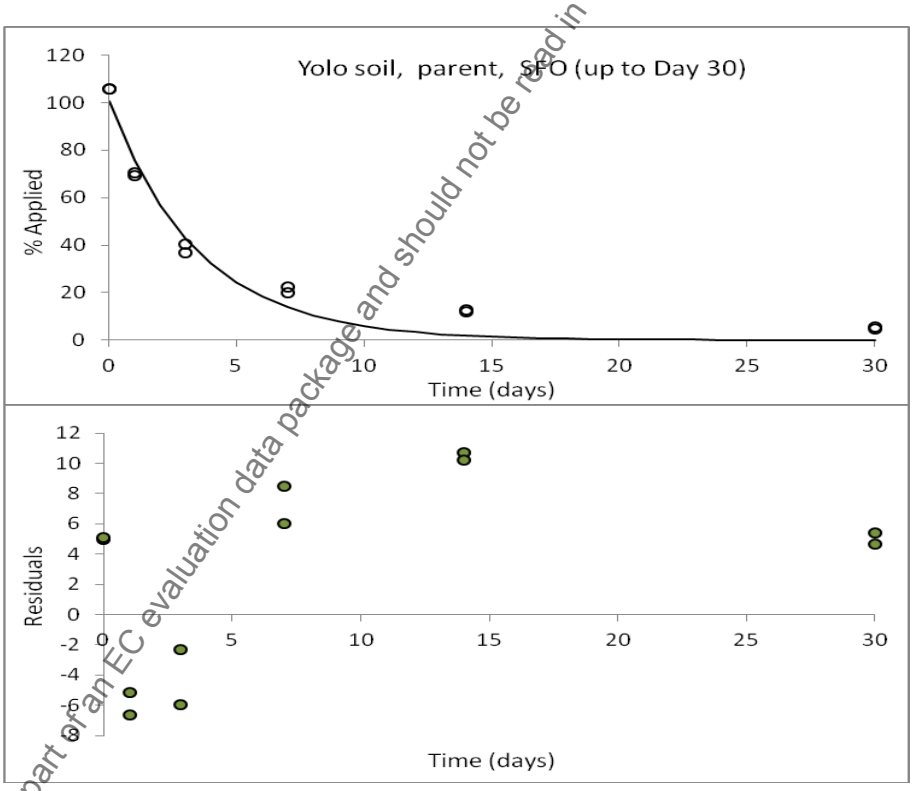
Figure B.8.4 Visual and residual kinetic fits for XDE-729 methyl in Yolo aerobic soil





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Table B.8.39 Statistical parameters for kinetic assessment of XDE-729 methyl in Yolo aerobic soil

Kinetics Model	Parameter	Value	Lower CI	Upper CI	Std Dev	Prob > t	DT_{50} (d)	DT_{90} (d)	% χ^2 error
SFO	M_0 (%) k (d^{-1})	100.6 0.2838	93.3 0.2296	108.0 0.3381	3.5 0.0261	- 2.2e-10	2.4	8.1	18.1
FOMC	M_0 (%) alpha beta	106.1 1.0020 1.8206	104.3 0.9128 1.5240	107.8 1.0911 2.1172	0.8 0.0427 0.1422	 2.8e-16 2.1e-11	1.8	16.3	3.3
DFOP	M_0 (%) k1 (d^{-1}) k2 (d^{-1}) g	105.0 0.5015 0.0337 0.7959	102.3 0.4358 0.0230 0.7500	107.7 0.5671 0.0443 0.8418	1.3 0.0314 0.0051 0.0219	 8.9e-13 1.2e-06 2.6e-19	1.9	21	6.0
SFO (0 to 30d)	M_0 (%) k (d^{-1})	100.6 0.2838	90.4 0.2082	110.9 0.3595	4.6 0.0340	- 4.0e-06	2.4	8.1	12.5

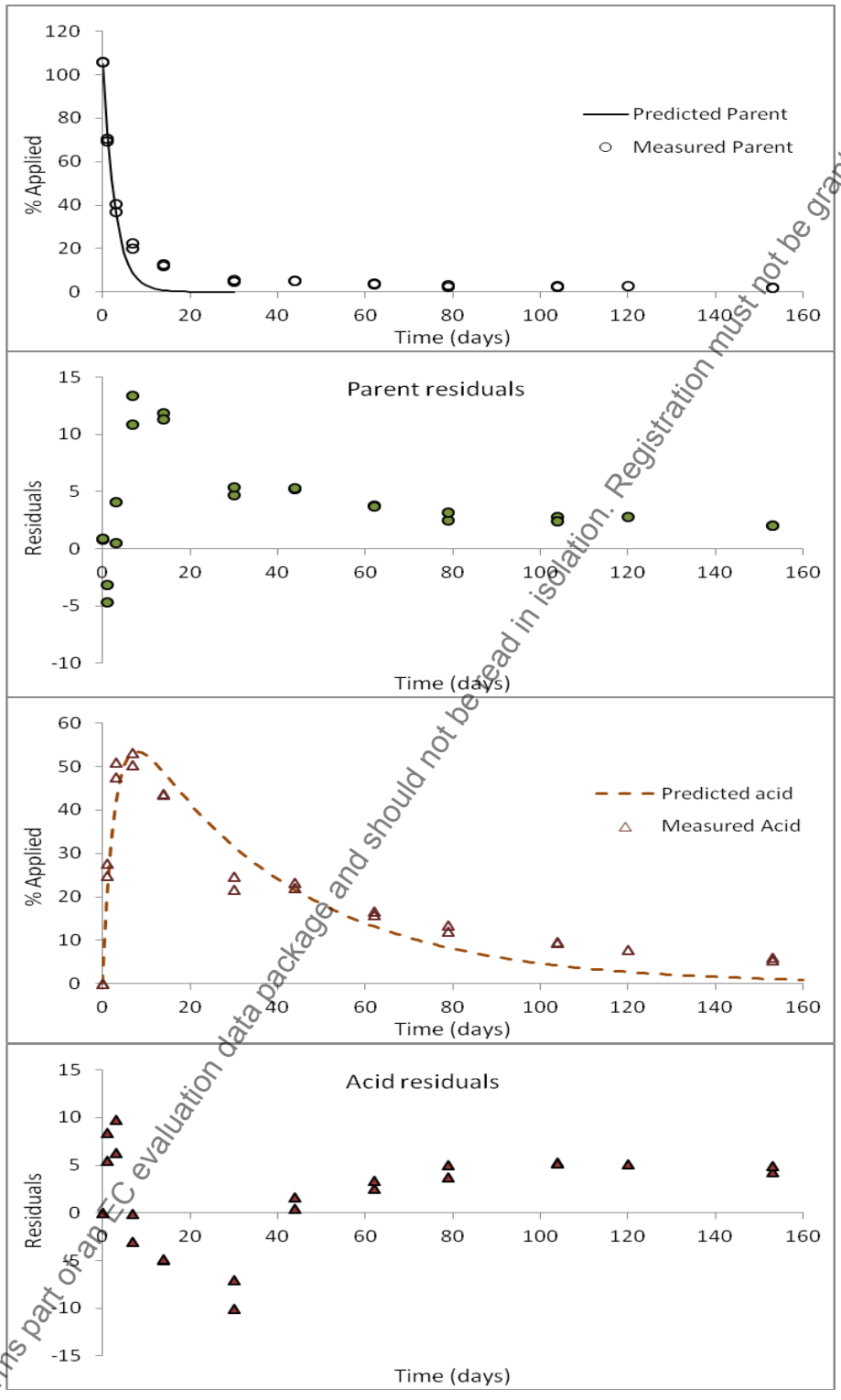
Whilst all three kinetic fits using the complete database systematically underestimated concentrations from approximately 15 - 25 DAT onwards, the FOMC fit was considered to be superior based on the better FOMC χ^2 statistic. It is also noted that the confidence intervals around the α and β values do not include zero. FOMC parameters are DT50 1.8 days, DT90 16.3 days. This is considered by the RMS to be appropriate as a persistence endpoint for this soil. However, the fit is likely to be influenced by the long 'tail' of relatively low concentrations from day 30 onwards. Given that SFO kinetics are preferred for modelling and that the DT90 is reached within the first 30 days, the study author refitted SFO kinetics to the parent data using data up to day 30 only, using six sample points with two replicates each. The exclusion of the 'tail' improved the χ^2 statistic with no change of the SFO DT50. Thus the SFO modelling endpoint of DT50 2.4 days, DT90 8.1 days can be accepted by the RMS.

Yolo soil - X11393729

Data for metabolite X11393729 were fitted in series using SFO kinetics for the metabolite with both SFO and FOMC kinetics for the parent using the whole dataset. In fitting the whole data set, the study author considered that there may be the possibility that day 30 data for the metabolite may have been outliers as the residuals seem to be high at this time point. The study author thus re-fitted the data excluding day 30 data for both parent and metabolite. The SFO/SFO fit with the whole data set is shown below for illustration as the FOMC/SFO fit with the whole dataset was very similar. SFO/SFO and FOMC/SFO fits excluding day 30 data are also shown.

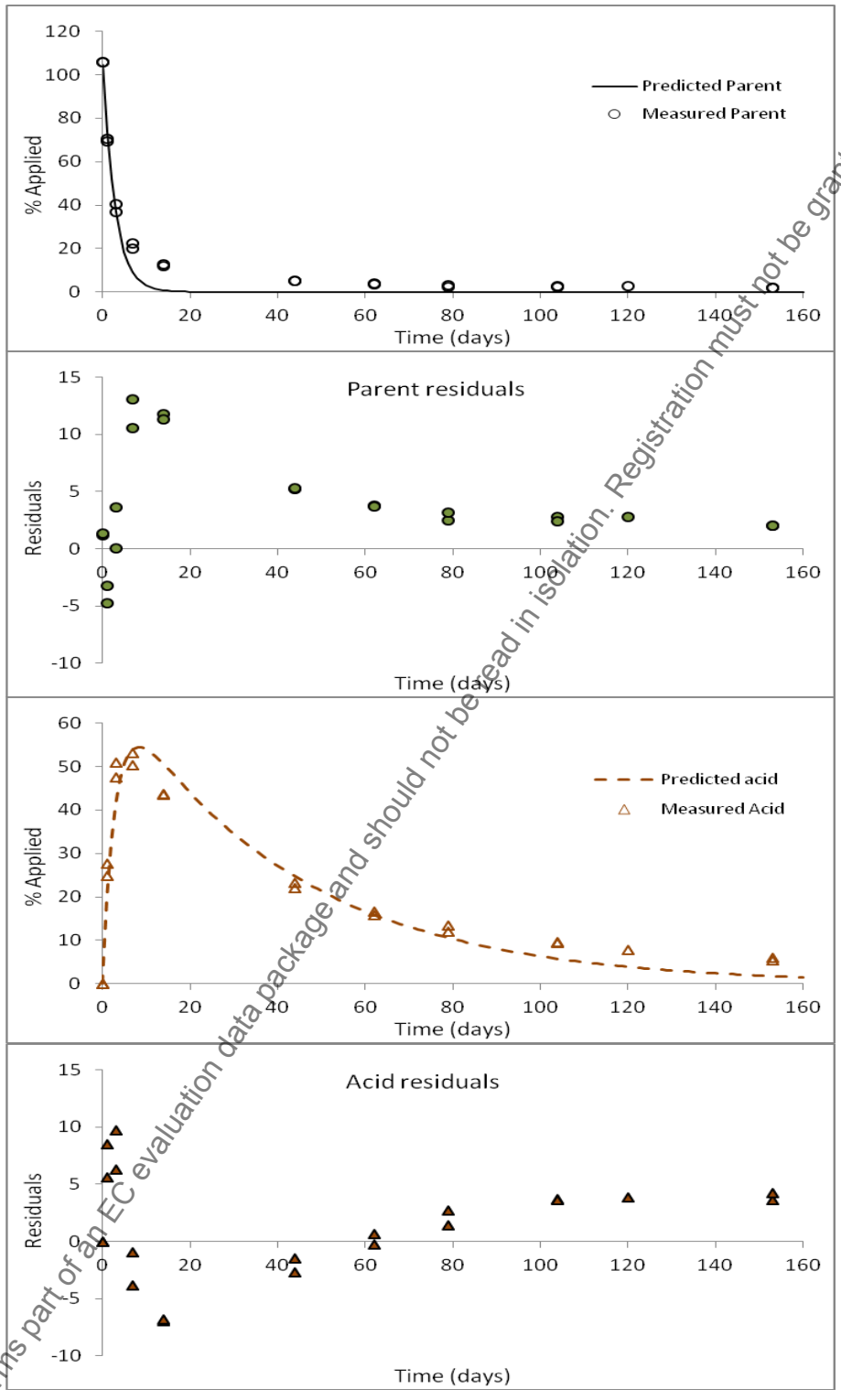
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Figure B.8.5 SFO/SFO visual and residual kinetic fits for XDE-729 methyl and X11393729 in Yolo aerobic soil, entire dataset



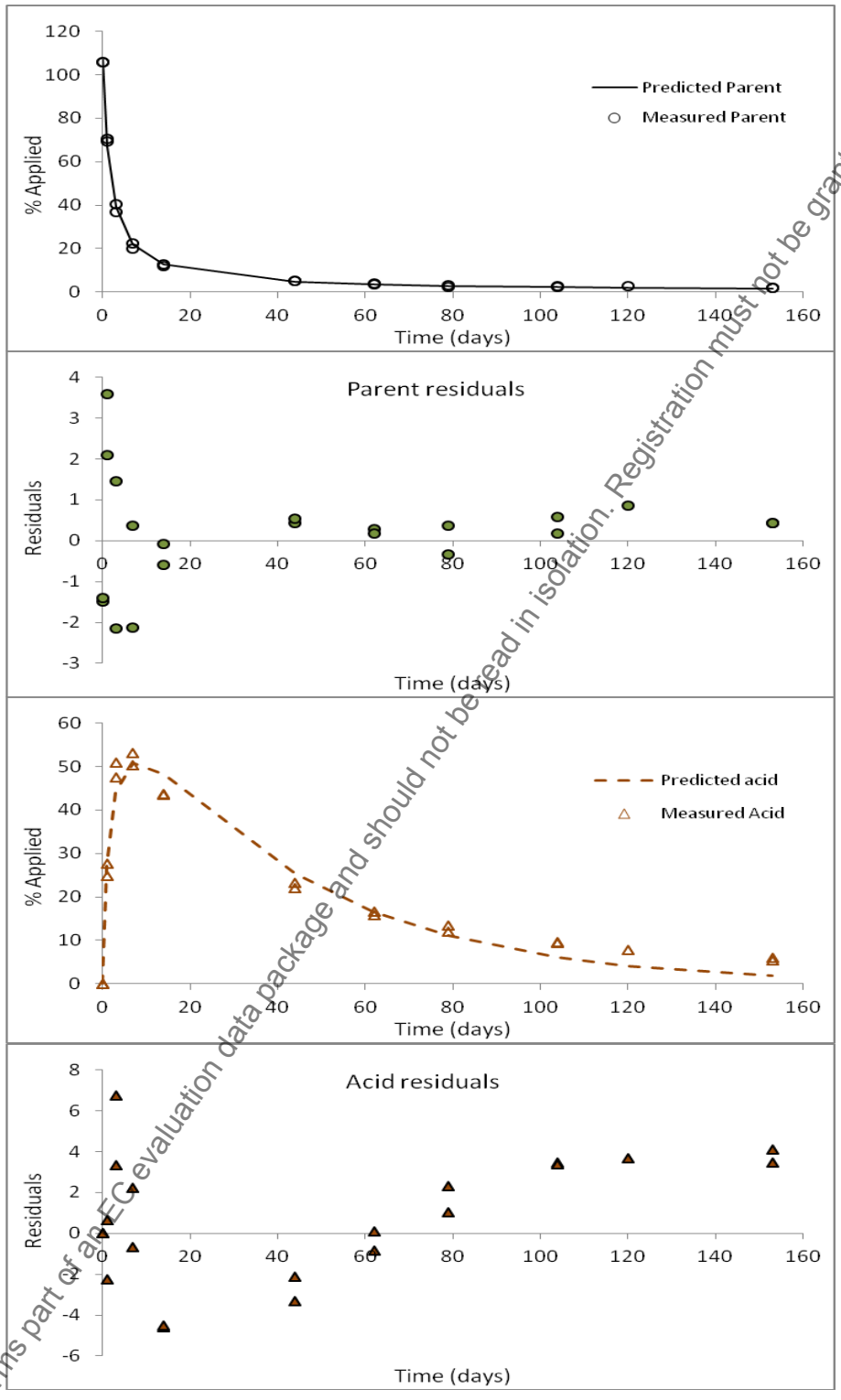
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Figure B.8.6 SFO/SFO visual and residual kinetic fits for XDE-729 methyl and X11393729 in Yolo aerobic soil, dataset excluding 30 DAT



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Figure B.8.7 FOMC/SFO visual and residual kinetic fits for XDE-729 methyl and X11393729 in Yolo aerobic soil, dataset excluding 30 DAT



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Table B.8.40 Statistical parameters for kinetic assessment of XDE-729 methyl and X11393729 in Yolo aerobic soil

Substance + Model	Parameter	Value	Lower CI	Upper CI	Std Dev	Prob > t	DT50 (d)	DT90 (d)	% χ2 error
Parent (SFO) + Acid (SFO)	M0 (%)	104.8	97.4	112.2	3.7	-			
	k (d-1)	0.3515			0.0298	3.2e-15	2.0	6.6	19.8
	ff	0.6324	0.5340	0.7309	0.0488	-			
	k (d-1)	0.0273	0.0210	0.0337	0.0032	3.5e-11	25.4	84	18.8
Parent (FOMC) + Acid (SFO)	M0 (%)	107.3	102.8	111.9	2.3	-			
	alpha	0.9204	0.7386	1.1022	0.0900	3.8e-13	1.7	16.7	4.1
	beta	1.4873	0.9484	2.0262	0.2668	8.7e-07			
	ff	0.6793	0.6134	0.7451	0.0326	-			
	k (d-1)	0.0293	0.0253	0.0332	0.0019	1.3e-18	23.7	79	15.2
Parent (SFO) + Acid (SFO) exc Day 30	M0 (%)	104.4	97.3	111.5	3.5	-			
	k (d-1)	0.3460	0.2894	0.4025	0.0279	3.2e-15	2.0	6.7	18.3
	ff	0.6372	0.5446	0.7299	0.0458	-			
	k (d-1)	0.0242	0.0188	0.0296	0.0027	2.3e-11	28.7	95	16.4
Parent (FOMC) + Acid (SFO) exc Day 30	M0 (%)	107.1	103.7	110.5	1.7				
	alpha	0.9089	0.7655	1.0523	0.0708	1.6e-15	1.7	17.2	3.6
	beta	1.4812	1.0609	1.9015	0.2074	9.2e-09			
	ff	0.6847	0.6354	0.7339	0.0243	-			
	k (d-1)	0.0260	0.0234	0.0286	0.0013	8.7e-22	26.6	88	10.9

ff = formation fraction

As can be seen, exclusion of the day 30 data has little influence on the magnitude of DT50/DT90 values for the parent irrespective of kinetic model. The impact on the metabolite X11393729 is to slightly increase the magnitude of DT50/DT90 and slightly increase formation fraction following exclusion of day 30 data. However, concentrations are still consistently under-estimated from approx day 80 onwards, this being an improvement over fits where the day 30 data are retained. With respect to modelling endpoints for X11393729, the study author considered that the DegT50 of 26.6 days and formation fraction of 0.6847 could be accepted. The RMS notes that these values are from the FOMC/SFO fit and the DT50 is slightly shorter but the formation fraction slightly greater than those from the SFO/SFO fit. Given that the modelling will use SFO parameters throughout, the RMS considers it is better in principle to preserve the SFO/SFO linkage between parent and metabolite and choose the SFO/SFO parameters, although this recognises that the fit itself for metabolite from SFO/SFO is slightly inferior to FOMC/SFO. The RMS also notes general difficulties in obtaining appropriate FOMC modelling parameters for a parent substance when modelling metabolite formed from a parent substance.

The study author also conducted a 'top-down' approach for X11393729 using SFO kinetics, with and without day 30 data. The statistics are presented only; fits were generally acceptable, with under-prediction of concentrations from approximately the 6th sample time, however, exclusion of day 30 data improved the fit. The top down kinetics are considered by the RMS to be appropriate for use as persistence endpoints of a metabolite as this is a better reflection of the overall rate of decline in soil, rather than from a sequential fit with the parent where the DT50 represents the metabolite degradation rate only. Thus the top down SFO DisT50 of 35.9 days is accepted as the persistence endpoint for X11393729 in this soil.

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Table B.8.41 Kinetic parameter statistics for top down fit for X11393729 in Yolo aerobic soil.

Substance + Model	Parameter	Value	Lower CI	Upper CI	Std Dev	Prob > t	DT50 (d)	DT90 (d)	% χ2 error
Acid (SFO) (top down)	**M0 (%)** **k (d-1)**	**48.9** **0.0205**	**44.8** **0.0169**	**53.0** **0.0240**	**1.9** **0.0017**	**-** **1.5e-09**	**33.8**	**112**	**11.6**
Acid (SFO) (exc Day 30)	**M0 (%)** **k (d-1)**	**50.4** **0.0193**	**48.1** **0.0175**	**52.6** **0.0211**	**1.0** **0.0008**	**-** **2.3e-12**	**35.9**	**119**	**6.0**

Yolo soil - X11449757

For metabolite X11449757, the study author attempted to obtain kinetic parameters by fitting this metabolite sequentially after parent followed by X11393729 (i.e. FOMC/SFO/SFO). The statistical results are shown below. Given the high χ^2 value for this metabolite and standard deviations for formation fraction and rate constant approaching the optimised values, the study author considered that it was inappropriate to use the parameters for modelling. The RMS notes that relatively speaking, the visual and residual fits were not bad, although there was a significant relative under prediction of concentrations for more than half the time points. However, given the relatively low concentrations of this metabolite throughout this incubation, the statistics from this sequential fit are unsurprising. As an alternative, the study author used an SFO top down approach which gave more reliable statistics and a better spread of residuals. The study author proposed the top down kinetic parameters as the basis of the modelling parameters; the RMS considers that this can also be used as a persistence endpoint as well. Thus an SFO DisT50 of 76.7 days is proposed, along with an assumed formation fraction of 1, for X11449757 in Yolo soil. As a terminal metabolite, the long DT50 from the top-down approach will not influence the leaching concentrations of any further metabolites and was therefore accepted by the RMS as being appropriately conservative.

Table B.8.42 Statistical parameters for kinetic assessment of X11449757 in Yolo aerobic soil

Substance + Model	Parameter	Value	Lower CI	Upper CI	Std Dev	Prob > t	DT50 (d)	DT90 (d)	% χ2 error
Parent (FOMC) +	M0 (%) alpha beta	107.3 0.9163 1.4728	103.6 0.7670 1.0316	111.1 1.0655 1.9141	1.9 0.0747 0.2208	- 1.5e-18 4.0e-09	1.7	17	4.2
Acid (SFO) +	ff k (d-1)	0.6768 0.0290	0.6226 0.0258	0.7310 0.0322	0.0271 0.0016	- 1.0e-26	24	79	15.2
X-757 (SFO)	ff* k (d-1)*	0.9584 0.2014	-0.2476 -0.0826	2.1644 0.4853	0.6033 0.1420	- 0.0807	3.4	11	32.2
X-757 (SFO) (top down)	M0 (%) k (d-1)	5.0 0.0090	4.7 0.0078	5.3 0.0102	0.1 0.0006	- 2.5e-10	76.7	255	5.2

* standard deviation > optimised value and/or lower CI < 0 ff = formation fraction

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RefSol 03-G soil

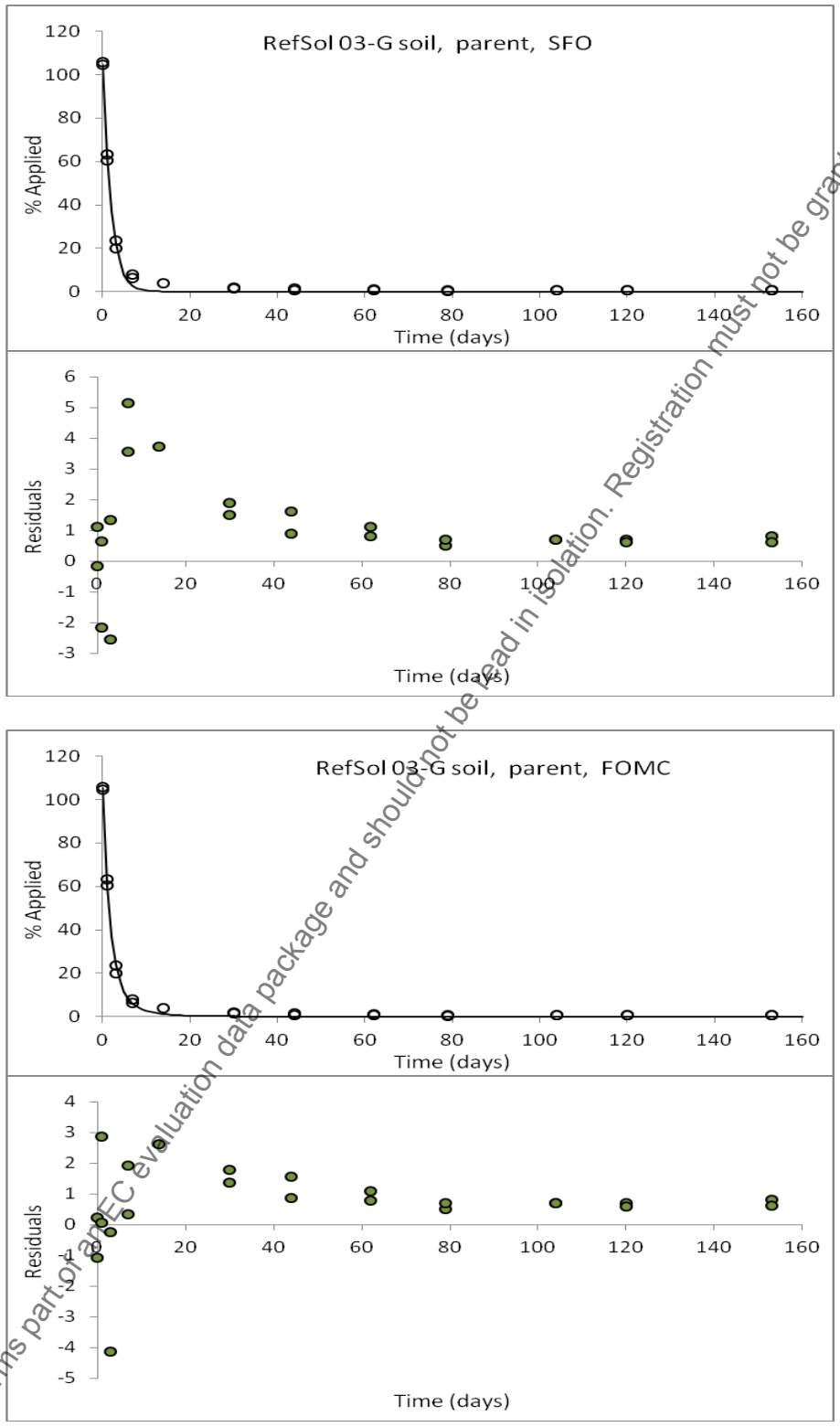
RefSol 03-G soil – parent

The study authors only tested SFO and FOMC. Whilst FOMC kinetics gave a better fit in terms of the χ^2 value, there is very little difference in visual fit and the DT50 and DT90 values are virtually identical. The study author proposes an SFO DT50 of 1.3 days with χ^2 of 8.4. The RMS considers that the choice of SFO kinetics for both modelling and persistence endpoints is pragmatic and acceptable.

The RMS notes that the residues decline very quickly leaving a tail of very low residues from before day 20. If data were excluded from time points after day 30, it is likely that better statistics would have been achieved with little change of optimised parameters. This has actually been demonstrated in the fitting for the metabolite X11393729 where data after 44 DAT were excluded resulting in an improved fit and χ^2 value with no change to the optimised parameters. Thus the approach used is considered acceptable by the RMS.

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Figure B.8.8 Visual and residual kinetic fits for XDE-729 methyl in RefSol 03-G aerobic soil



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Table B.8.43 Statistical parameters for kinetic assessment of XDE-729 methyl in RefSol 03-G aerobic soil

Kinetics Model	Parameter	Value	Lower CI	Upper CI	Std Dev	Prob > t	DT50 (d)	DT90 (d)	% χ2 error
SFO	M0 (%) k (d-1)	104.7 0.5146	101.9 0.4795	107.5 0.5497	1.3 0.0169	- 3.6e-19	1.3	4.5	8.4
FOMC	M0 (%) alpha beta	105.6 3.9001 6.4819	103.2 1.7952 2.3787	107.9 6.0050 10.585	1.1 1.0091 1.9671	- 4.8e-04 0.0018	1.3	5.2	6.4

RefSol 03-G soil – X11393729

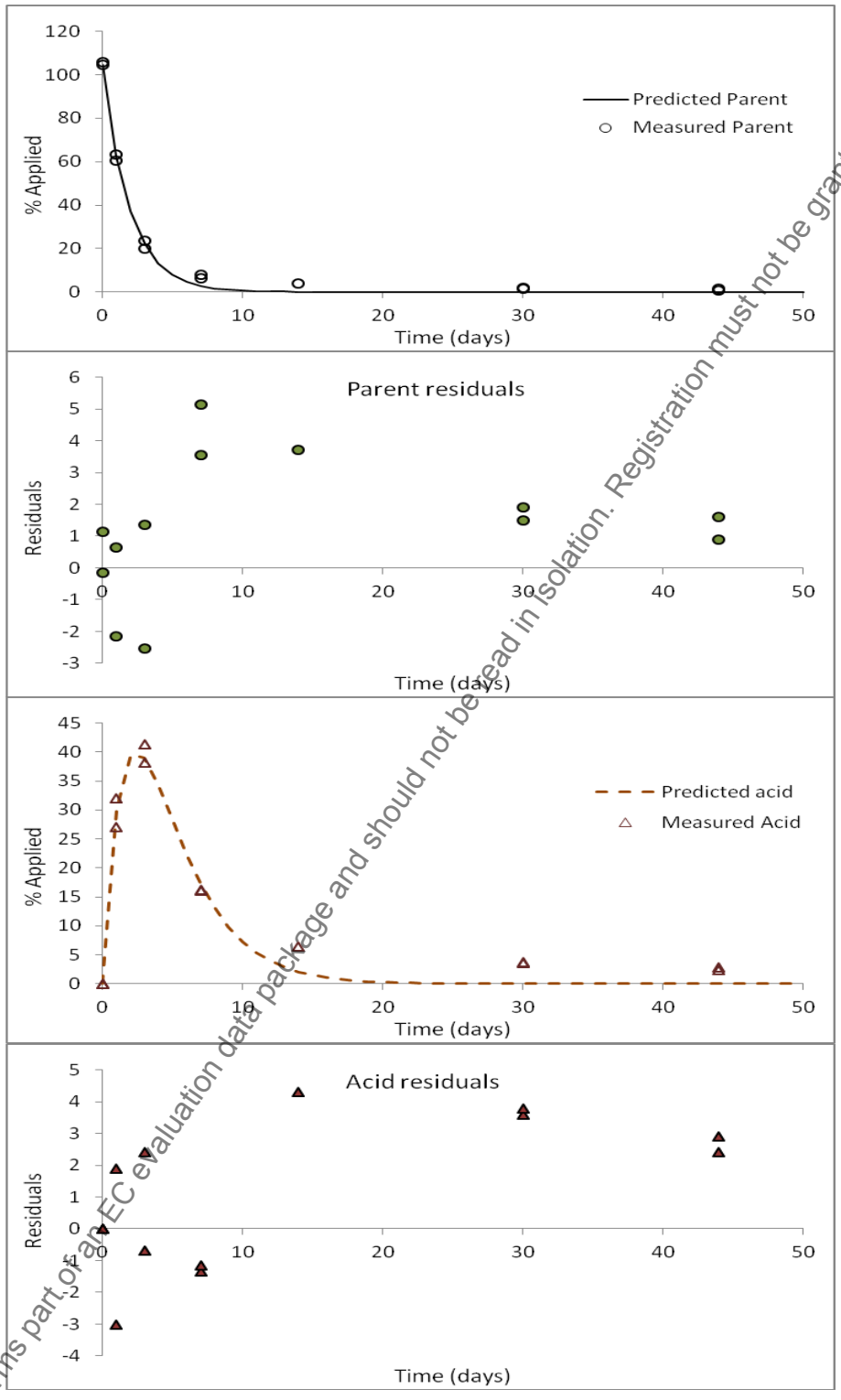
The study authors initially fitted X11393729 in series with parent (SFO-SFO kinetics) using the complete dataset. Whilst there was little change to the parent fitting by sequentially adding the metabolite, initial fitting for the metabolite was deemed by the study author to be relatively poor, with a χ^2 value of 19.6 and under-estimation of the final eight samples which represents a tail of low concentrations. However, the study author noted that following an observed peak of the metabolite of 38 – 41% AR at 3 DAT, concentrations decreased to < 3% AR at 44 DAT. Parent residues were <2% AR at 44 DAT. The study author thus argued that the metabolite had undergone greater than 90% degradation of the observed peak by 44 DAT. Therefore, refitting was performed on parent and metabolite excluding data after 44 DAT. Exclusion of these data gave improved fits for both parent and metabolite with no change in parent degradation rate and little change in the DT50/DT90 values. Considering the long tail of low concentrations, the RMS considers this to be a reasonable approach and in line with FOCUS kinetics recommendations. Modelling endpoints of SFO DegT50 2.0 days and formation fraction of 0.8548 can be accepted by the RMS.

A top down fitting approach from the peak concentration was also used on X11393729 using the complete dataset which gave a relatively high χ^2 value of 20.1. It is likely that the fitting could be improved by elimination of the tail of low concentrations as performed with the sequential fitting described above, however, the RMS considers that the SFO DisT50 value can be accepted as a persistence endpoint. The SFO DisT50 value of 3.3 days can be accepted for X11393729 on this soil.

Fitting of parent and X11393729 sequentially excluding data after 44 DAT are shown below. The fitting with the complete data set is not presented as the overall fit to earlier timepoints is very similar, the only difference being the long tail of low concentrations being slightly under-predicted.

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Figure B.8.9 Visual and residual kinetic fits for SFO/SFO fit for XDE-729 methyl and X11393729 in RefSol 03-G aerobic soil, 0-44 DAT data



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Figure B.8.10 Top down SFO fit for X11393729 in RefSol 03-G aerobic soil

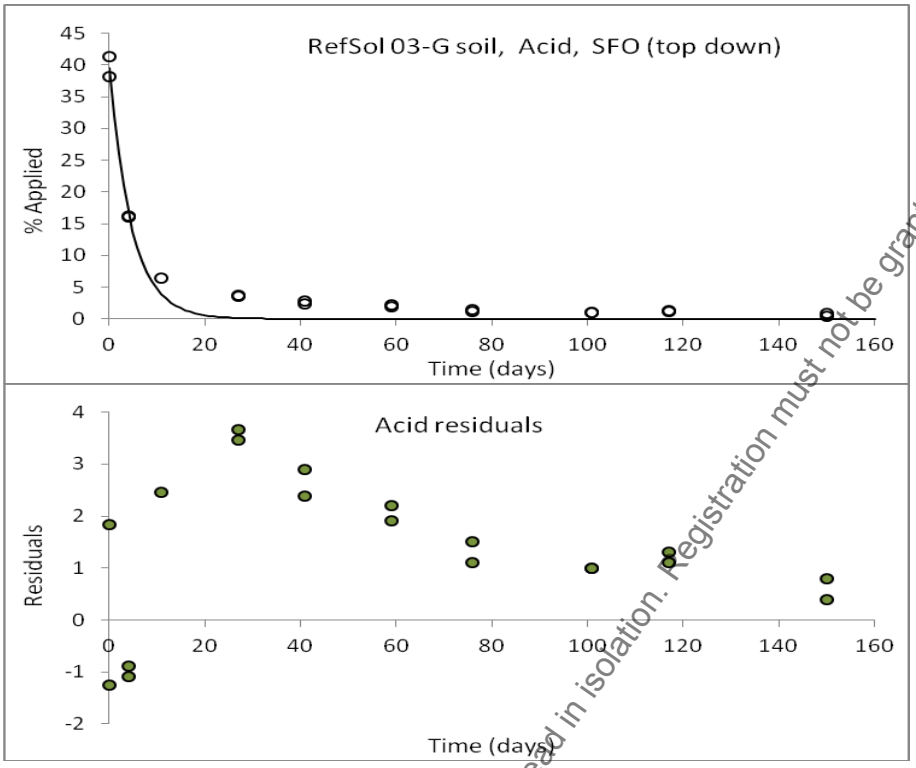


Table B.8.44 Statistical parameters for kinetic assessment of X11393729 in RefSol 03-G aerobic soil

Substance	Parameter	Value	Lower CI	Upper CI	Std Dev	Prob > t	DT50 (d)	DT90 (d)	% χ2 error
Parent (SFO) + Acid (SFO)	M0 (%)	104.7	101.8	107.5	1.4	-			
	k (d-1)	0.5149	0.4792	0.5507	0.0177	9.8e-30	1.3	4.5	8.4
	ff	0.8542	0.7475	0.9610	0.0529	-			
	k (d-1)	0.3381	0.2814	0.3948	0.0281	1.7e-15	2.1	6.8	19.6
Parent (SFO) + Acid (SFO) (0-44 days)	M0 (%)	104.7	100.9	108.4	1.8	-			
	k (d-1)	0.5147	0.4672	0.5621	0.0229	5.7e-17	1.3	4.5	6.0
	ff	0.8548	0.7130	0.9966	0.0684	-			
	k (d-1)	0.3381	0.2629	0.4134	0.0363	2.1e-09	2.0	6.8	14.4
Acid (SFO) (top down)	M0 (%)	39.5	36.4	42.5	1.4	-			
	k (d-1)	0.2092	0.1654	0.2530	0.0208	6.9e-09	3.3	11.0	20.1

ff = formation fraction; Acid = X11393729

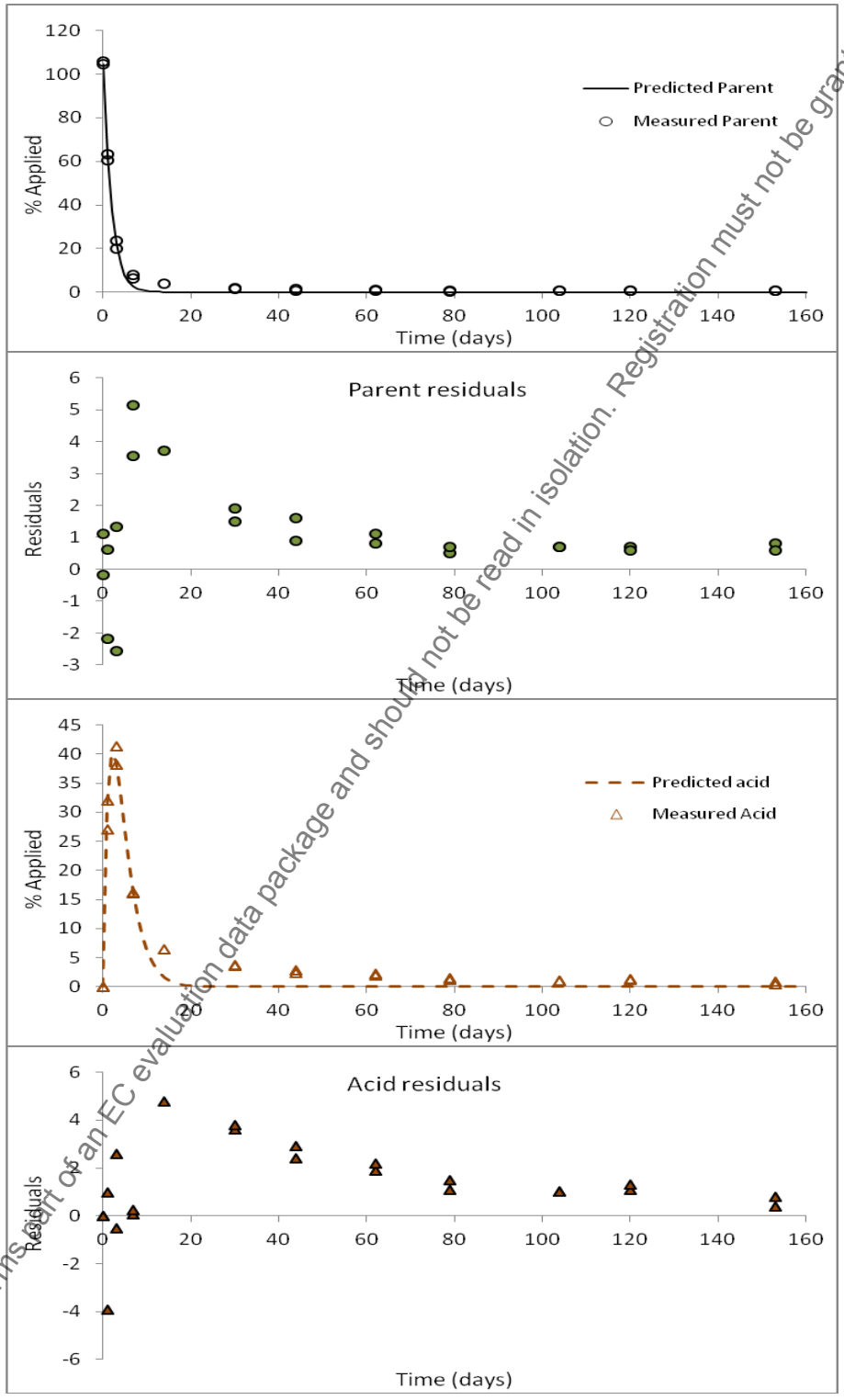
RefSol 03-G soil – X11449757

The study author initially attempted a sequential fit of X11449757 following parent and X11393729; the complete dataset was used for this fitting. Fits of parent and X11393729 were little affected by the addition of X11449757, however, the relatively high χ^2 value of 36.3 prompted the applicant to pursue a top down approach. The top down approach gave an improved χ^2 value. The study author proposed to use the top down SFO DisT50 of 25.1 days as a modelling endpoint alongside a formation fraction of 1. The RMS can accept this, particularly as it is a terminal metabolite in exposure

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modelling. In addition, the RMS proposes that this top down DisT50 can be used as a persistence endpoint for X11449757 in RefSol 03-G soil.

Figure B.8.11 Visual and residual kinetic fits for XDE-729 methyl, X11393729 (= Acid in graphs) and X11449757 in RefSol 03-G aerobic soil



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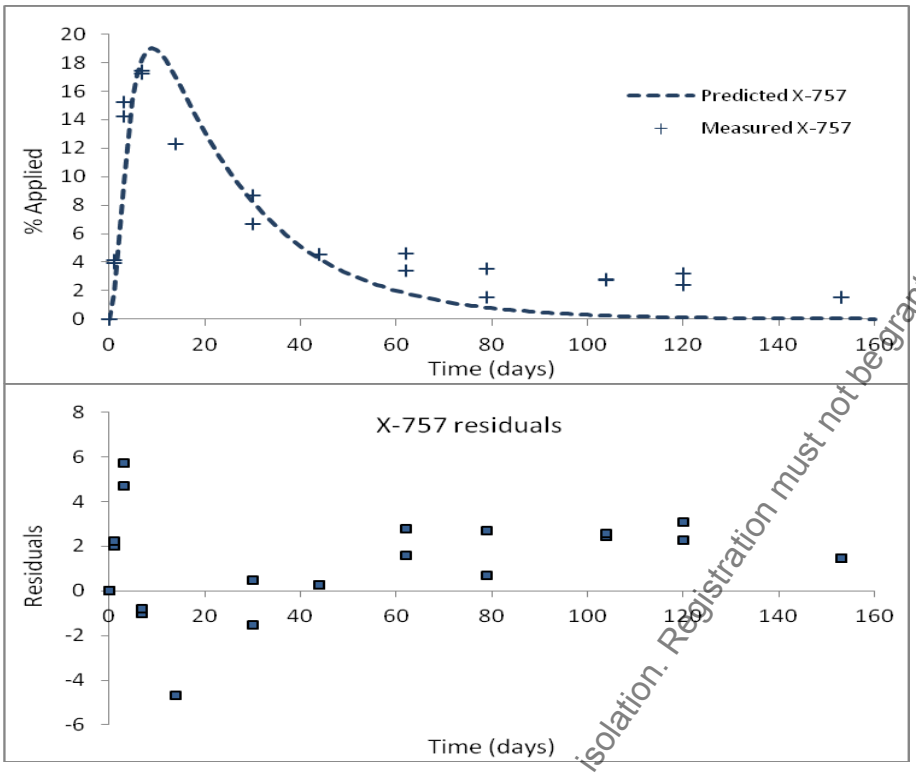
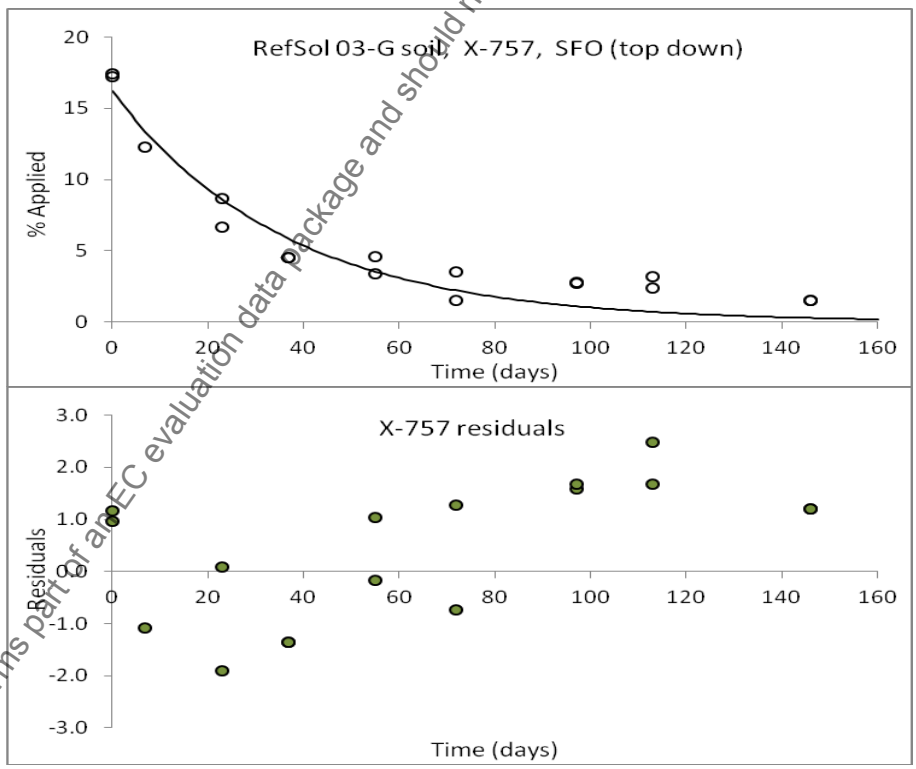


Figure B.8.12 Visual and residual kinetic fits for SFO top down approach with X11449757 in RefSol 03-G aerobic soil



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Table B.8.45 Statistical parameters for kinetic assessment of X11449757 in RefSol 03-G aerobic soil

Substance	Parameter	Value	Lower CI	Upper CI	Std Dev	Prob > t	DT50 (d)	DT90 (d)	% χ2 error
Parent (SFO) + Acid (SFO) + X-757 (SFO)	M0 (%)	104.7	101.6	107.8	1.5	-			
	k (d-1)	0.5144	0.4757	0.5532	0.0194	3.6e-36	1.3	4.5	8.4
	ff	0.8960	0.7737	1.0184	0.0612	-			
	k (d-1)	0.3699	0.3042	0.4356	0.0329	5.2e-17	1.9	6.2	20.6
	ff	0.2867	0.2181	0.3553	0.0343	-			
	k (d-1)	0.0472	0.0336	0.0608	0.0068	1.4e-09	14.7	49	36.3
X-757 (SFO) (top down)	M0 (%)	16.2	14.3	18.1	0.9	-			
	k (d-1)	0.0276	0.0214	0.0337	0.0029	4.3e-08	25.1	84	17.0

ff = formation fraction

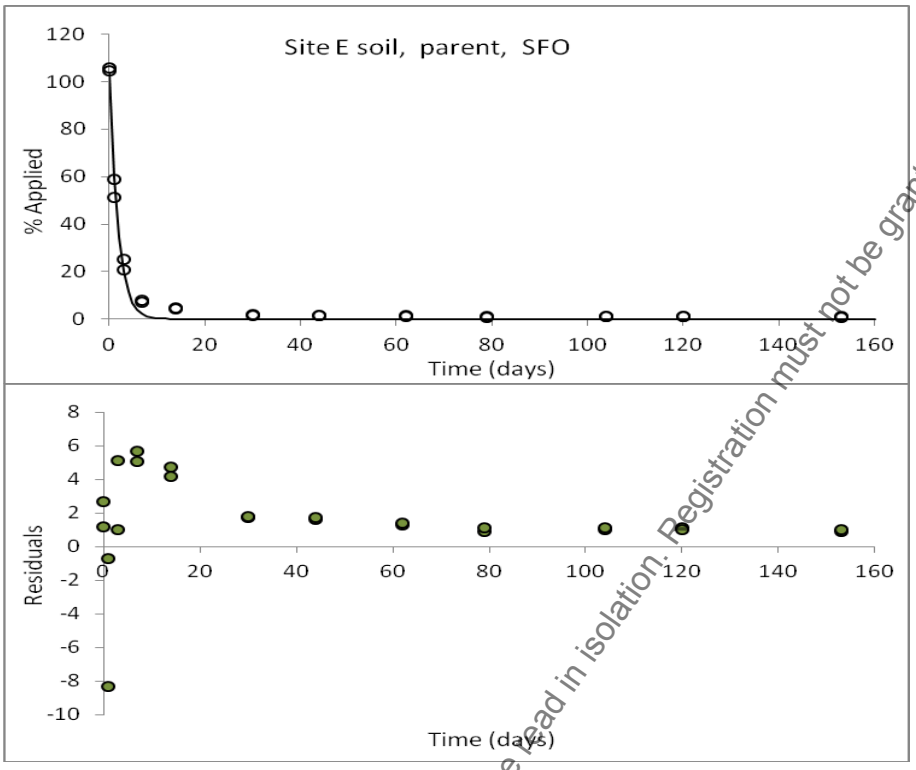
Site E soil

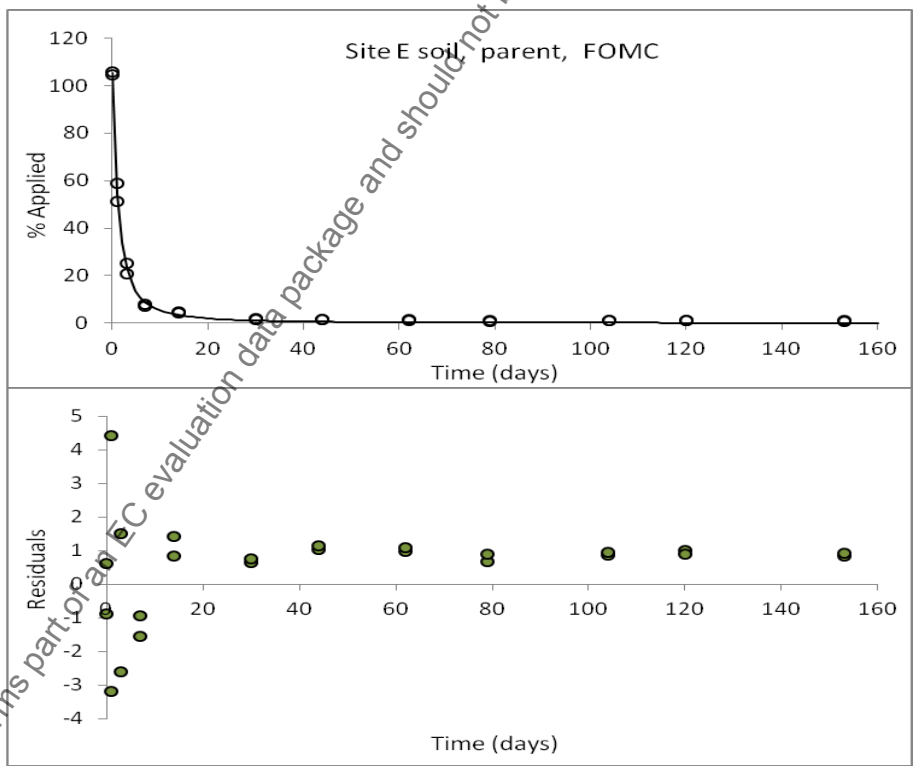
Site E soil – parent

The study author fitted the parent data for Site E soil to both SFO and FOMC. FOMC gave a better fit visually, in terms of residual and for the χ^2 value. However, as the actual DT50 and DT90 values for SFO and FOMC were very similar, the study author proposed the SFO parameters for modelling. Given the χ^2 value of 13.3 for the SFO fit and the fact that from 30 DAT the parent residues were <2% AR, i.e. there is likely to be a significant influence of a long tail of low residues, the RMS considers this to be acceptable. For the persistence endpoint for this soil, the RMS proposes to use the FOMC parameters, i.e. DT50 1.1 days, DT90 6.1 days.

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Figure B.8.13 Visual and residual kinetic fits for XDE-729 methyl in Site E aerobic soil





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Table B.8.46 Statistical parameters for kinetic assessment of XDE-729 methyl in Site E aerobic soil

Kinetics Model	Parameter	Value	Lower CI	Upper CI	Std Dev	Prob > t	DT50 (d)	DT90 (d)	%χ2 error
SFO	M0 (%) k (d-1)	103.2 0.5491	98.7 0.4872	107.8 0.6110	2.2 0.0298	- 3.8e-15	1.3	4.2	13.3
FOMC	M0 (%) alpha beta	105.3 1.6863 2.0924	102.9 1.2858 1.3758	107.7 2.0867 2.8090	1.2 0.1926 0.3446	- 9.4e-09 2.5e-06	1.1	6.1	4.4

Site E soil – X11393729

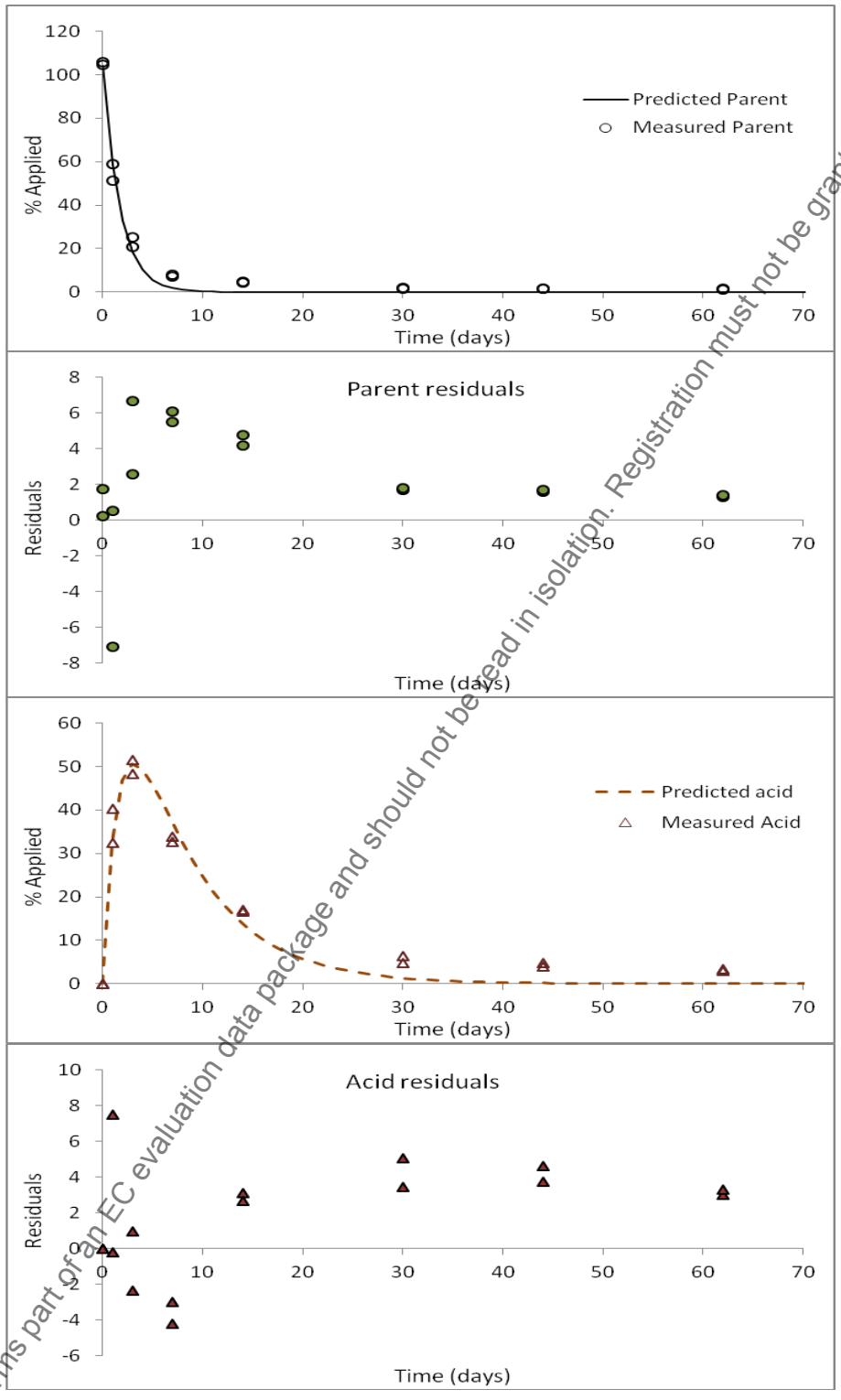
Given the selection of SFO as the kinetics of choice for modelling parameters, the study author fitted X11393729 in series with parent with SFO/SFO. In view of the relatively high χ^2 value of 18.2 for X11393729, the study author refitted with a more limited dataset. Peak observed formation of X11393729 was 48 – 51 % AR at 3 DAT and residues had fallen to approx 3% AR at 62 DAT. The study author considered that 90% degradation of X11393729 had occurred by 62 DAT and therefore it was justified to exclude data points after this sample time. Parent residues at day 62 were <2% AR. Excluding these data improved the fit with virtually no change in the optimised parameters for either parent or metabolite. Thus the study author proposes a modelling endpoint for X11393729 in Site E soil of SFO DegT50 4.7 days with formation fraction of 0.7733. The RMS can accept these values.

The study author also conducted a top down approach for X11393729 using SFO kinetics. This is considered to be a reasonable fit and the RMS considers that the SFO DisT50 of 7.6 days can be accepted as the persistence endpoint for X11393729 in Site E soil.

Visual and residual fits and statistics are given below. The graphical fitting of parent and metabolite with the complete database is not presented as the overall fit to earlier time points is very similar, the only difference being the long tail of low concentrations being slightly under-predicted.

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Figure B.8.14 Visual and residual kinetic fits for SFO/SFO fit for XDE-729 methyl and X11393729 in Site E aerobic soil, 0-62 DAT data



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Figure B.8.15 Top down SFO fit for X11393729 in Site E aerobic soil

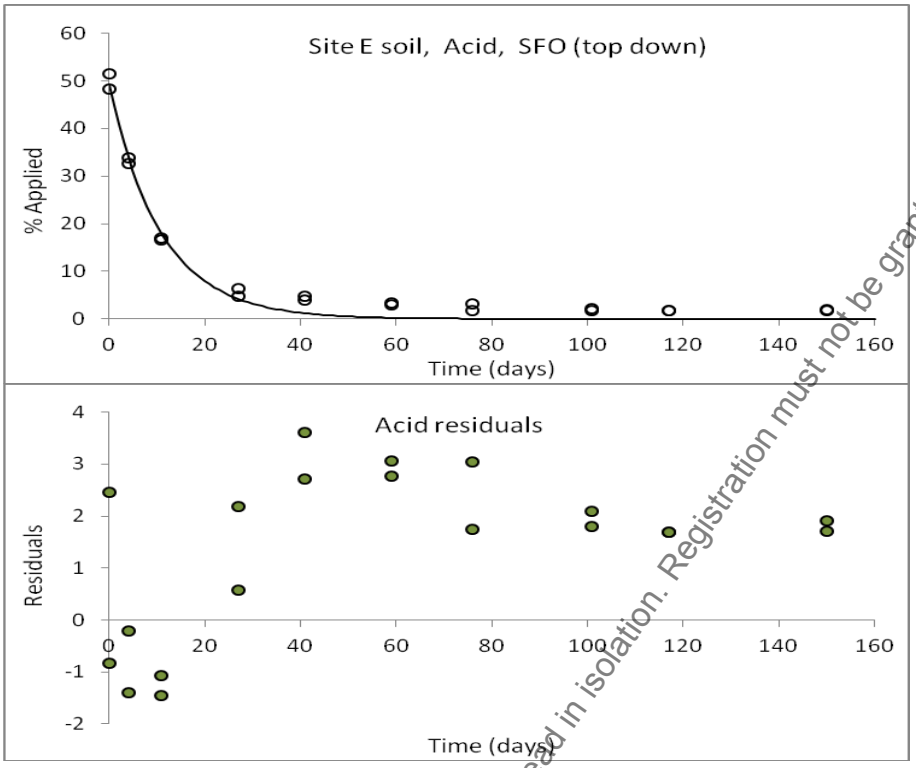


Table B.8.47 Statistical parameters for SFO kinetic assessment of X11393729 in Site E aerobic soil

Substance	Parameter	Value	Lower CI	Upper CI	Std Dev	Prob > t	DT50 (d)	DT90 (d)	% χ2 error
Parent (SFO) + Acid (SFO)	M0 (%)	104.2	99.7	108.6	2.2	-			
	k (d-1)	0.5788	0.5170	0.6406	0.0307	5.1e-23	1.2	4.0	13.6
	ff	0.7732	0.6716	0.8748	0.0504	-			
	k (d-1)	0.1461	0.1173	0.1748	0.0143	1.6e-13	4.7	15.8	18.2
Parent (SFO) + Acid (SFO) (0-62 days)	M0 (%)	104.2	98.8	109.6	2.6	-			
	k (d-1)	0.5788	0.5036	0.6540	0.0367	9.3e-16	1.2	4.0	10.9
	ff	0.7733	0.6496	0.8969	0.0604	-			
	k (d-1)	0.1462	0.1111	0.1812	0.0171	1.4e-09	4.7	15.8	14.4
Acid (SFO) (top down)	M0 (%)	49.0	46.0	52.0	1.4	-			
	k (d-1)	0.0908	0.0768	0.1049	0.0067	3.4e-11	7.6	25.4	13.1

ff = formation fraction

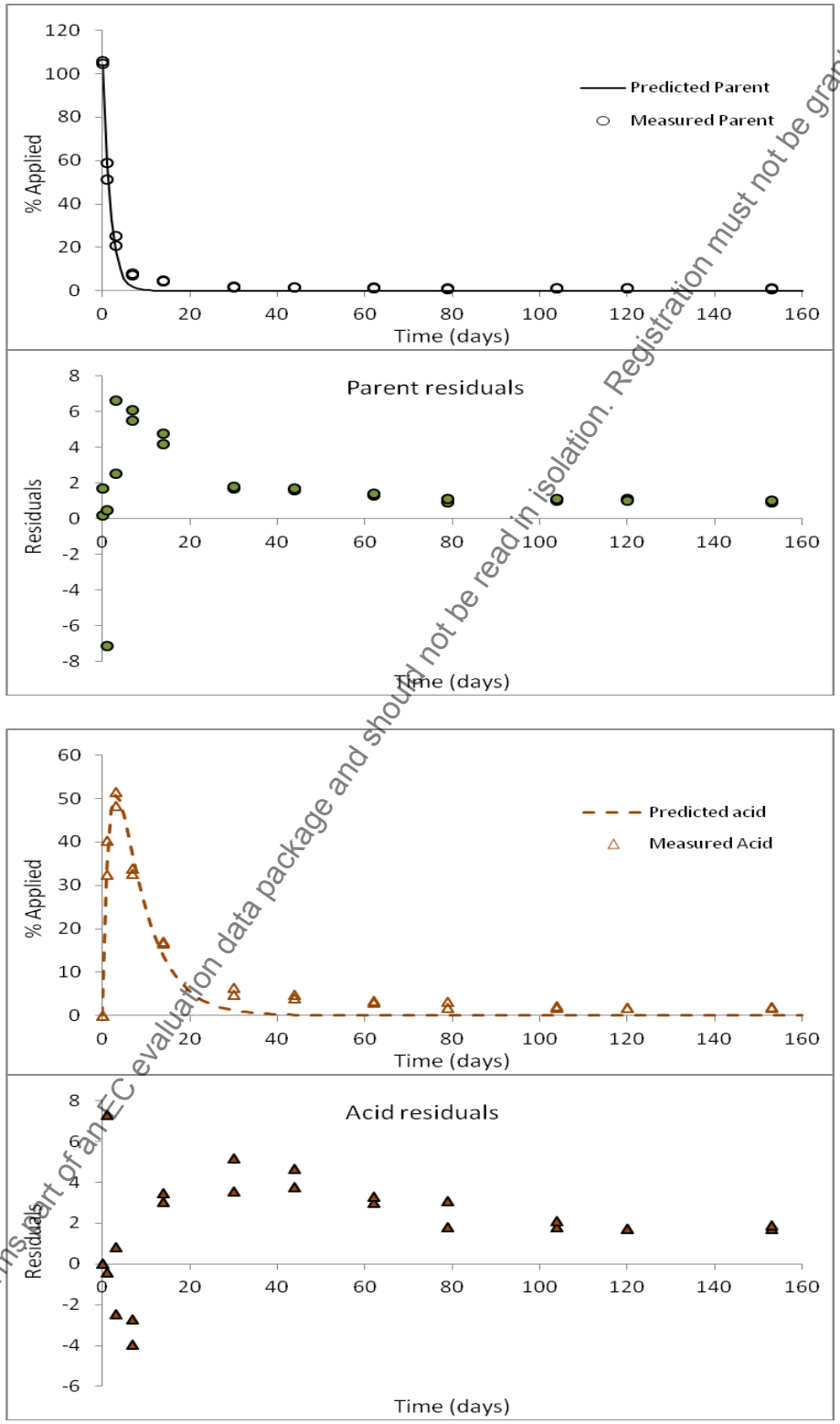
Site E soil - X11449757

The study author initially attempted a sequential fit of X11449757 following parent and X11393729; the complete dataset was used for this fitting. Fits of parent and X11393729 were little affected by the addition of X11449757, however, the relatively high χ^2 value of 29.2 prompted the applicant to pursue a top down approach. The top down approach gave an improved χ^2 value. The study author proposed to use the top down SFO DisT50 of 31.8 days as a modelling endpoint alongside a formation fraction of 1. The RMS can accept this, particularly as it is a terminal metabolite in exposure

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modelling. In addition, the RMS proposes that this top down DisT50 can be used as a persistence endpoint for X11449757 in Site E soil.

Figure B.8.16 Visual and residual kinetic fits for XDE-729 methyl, X11393729 (= Acid in graphs) and X11449757 in Site E aerobic soil



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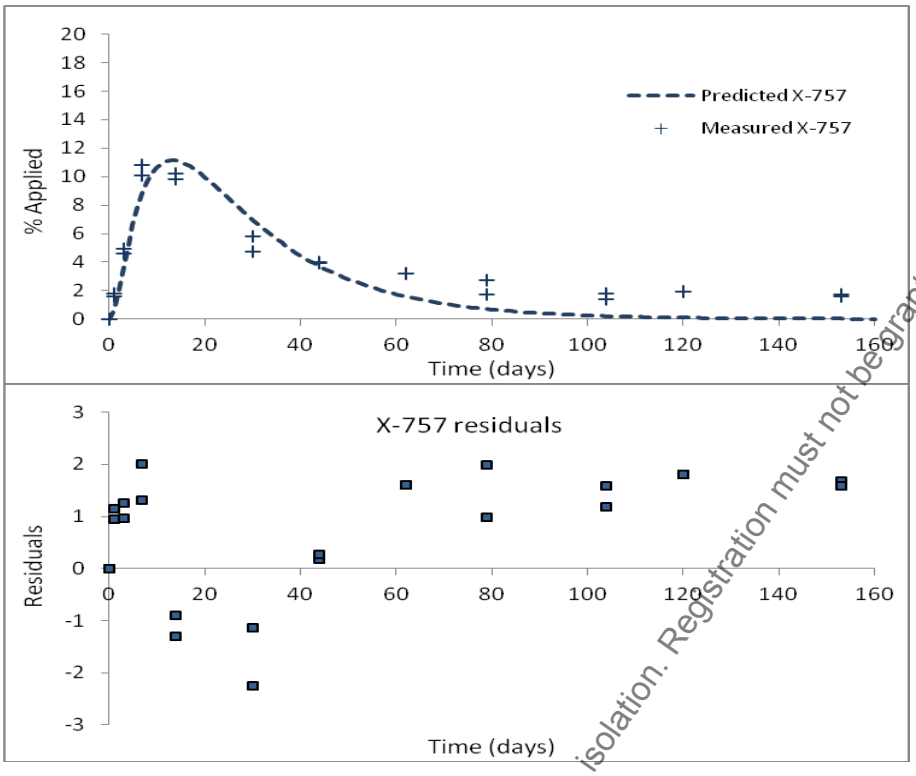
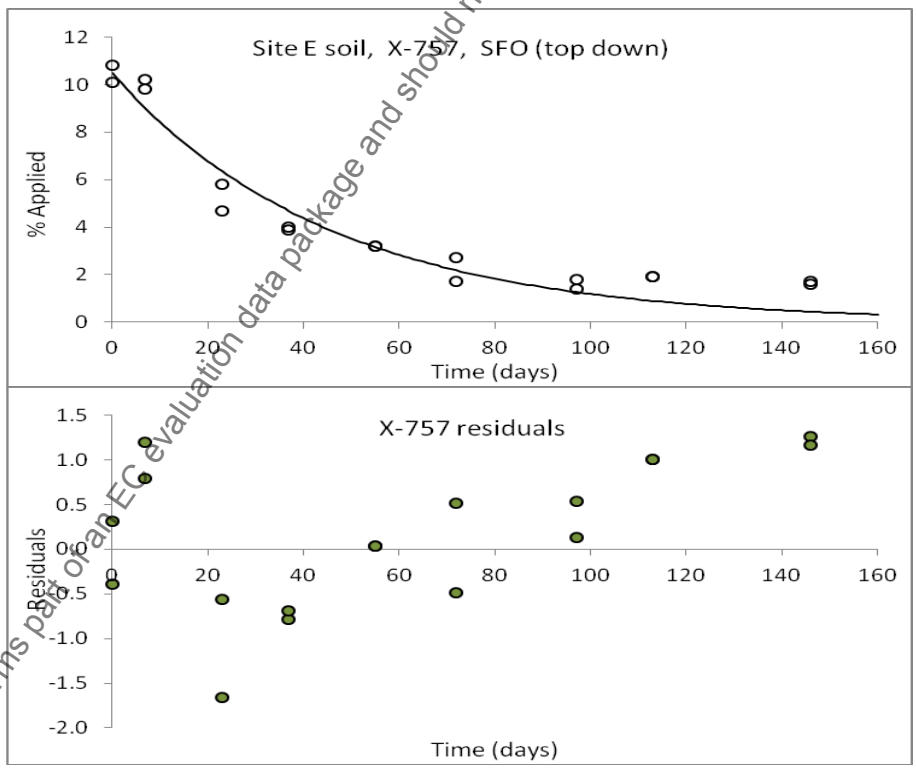


Figure B.8.17 Visual and residual kinetic fits for X11449757 in Site E aerobic soil using SFO 'top down' approach



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Table B.8.48 Statistical parameters for kinetic assessment of X11449757 in Site E aerobic soil

Substance	Parameter	Value	Lower CI	Upper CI	Std Dev	Prob > t	DT50 (d)	DT90 (d)	% χ2 error
Parent (SFO) + Acid (SFO) + X-757 (SFO)	M0 (%)	104.2	100.4	108.0	1.9	-			
	k (d-1)	0.5783	0.5260	0.6307	0.0262	1.8e-32	1.2	4.0	13.6
	ff	0.7794	0.6924	0.8663	0.0436	-			
	k (d-1)	0.1490	0.1243	0.1738	0.0124	1.4e-18	4.7	15.5	18.2
	ff	0.2374	0.1454	0.3294	0.0461	-			
	k (d-1)	0.0477	0.0218	0.0737	0.0130	2.4e-04	14.5	48.2	29.2
X-757 (SFO) (top down)	M0 (%)	10.5	9.5	11.5	0.5	-			
	k (d-1)	0.0218	0.0175	0.0260	0.0020	4.2e-09	31.8	106	13.8

ff = formation fraction

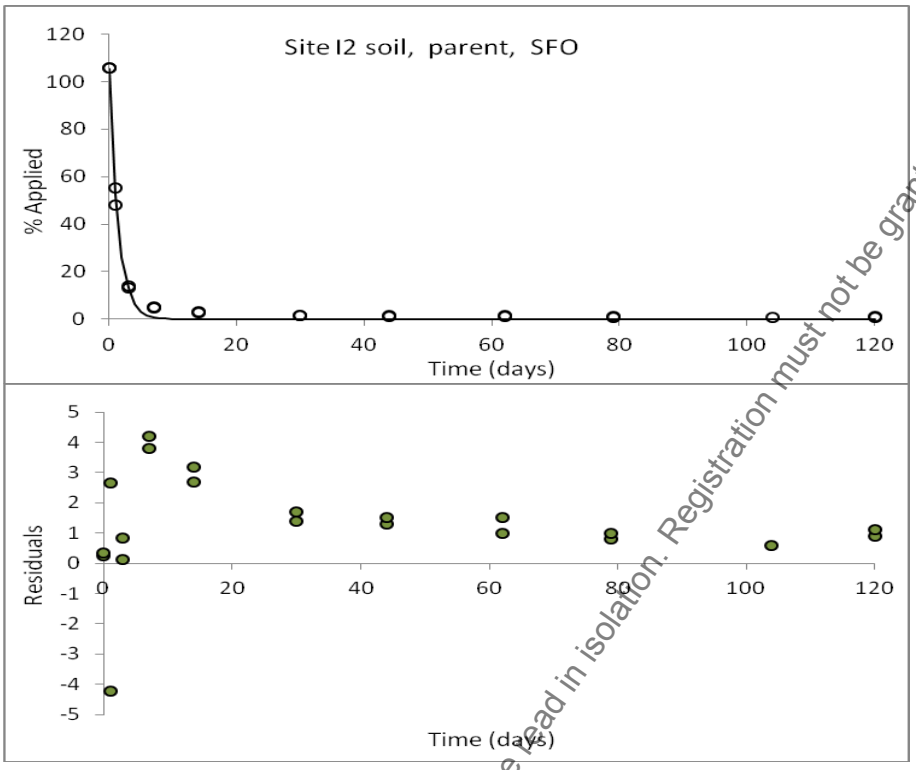
Site I2 soil

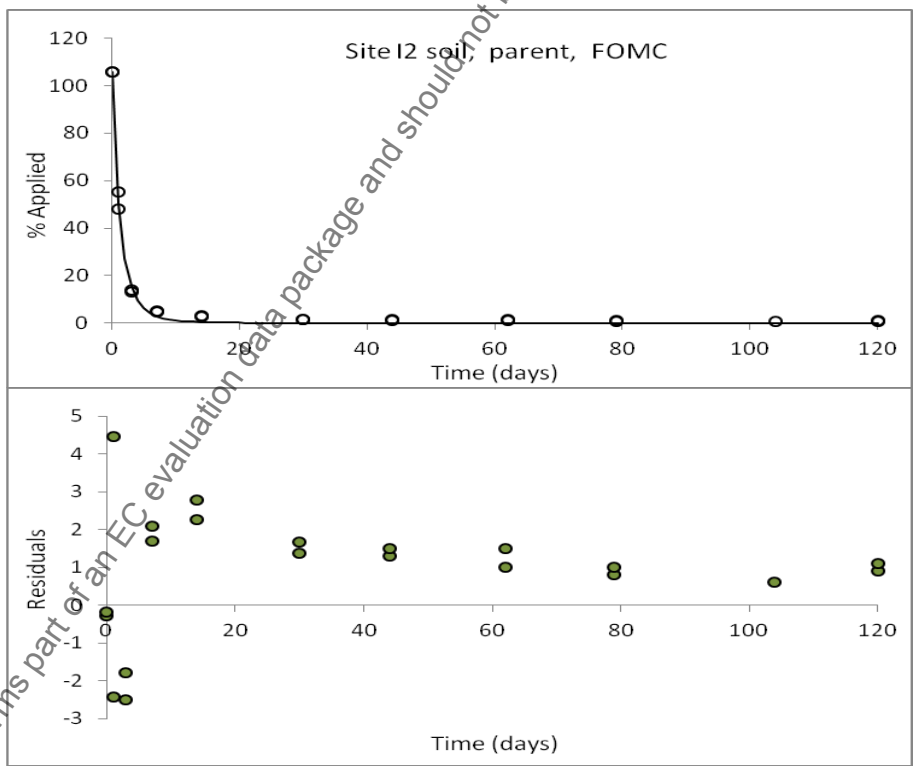
Site I2 soil – parent

The study author fitted the parent data for Site I2 soil to both SFO and FOMC. FOMC gave a marginally better fit visually, in terms of residual and for the χ^2 value. However, as the actual DT50 and DT90 values for SFO and FOMC were very similar, the study author proposed the SFO parameters for modelling. Given the χ^2 value of 8.0 for the SFO fit and the fact that from 30 DAT the parent residues were <2% AR, i.e. there is likely to be a significant influence of a long tail of low residues, the RMS considers this to be acceptable; the SFO modelling parameters of DT50 1.0 days is considered acceptable by the RMS. For the persistence endpoint for this soil, the RMS proposes to use the FOMC parameters, i.e. DT50 0.9 days, DT90 3.8 days.

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Figure B.8.18 Visual and residual kinetic fits for XDE-729 methyl in Site I2 aerobic soil





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Table B.8.49 Statistical parameters for kinetic assessment of XDE-729 methyl in Site I2 aerobic soil

Kinetics Model	Parameter	Value	Lower CI	Upper CI	Std Dev	Prob > t	DT50 (d)	DT90 (d)	%χ2 error
SFO	M0 (%) k (d-1)	105.4 0.6986	102.3 0.6439	108.6 0.7533	1.5 0.0261	- 7.6e-17	1.0	3.3	8.0
FOMC	M0 (%) alpha beta	106.0 4.2584 5.2799	103.0 1.0142 0.6124	108.9 7.5027 9.9473	1.4 1.5442 2.2216	- 0.0065 0.0144	0.9	3.8	7.0

Site I2 soil – X11393729

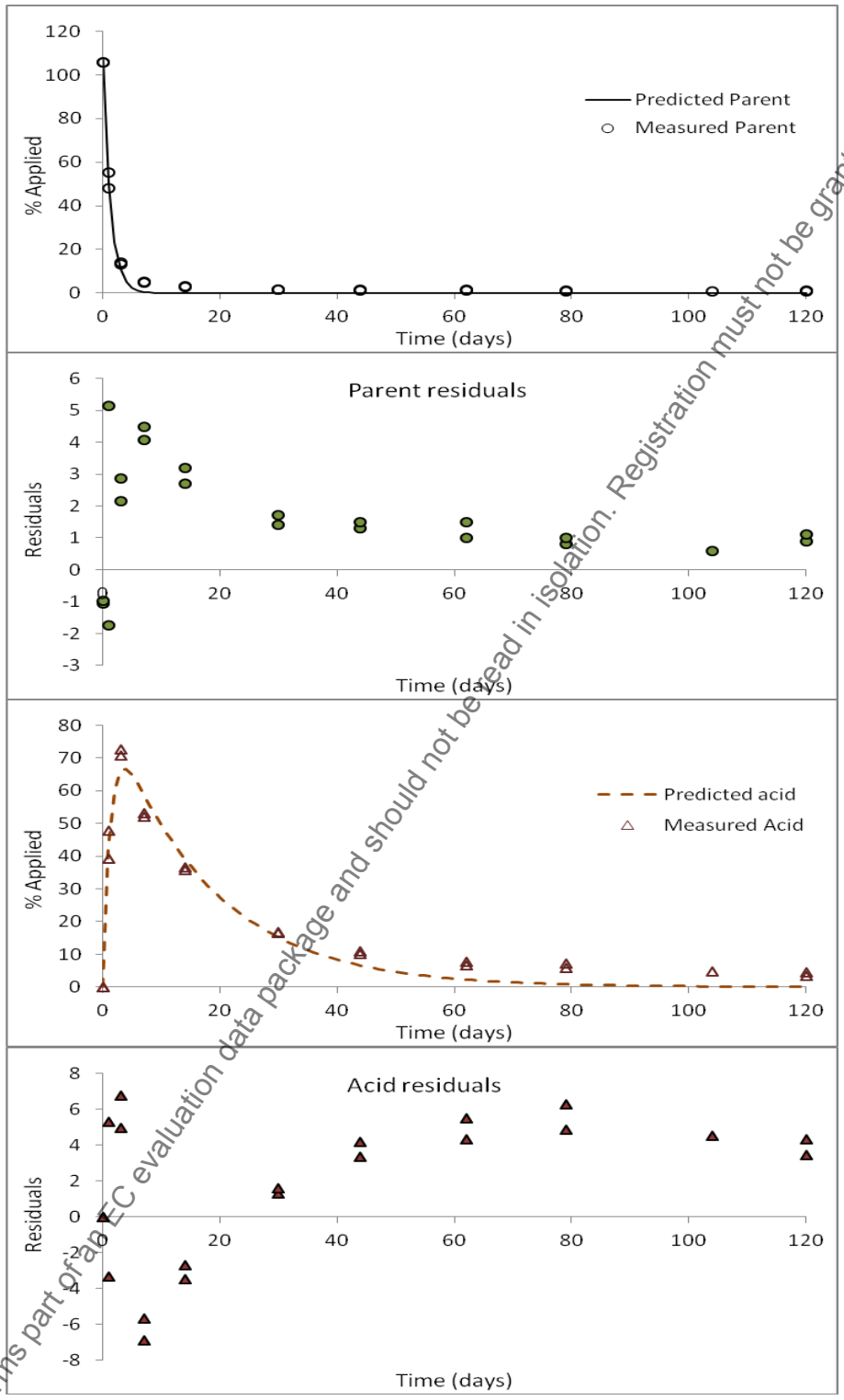
Given the selection of SFO as the kinetics of choice for modelling parameters, the study author fitted X11393729 in series with parent with SFO/SFO. Fitting with the metabolite in sequence resulted in a slightly reduced, but still acceptable, goodness of fit for the parent and with a slightly reduced DT50. The χ^2 value of 14.7 for the metabolite was considered to be acceptable. Thus the study author proposes a modelling endpoint for X11393729 in Site I2 soil of SFO DegT50 11.7 days with formation fraction of 0.7753. The RMS can accept these values.

The study author also conducted a top down approach for X11393729 using SFO kinetics. This is considered to be a reasonable fit given only slight under-estimation of the tail of concentrations towards study end. The RMS considers that the SFO DisT50 of 13.6 days can be accepted as the persistence endpoint for X11393729 in Site E soil.

Visual and residual fits and statistics are given below.

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Figure B.8.19 Visual and residual kinetic fits for SFO/SFO fit for XDE-729 methyl and X11393729 in Site I2 aerobic soil



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Figure B.8.20 Top down SFO fit for X11393729 in Site I2 aerobic soil

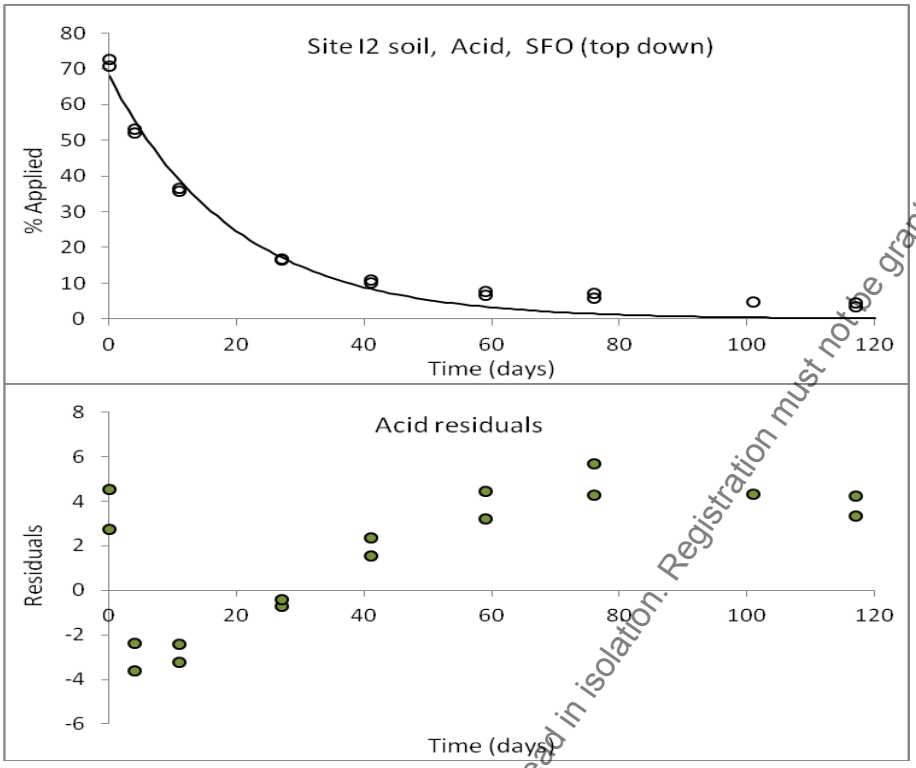


Table B.8.50 Statistical parameters for SFO kinetic assessment of X11393729 in Site I2 aerobic soil

Substance	Parameter	Value	Lower CI	Upper CI	Std Dev	Prob > t	DT50 (d)	DT90 (d)	% χ2 error
Parent (SFO) + Acid (SFO)	M0 (%)	106.8	101.6	111.9	2.5	-			
	k (d-1)	0.7595	0.6739	0.8451	0.0423	1.9e-20	0.9	3.0	9.3
	ff	0.7753	0.7019	0.8486	0.0362	-			
	k (d-1)	0.0592	0.0501	0.0683	0.0045	5.7e-16	11.7	38.9	14.7
Acid (SFO) (top down)	M0 (%)	68.2	63.7	72.7	2.1	-			
	k (d-1)	0.0509	0.0427	0.0592	0.0039	5.7e-10	13.6	45.2	11.3

ff = formation fraction

Site I2 soil - X11449757

As the maximum observed concentration of X11449757 in I2 soil was 3.1% at 3 DAT, the study author attempted to calculate kinetic parameters for this metabolite using the top down method.

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Figure B.8.21 Visual and residual kinetic fits for X11449757 in Site I2 aerobic soil using SFO 'top down' approach

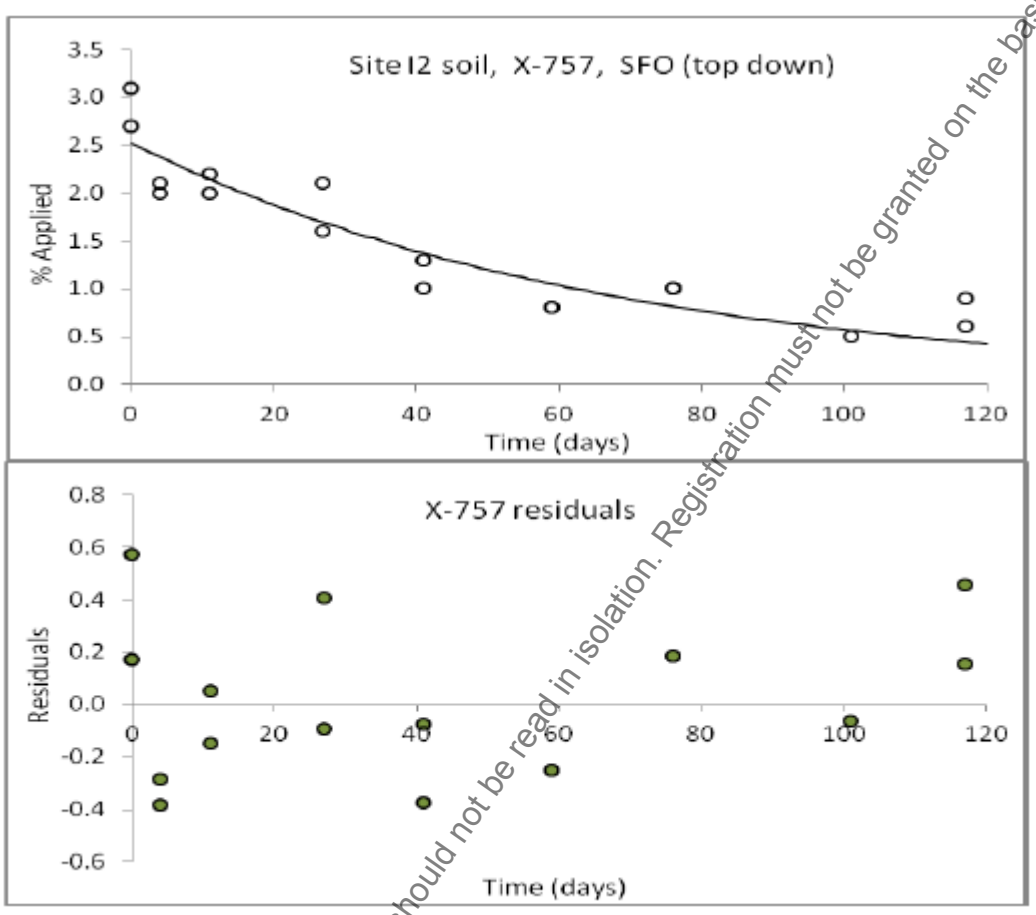


Table B.8.51 Statistical parameters for SFO kinetic assessment of X11393729 in Site I2 aerobic soil

Kinetics Model	Parameter	Value	Lower CI	Upper CI	Std Dev	Prob > t	DT50 (d)	DT90 (d)	% χ2 error
X-757 (SFO) (top down)	M0 (%) k (d^{-1})	2.53 0.0149	2.24 0.0107	2.82 0.0191	0.14 0.0020	- 8.5e-07	46.6	155	12.7

Summaries of optimised parameters for persistence and modelling endpoints are given below. As proposed above, the modelling endpoints for parent are taken from the SFO/SFO sequential fits to preserve the linkage between parent and metabolite parameters.

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Table B.8.52 Soil persistence endpoints for XDE-729 methyl and its soil metabolites (values in parentheses for RefSol 03-G soil are moisture corrected)

	XDE-729 methyl	**X11393729**	**X11449757**
Yolo			
Kinetics	FOMC	Top down SFO	Top down SFO
DT50	1.8 d	35.9 d	76.7 d
DT90	16.3 d	119 d	255 d
χ^2	3.3	6.0	5.2
RefSol 03-G			
Kinetics	SFO	Top down SFO	Top down SFO
DT50	1.3 d (1.1 d)	3.3 d (2.7 d)	25.1 d (20.4 d)
DT90	4.5 d (3.7 d)	11 d (9.0 d)	84 d (68.4 d)
χ^2	8.4	20.1	17.0
Site E			
Kinetics	FOMC	Top down SFO	Top down SFO
DT50	1.1 d	7.6 d	31.8 d
DT90	6.1 d	25.4 d	106 d
χ^2	4.4	13.1	13.8
Site I2			
Kinetics	FOMC	Top down SFO	Top down SFO
DT50	0.9 d	13.6 d	46.6 d
DT90	3.8 d	45.2 d	155 d
χ^2	7.0	11.3	12.7
Worst case			
DT50	1.8 d	35.9 d	76.7 d
DT90	16.3 d	119 d	255 d

The RMS notes that XDE-729 methyl DT50 or DT90 values do not trigger field dissipation studies.

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Table B.8.53 Soil modelling endpoints for XDE-729 methyl and its soil metabolites (values in parentheses for RefSol 03-G soil are moisture corrected)

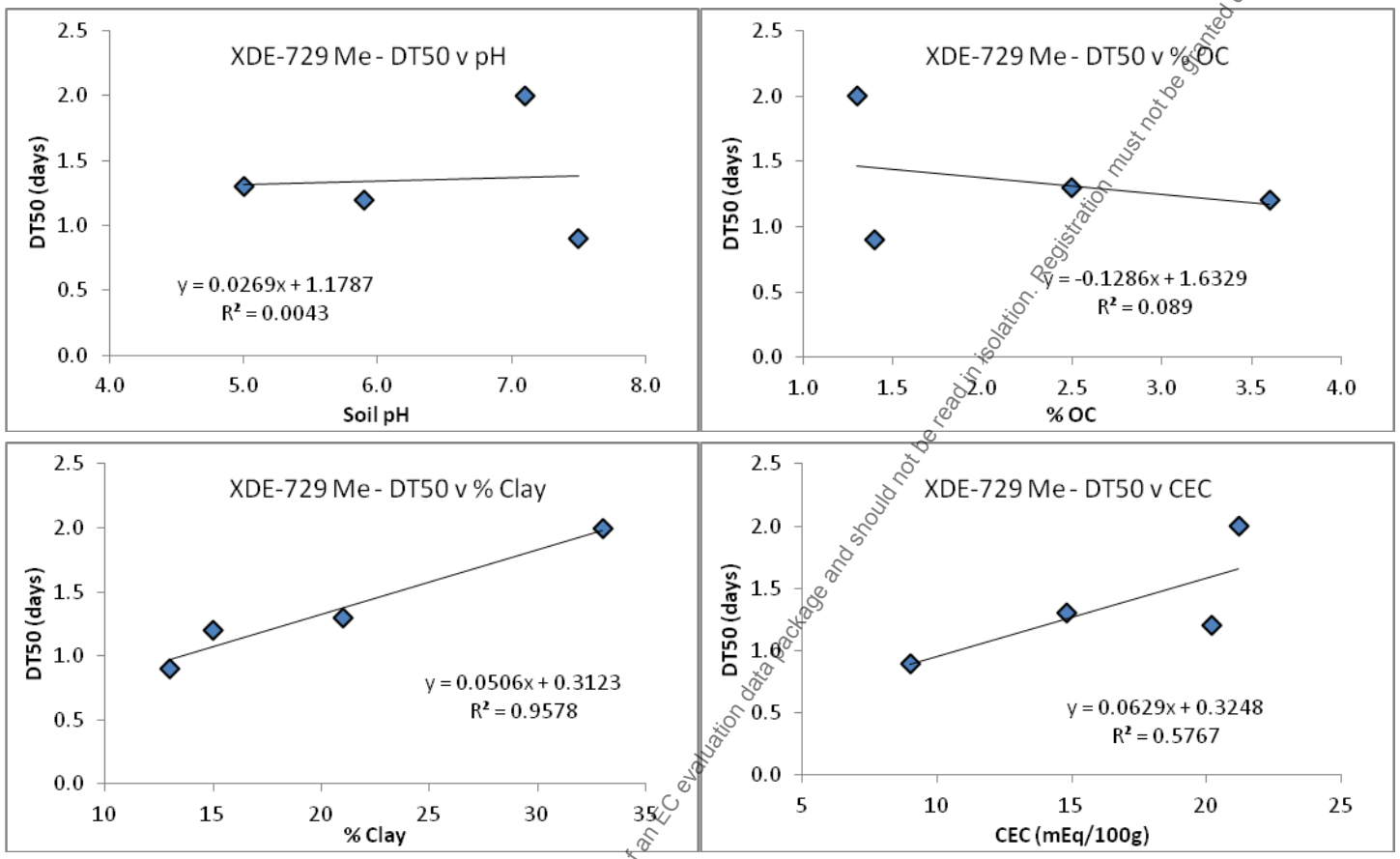
	XDE-729 methyl	**X11393729**	**X11449757**
Yolo			
Kinetics	SFO	SFO (in series)	Top down SFO
DT50	2.0 d	28.7 d	76.7
DT90	6.7 d	95 d	255
Formation fraction	-	0.6372	1**
χ^2	18.3	16.4	5.2
RefSol 03-G			
Kinetics	SFO	SFO (in series)	Top down SFO
DT50	1.3 d (1.1 d)	2.0 d (1.6 d)	25.1 (20.4 d)
DT90	4.5 d (3.7 d)	6.8 d (5.5 d)	84 (68.4 d)
Formation fraction	-	0.8548	1**
χ^2	6.0	14.4	17.0
Site E			
Kinetics	SFO	SFO (in series)	Top down SFO
DT50	1.2 d	4.7 d	31.8
DT90	4.0 d	15.8 d	106
Formation fraction	-	0.7733	1**
χ^2	10.9	14.4	13.8
Site I2			
Kinetics	SFO	SFO (in series)	Top down SFO
DT50	0.9 d	11.7 d	46.6
DT90	3.0 d	38.9 d	155
Formation fraction	-	0.7753	1**
χ^2	9.3	14.7	12.7
Geometric mean			
DT50 (rate constant, d^{-1})	1.3 d (0.5290)	7.5 d (0.0917)	41.1 d (0.0169)
Formation fraction*	-	0.7602	1**

*Arithmetic mean **Worst case assumption using top down DT50 values

Following discussions between the RMS and the Applicant, the Applicant undertook investigations into the possibility of pH dependence of degradation of XDE-729 methyl and the main soil metabolites. This investigation took the form of plotting persistence and modelling DT50 values against physical/chemical properties of pH, % organic carbon, % clay content, cation exchange capacity (CEC) and total soil biomass in order to determine whether significant correlations existed. These correlation plots are shown below.

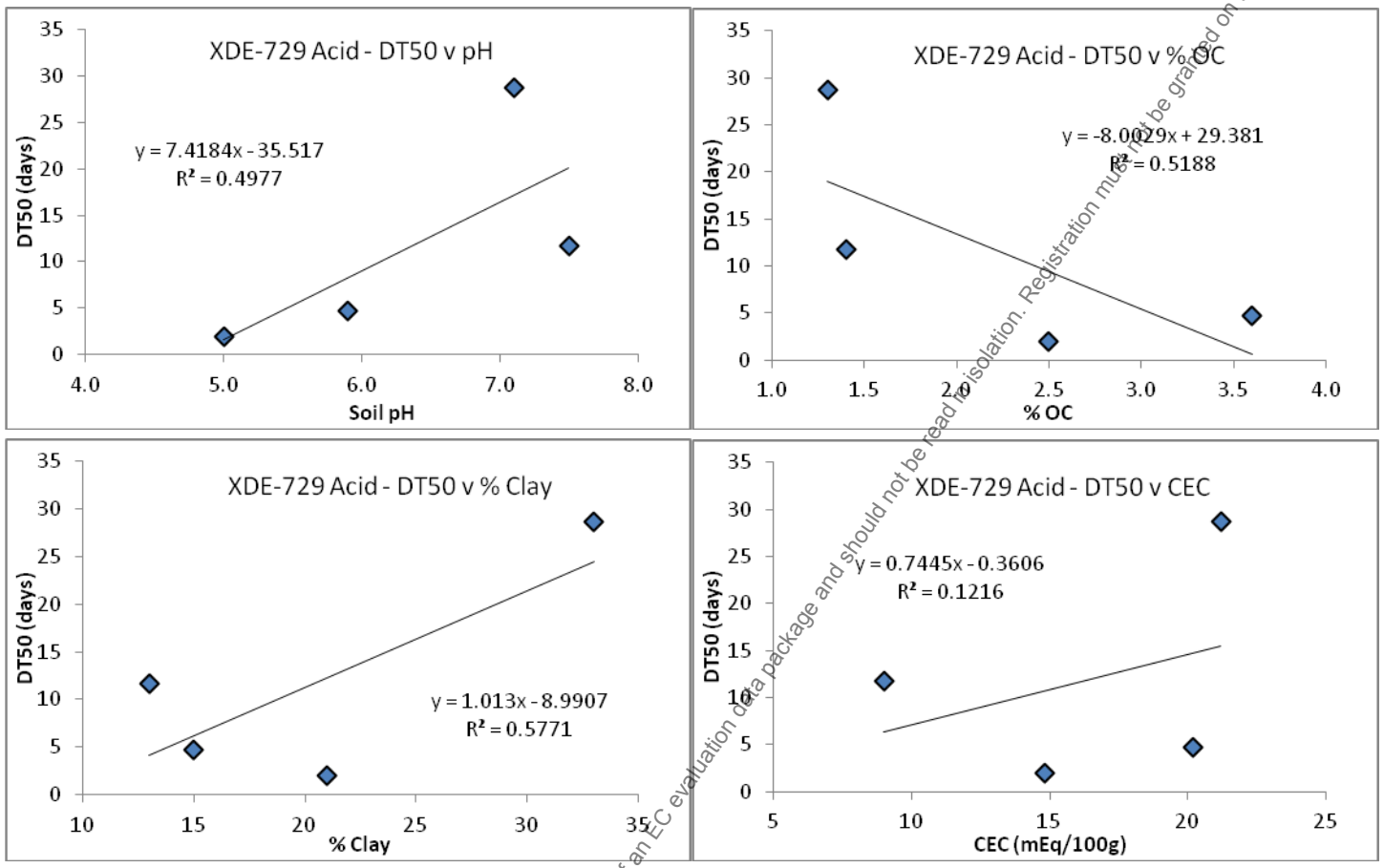
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Figure B.8.22 Correlation of XDE-729 methyl modelling DT50 with soil properties



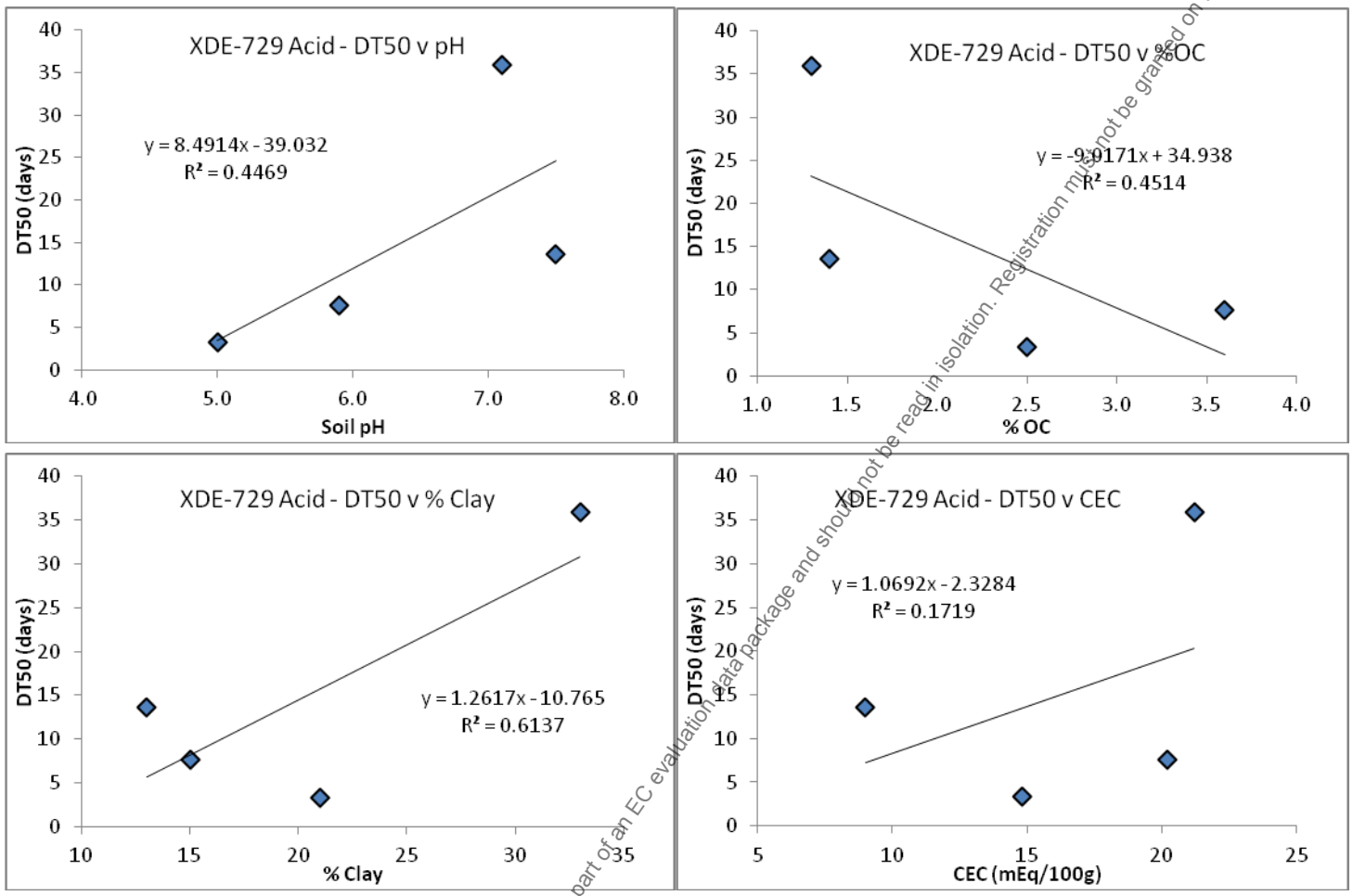
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Figure B.8.23 Correlation of X11393729 modelling DT50 with soil properties



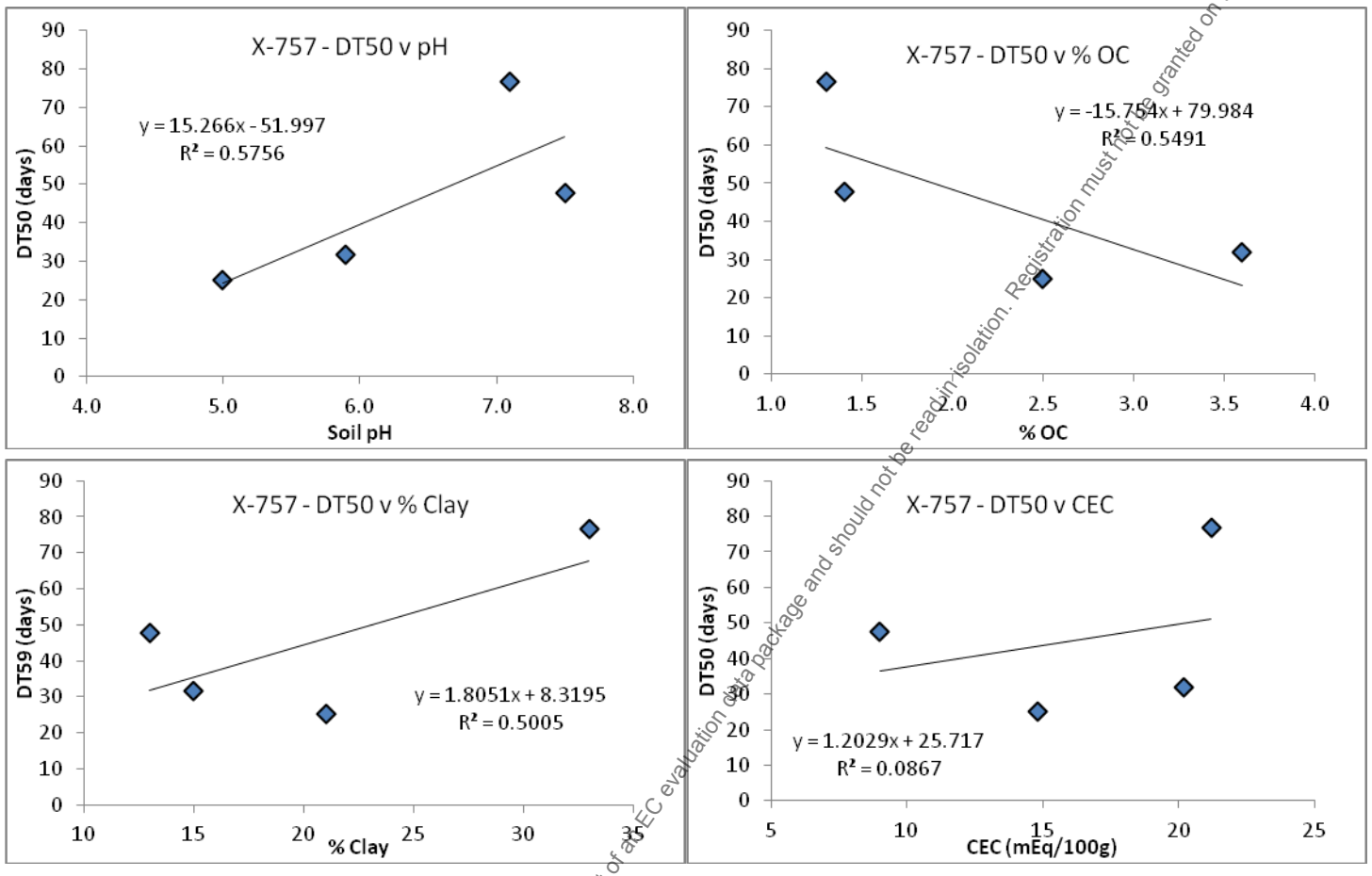
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Figure B.8.24 Correlation of X11393729 (XDE-729 Acid) persistence DT50 with soil properties



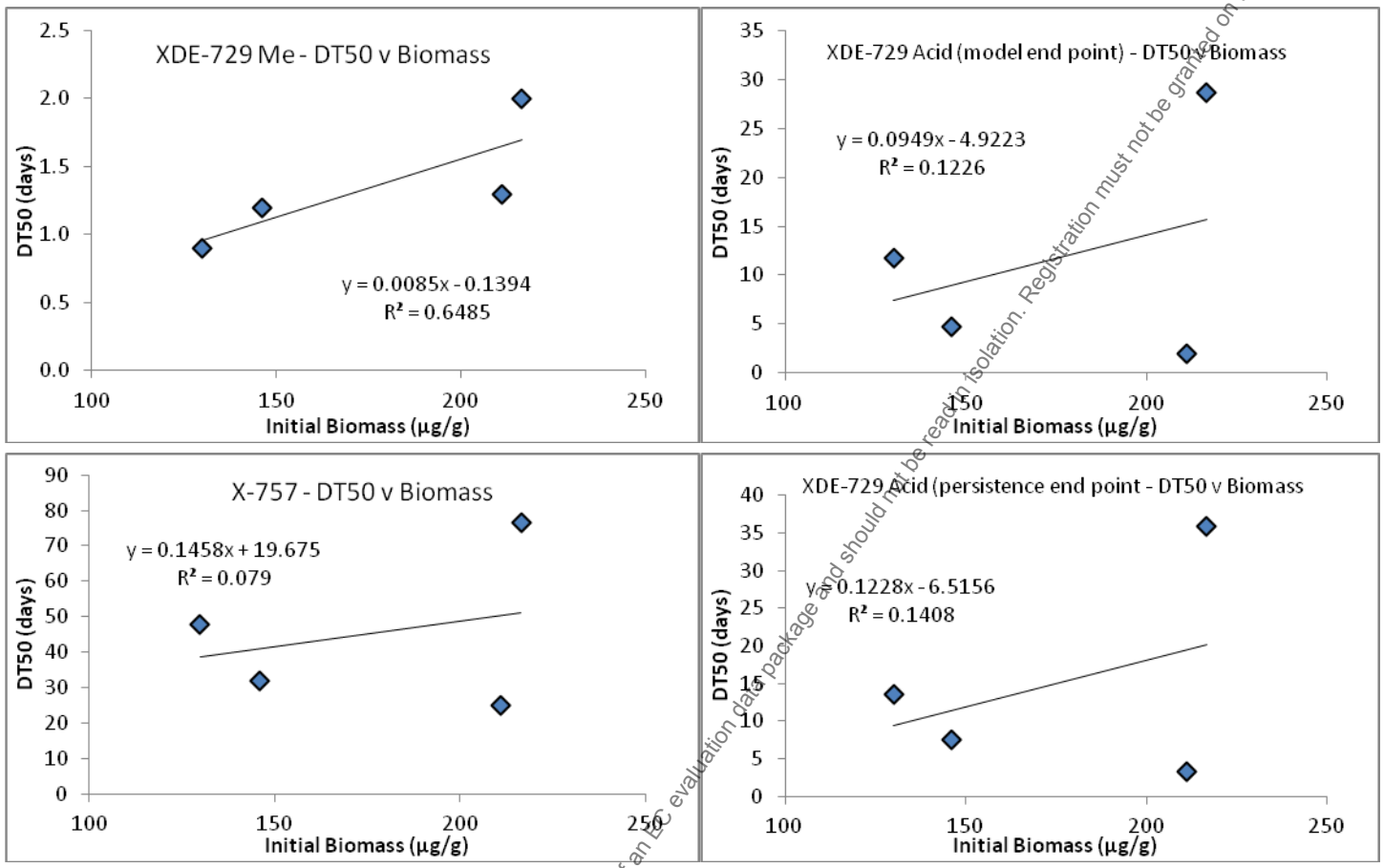
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Figure B.8.25 Correlation of X11449757 (X-757) modelling/persistence DT50 with soil properties



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Figure B.8.26 Correlation of XDE-729 methyl and metabolites DT50 with soil biomass



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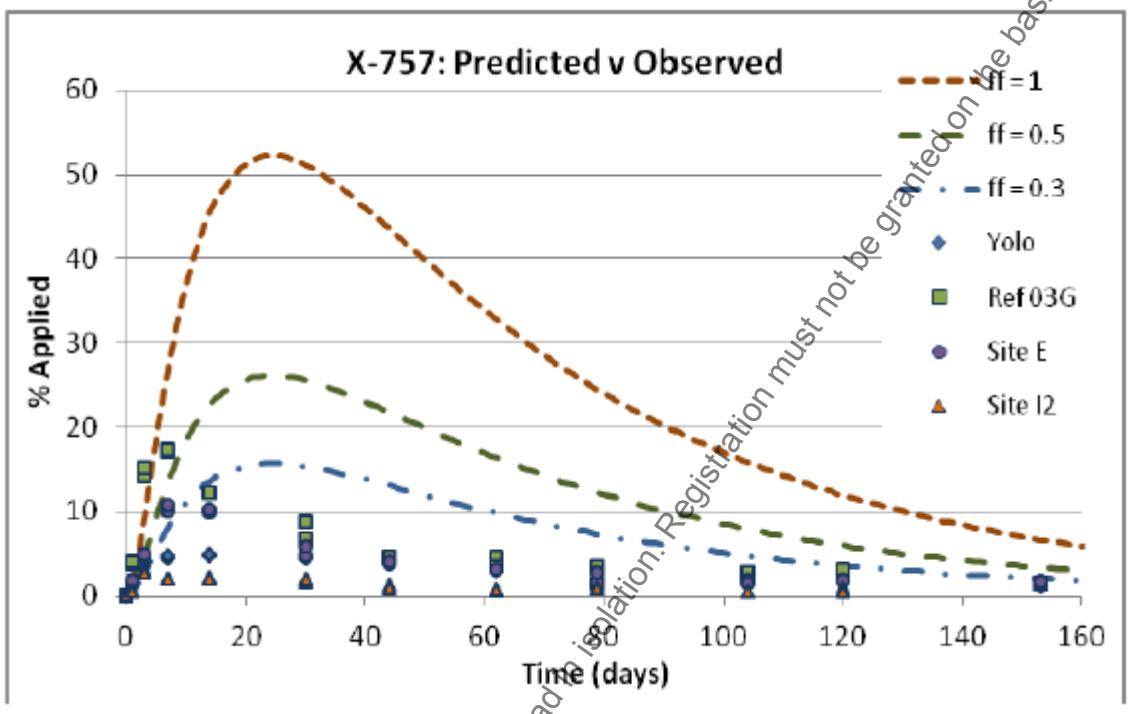
The Applicant considered that for each of the substances, there was only limited evidence for a strong correlation of degradation with any of the examined soil properties. The RMS also notes that there is also a tendency for higher organic carbon on more acidic soils. Certainly for the parent substance, the RMS considers that there appears to be a better correlation between degradation rate and % clay or CEC than there is for pH. The RMS also notes that the pKa of the parent is 2.84 which suggests that at environmental pH, the substance is unlikely to undergo any change in extent of dissociation; however, the Applicant recognises that degradation in relation to pH is likely to be far more complex than extent of dissociation. The Applicant considered that this may be explained by higher clay content or CEC leading to relatively higher adsorption in soil which could have the effect of increasing DT50 value due to relatively lower bioavailability. The RMS considers that this is a plausible explanation. However, given the overall rapid degradation of the parent across the four soils tested, it seems unlikely that taking into account any relationship will impact on the exposure assessment.

For both X11393729 and X11449757, the correlation between DT50 and pH appears to be more convincing, although it is clear that the results from the Yolo soil with the longest DT50 have a strong effect on the slope of the best fit line through the DT50/soil pH data. The evidence for an effect of other soil properties, particularly clay content and CEC, is less convincing. It is noted that the longest DT50 for both metabolites occurs in the Yolo soil which has the highest clay content and CEC value, but it is only the Yolo soil results which give any semblance of a positive correlation between DT50 and clay content or CEC for these metabolites. However, it is noted that the Yolo soil also has the lowest organic carbon content. Given that both X11393729 and X11449757 are weak acids, (pKa for X11393729 is 5.1; X11449757 has two separate pKa values, 5.6 for the carboxylic acid group and 7.1 for the phenolic functional group), this would suggest that there could well be differences in extent of dissociation in the environmental range of pH which could theoretically influence speed of degradation. However, the RMS also notes the trend for increased organic carbon at acidic pH which may influence any apparent pH/degradation relationships. Whilst the RMS considers that pH dependence of degradation could be potentially much more complex than simply being related to dissociation or solubility, the RMS considers that on the basis of the results of the laboratory studies in isolation, it is prudent to include pH dependent degradation in the environmental exposure assessment. Note that further information on potential pH dependence is presented in section B.8.1.5 b) in relation to field studies.

Given the calculation of top-down SFO DT50 for the X11449757 metabolite, the study author was concerned that attributing a worst-case formation fraction of 1 for formation from X11393729 would lead to over-estimation of X11449757 in the exposure assessment. For this reason, the study author conducted an exercise plotting the predicted residues using the mean optimised parameters above against the observed residue profiles of XDE-729 methyl, X11393729 and X11449757. For X11449757, assumed formation fraction from X11393729 was varied with values of 1, 0.5 and 0.3. Given that the kinetic parameters for XDE-729 methyl and X11393729 used were the geometric means (arithmetic mean in the case of formation fraction for the route from parent to X11393729), the plots for simulated residue profile of X11449757 have only been shown.

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Figure B.8.27 Simulated residue profiles for X11449757 assuming formation fractions of 0.3, 0.5 and 1.0 from X11393729



It is noted that a formation fraction of 1.0 clearly over-predicts the residues in all four soils. A formation fraction of 0.5 also over-predicts residues but gives a delay in the time to the maximum formation. The formation fraction of 0.3 over-predicts residues in all four soils from 14 DAT onwards, and over predicts concentrations in two of the soils at 7 DAT. The simulated peak formation is also delayed in time compared to the actual results, although the peak simulated is only slightly lower than the highest observed. This may be the result of a slower decline rate being calculated using the 'top-down' method compared to a true degradation-only rate. The study author proposes using a formation fraction of 0.3 for X11449757 formed from X11393729. The RMS can accept this as overall, the simulated formation over-predicts the majority of the X11449757 profile in all four soils. Given that X11449757 would be the terminal metabolite in exposure modelling, the over-estimation is considered by the RMS to be acceptable. It should be noted that as the formation fraction from X11393729 to X11449757 in exposure modelling is assumed to be 0.3, exposure models such as FOCUS_PELMO would need to specify a degradation pathway from X11393729 to CO_2/unextracted residues described by the X11393729 rate constant multiplied by the formation fraction of 0.7.

The RMS notes that in practice, the results from field dissipation studies are used to derive endpoints for exposure modelling for groundwater and surface water.

(Yoder *et al* 2011a; Jackson 2012)

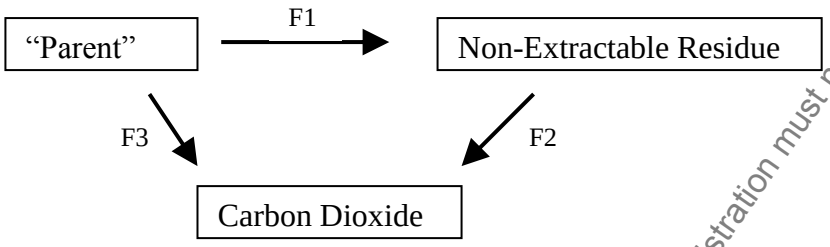
b) Given the high levels of unextracted residue seen in the laboratory dark aerobic soil degradation study, the Applicant undertook a modelling exercise to determine the kinetics of the formation of unextracted residue in order to predict long term accumulation of this residue. The purpose of this was to allow a risk assessment of the

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potential impact of the unextracted residue. As a modelling exercise, the study was not subject to GLP requirements.

In this modelling exercise, a three compartment model was established in KinGUI v 1.1. This is shown below.

Figure B.8.28 Three compartment model for simulation of kinetics of XDE-729 methyl related unextracted residue



The 'parent' in the initial compartment comprised the total extractable radiolabelled residue from the laboratory soil degradation studies. Data from each radiolabelled position and for the four different soils were treated as separate data sets. The model was initially run using 'parent' data only going to a single 'sink' compartment. Following this, the non-extractable residues data were added as a third compartment and the model re-run with the previously optimised parameters for parent as starting values. The modelling was run using both SFO and FOMC kinetics for parent with SFO kinetics for the non-extractable residue compartment. The study author applied the following principles to decide on the best-fit kinetics.

1. If the standard deviation for any parameter was greater than the optimised value, or the lower confidence interval was less than zero, then the model fit was rejected.
2. The residual plot was examined for systematic deviations of predicted values from measured values and, ideally, a random distribution of residuals around zero was looked for.
3. A χ^2 error value of 15% or less was selected as an acceptable fit for the parent and NER as recommended by FOCUS guidance (although higher error can be accepted with justification).
4. Visual assessment of data sets for outliers was conducted if necessary and models were re-run after removal of outliers (with justification).

Following this stage of modelling with KinGUI, the model was rebuilt in ModelMaker to run the optimised parameters for a period of 400 days to simulate formation and decline profiles. This predictive modelling was then further extended to run for a period of 100 years. The output of this long-term simulation in ModelMaker was then used to calculate accumulation of unextracted residue following annual applications of XDE-729 methyl. Microsoft Excel was used to predict accumulation of unextracted residue following multiple applications.

In general, the SFO modelling using KinGUI tended to under-estimate 'parent' concentrations towards the end of the study, i.e. the fitted curve fell below the

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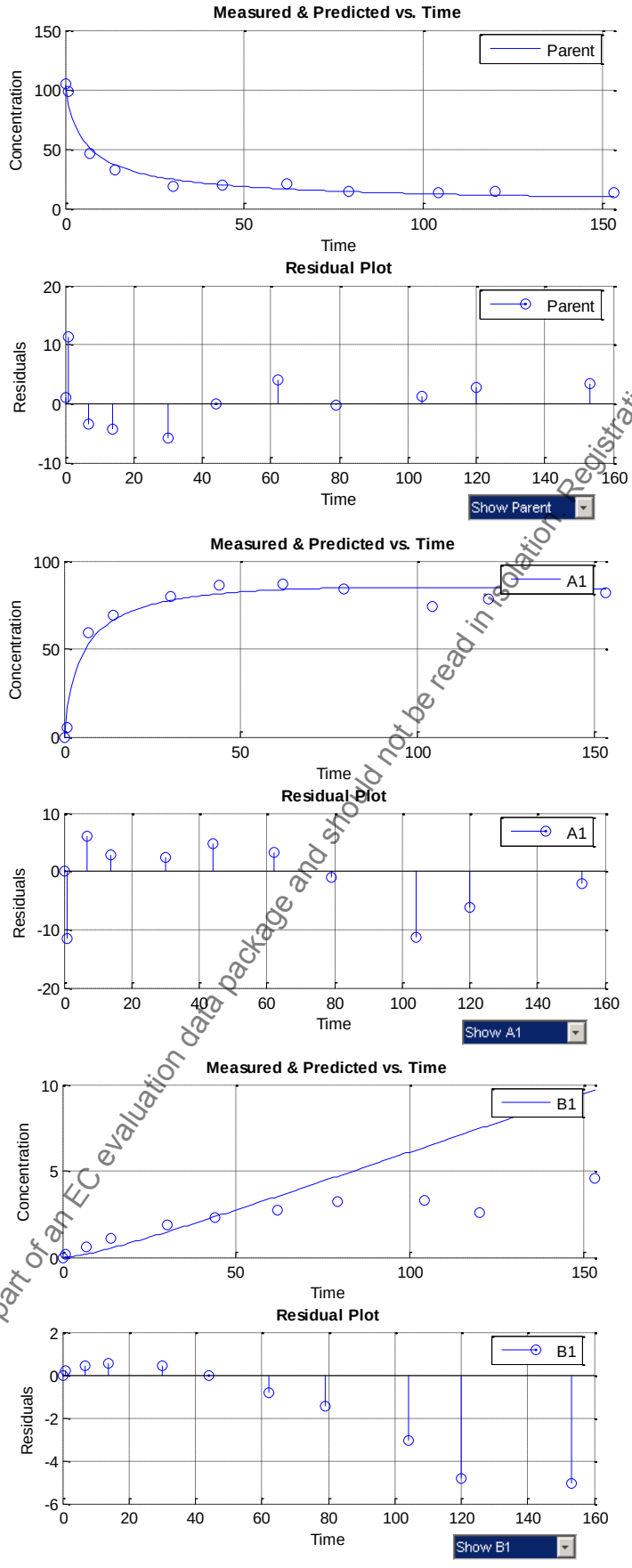
observed data points. FOMC always gave a much better fit to the 'parent' data. In addition, subsequent fitting of the unextracted residue using SFO kinetics was improved when FOMC kinetics were used for the 'parent'.

Given than 16 sets of sequential fitting were attempted for 'parent' and unextracted residue, the graphical output of the incubation that gave the longest unextracted residue DT50 has been reproduced below, followed by the details of statistics, rate constants etc from all soils.

It was noted that fitting of CO_2 was often relatively poor, although the example below appears to be the worst.

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Figure B.8.29 Visual and residual fits for 'parent', unextracted residue (denoted by A1) and CO_2 (denoted by B1), FOMC/SFO, RefSol 03-G soil, PY label



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Table B.8.54 Optimised Kinetic Parameters for Yolo Soil (standard deviations in parentheses)

Model	Parameter	PH label	PY Label
SFO/SFO	% χ^2 err (parent):	12.6	11.4
	% χ^2 err (NER):	10.6	14.6
	k_parent (days^{-1}):	0.0233 (0.0015)	0.0225 (0.0016)
	k_NER (days^{-1}):	0.0031 (8.9e-04)	0.0018 (9.2e-04)*
	Formation fraction:	0.9575 (0.0588)	1.0000 (0.0654)
	M_0 (%):	93.97 (2.24)	99.30 (2.77)
	DT50_parent (days):	29.8	30.8
	DT50_NER (days):	225	377
FOMC/SFO	% χ^2 err (parent):	6.4	5.7
	% χ^2 err (NER):	5.1	8.2
	alpha:	1.0152 (0.1280)	0.8812 (0.1287)
	beta:	23.36 (4.826)	20.00 (4.91)
	k_NER (days^{-1}):	0.0020 (4.0e-04)	8.9e-04 (4.4e-04)*
	Formation fraction:	0.9048 (0.0268)	0.9550 (0.0319)
	M_0 (%):	98.97 (1.28)	104.5 (1.63)
	DT50_parent (days):	22.9	23.9
	DT50_NER (days):	**345**	780

* lower confidence interval less than zero

Table B.8.55 Optimised Kinetic Parameters for RefSol 03-G Soil (standard deviations in parentheses)

Model	Parameter	PH label	PY Label
SFO/SFO	% χ^2 err (parent):	22.7	29.4
	% χ^2 err (NER):	16.1	9.2
	k_parent (days^{-1}):	0.0736 (0.0123)	0.0868 (0.0123)
	k_NER (days^{-1}):	0.0017 (8.9e-04)*	9.3e-04 (6.9e-04)*
	Formation fraction:	0.8632 (0.0611)	0.9996 (0.0582)
	M_0 (%):	91.56 (3.52)	93.83 (3.83)
	DT50_parent (days):	9.4	8.0
	DT50_NER (days):	408	742
FOMC/SFO	% χ^2 err (parent):	10.8	10.7
	% χ^2 err (NER):	11.4	7.8
	alpha:	0.7554 (0.1195)	0.6002 (0.0797)
	beta:	5.373 (1.674)	2.9857 (0.9273)
	k_NER (days^{-1}):	0.0019 (8.7e-04)	8.0e-04 (3.8e-04)
	Formation fraction:	0.8880 (0.0391)	1.0000 (0.0322)
	M_0 (%):	99.46 (2.48)	103.5 (2.32)
	DT50_parent (days):	8.1	6.5
	DT50_NER (days):	**361**	**870**

* lower confidence interval less than zero

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Table B.8.56 Optimised Kinetic Parameters for Site E Soil (standard deviations in parentheses)

Model	Parameter	PH label	PY Label
SFO/SFO	% χ^2 err (parent):	16.6	16.9
	% χ^2 err (NER):	8.8	9.8
	k_parent ($days^{-1}$):	0.0687 (0.0057)	0.0604 (0.0056)
	k_NER ($days^{-1}$):	0.0020 (5.4e-04)	0.0011 (7.5e-04)*
	Formation fraction:	0.8880 (0.0370)	0.9618 (0.0493)
	M_0 (%):	94.04 (2.25)	93.73 (2.65)
	DT50_parent (days):	10.1	11.5
	DT50_NER (days):	343	658
FOMC/SFO	% χ^2 err (parent):	9.5	6.9
	% χ^2 err (NER):	6.5	6.0
	alpha:	1.1301 (0.1702)	0.9863 (0.1181)
	beta:	10.591 (2.5699)	9.4141 (1.9002)
	k_NER ($days^{-1}$):	0.0021 (3.7e-04)	8.1e-04 (3.7e-04)
	Formation fraction:	0.9006 (0.0253)	0.9590 (0.0243)
	M_0 (%):	99.06 (1.70)	99.81 (1.50)
	DT50_parent (days):	9.0	9.6
	DT50_NER (days):	**327**	**855**

* lower confidence interval less than zero

Table B.8.57 Optimised Kinetic Parameters for Site I2 Soil (standard deviations in parentheses)

Model	Parameter	PH label	PY Label
SFO/SFO	% χ^2 err (parent):	11.5	13.8
	% χ^2 err (NER):	10.2	13.3
	k_parent ($days^{-1}$):	0.0473 (0.0032)	0.0396 (0.0032)
	k_NER ($days^{-1}$):	0.0035 (9.9e-04)	0.0023 (0.0011)
	Formation fraction:	0.7699 (0.0405)	0.8044 (0.0528)
	M_0 (%):	95.89 (2.11)	93.75 (2.50)
	DT50_parent (days):	14.7	17.5
	DT50_NER (days):	197	297
FOMC/SFO	% χ^2 err (parent):	7.4	8.4
	% χ^2 err (NER):	9.3	9.4
	alpha:	1.6208 (0.3788)	1.1976 (0.2415)
	beta:	23.84 (7.831)	18.01 (5.694)
	k_NER ($days^{-1}$):	0.0033 (7.3e-04)	0.0019 (7.1e-04)
	Formation fraction:	0.7670 (0.0302)	0.7930 (0.0351)
	M_0 (%):	99.44 (1.80)	98.58 (1.98)
	DT50_parent (days):	12.7	14.1
	DT50_NER (days):	**209**	**362**

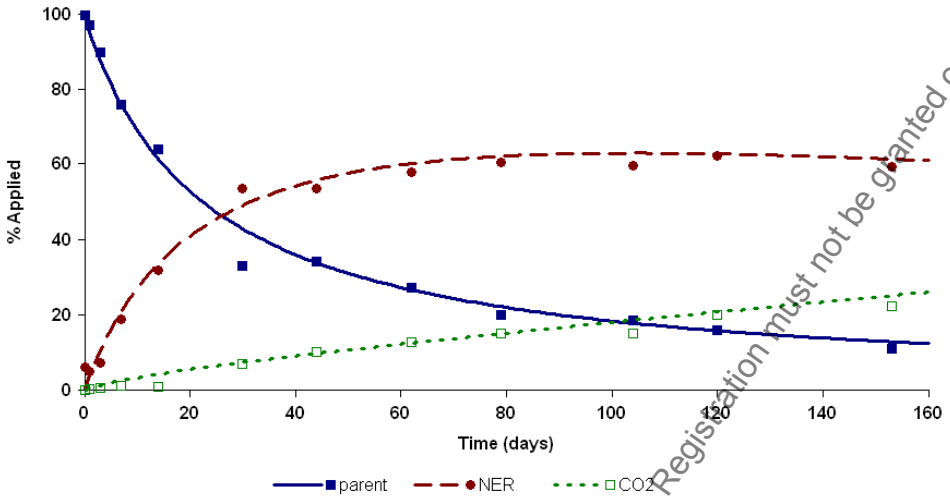
* lower confidence interval less than zero

Graphical representations of modelling over the study period, extrapolation to 400 days and prediction of accumulation over a 20 year period with annual application are presented below.

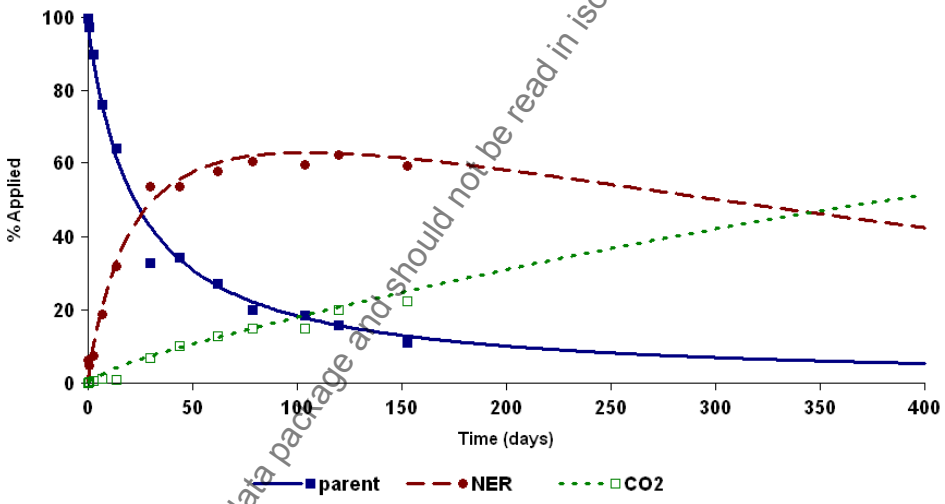
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Figure B.8.30 Prediction of unextracted residue and its accumulation in Yolo Soil (PH Label, FOMC/SFO Model)

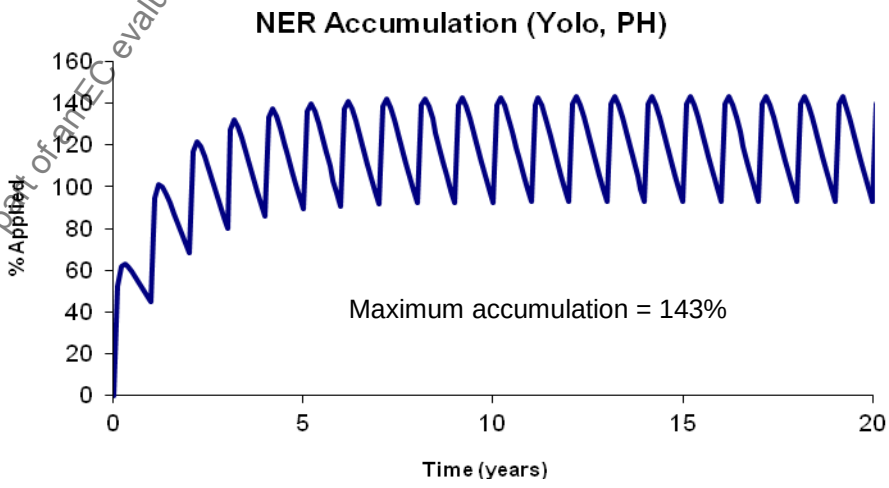
Measured and predicted vs time (for study duration)



Measured and predicted vs time (extrapolated to 400 days)



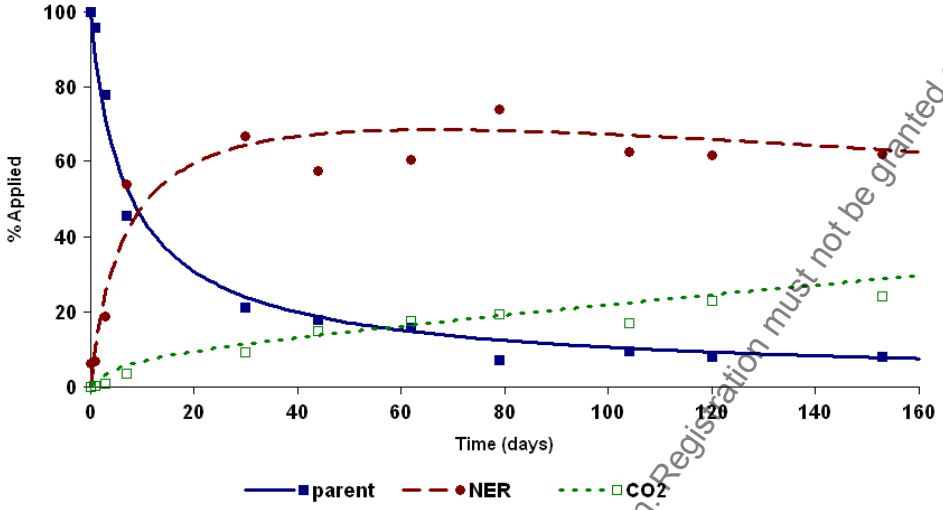
20 Year Accumulation



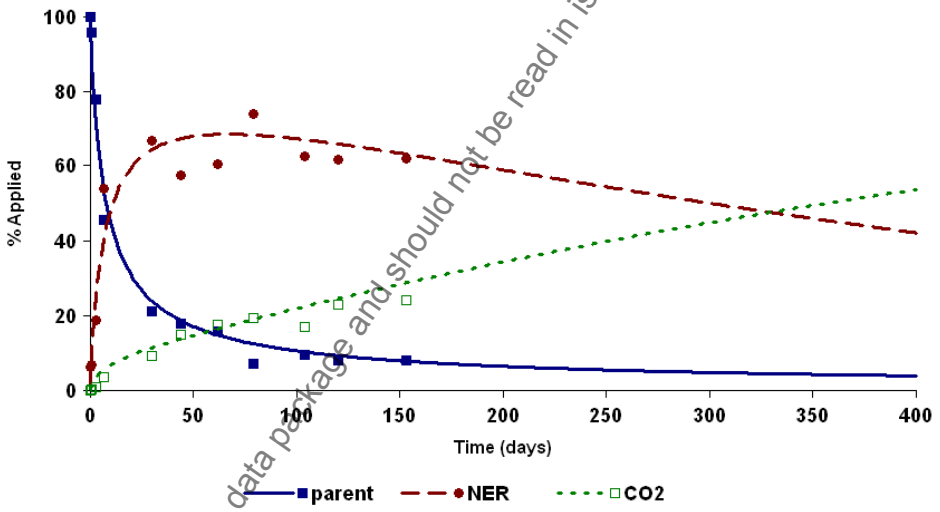
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Figure B.8.31 Prediction of unextracted residue and its accumulation in RefSol 03-G Soil (PH Label, FOMC/SFO Model)

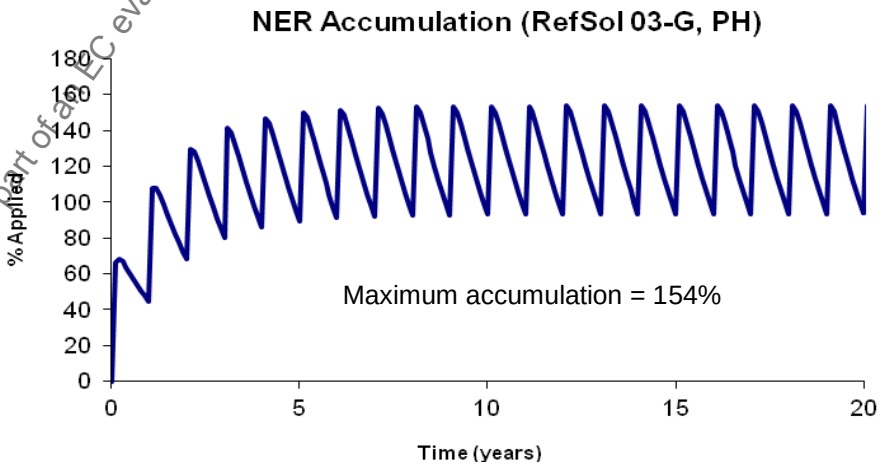
Measured and predicted vs time (for study duration)



Measured and predicted vs time (extrapolated to 400 days)



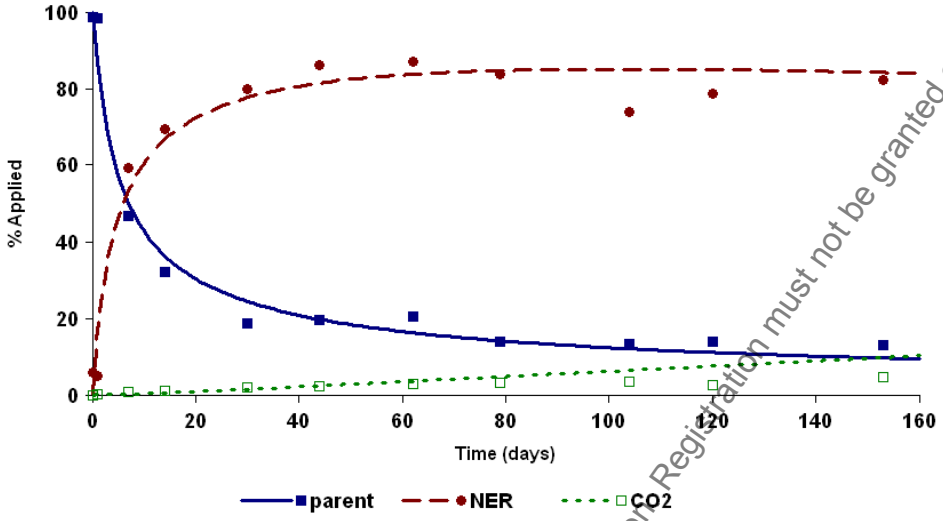
20 Year Accumulation



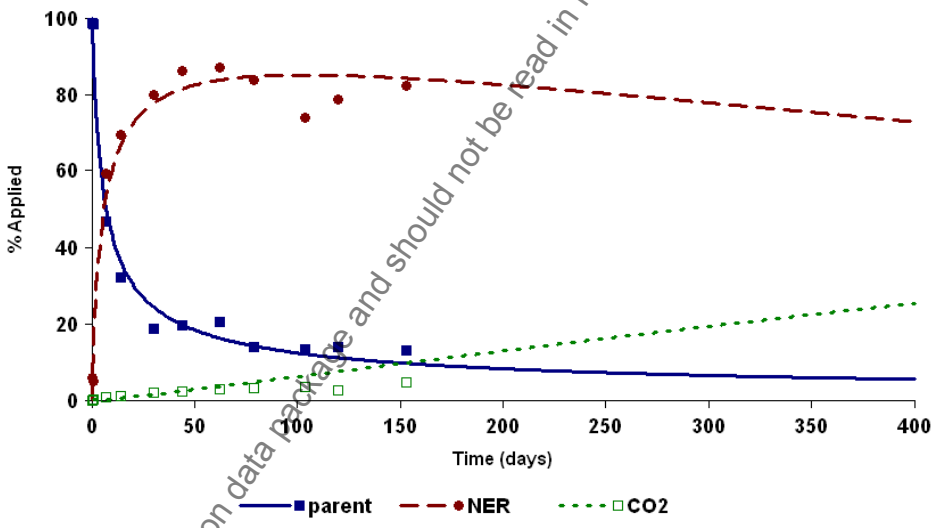
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Figure B.8.32 Prediction of unextracted residue and its accumulation in RefSol 03-G Soil (PY Label, FOMC/SFO Model)

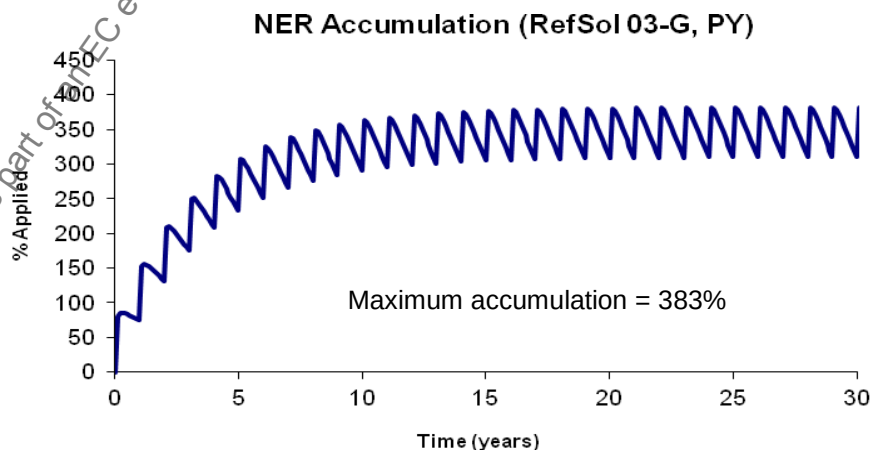
Measured and predicted vs time (for study duration)



Measured and predicted vs time (extrapolated to 400 days)



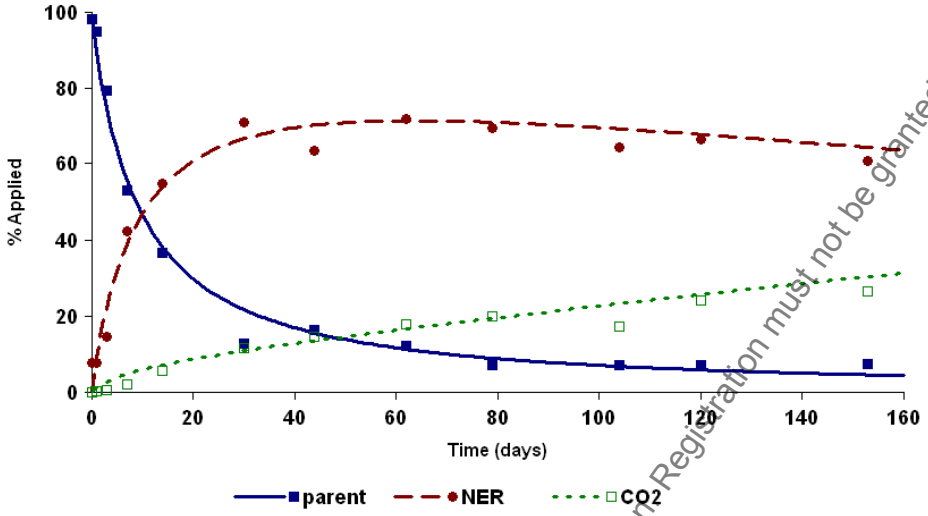
30 Year Accumulation



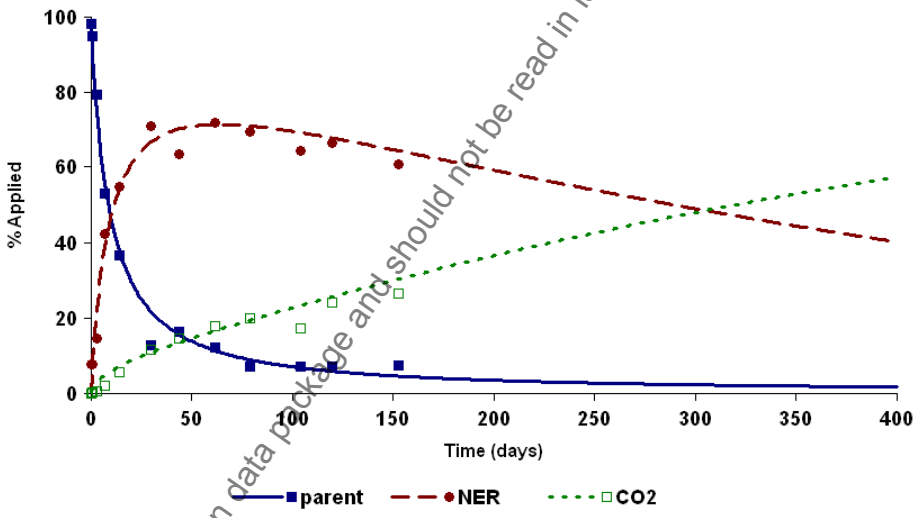
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Figure B.8.33 Prediction of unextracted residue and its accumulation in Site E Soil (PH Label, FOMC/SFO Model)

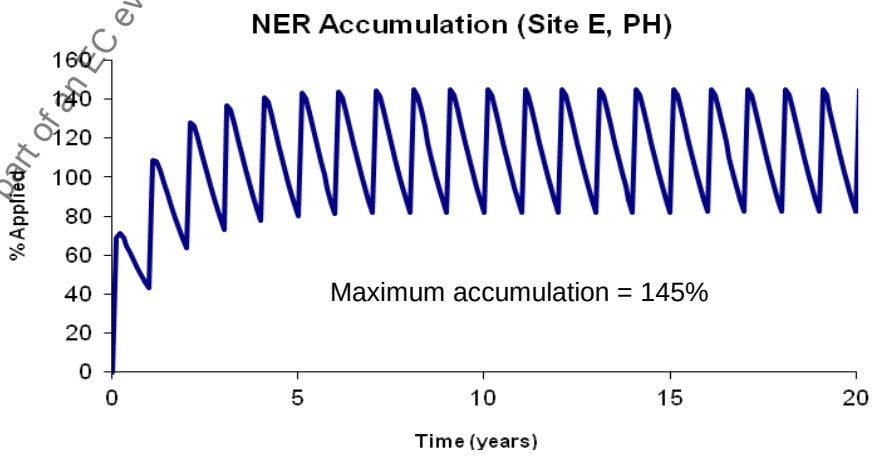
Measured and predicted vs time (for study duration)



Measured and predicted vs time (extrapolated to 400 days)



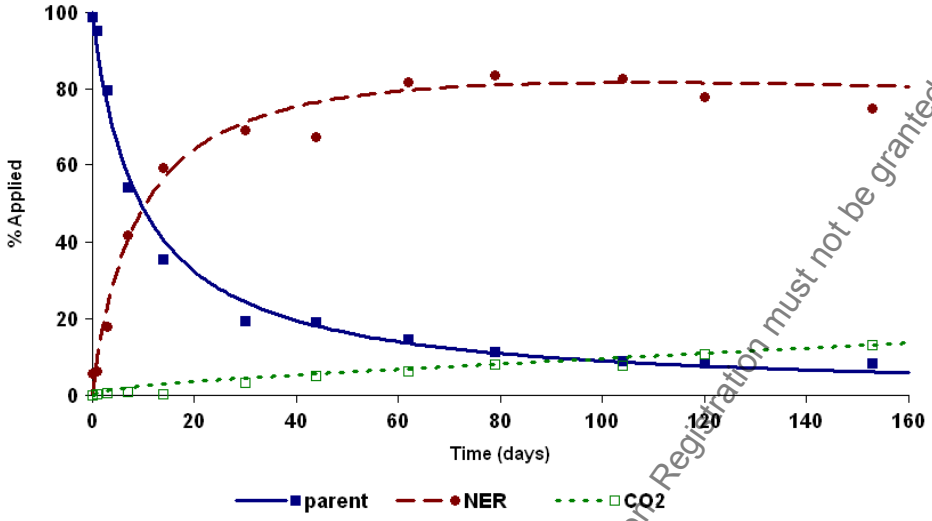
20 Year Accumulation



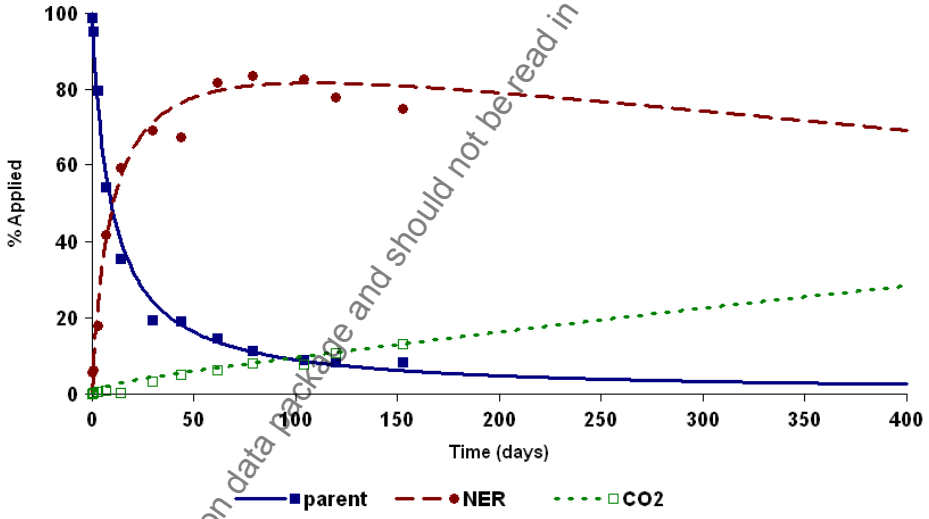
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Figure B.8.34 Prediction of unextracted residue and its accumulation in Site E Soil (PY Label, FOMC/SFO Model)

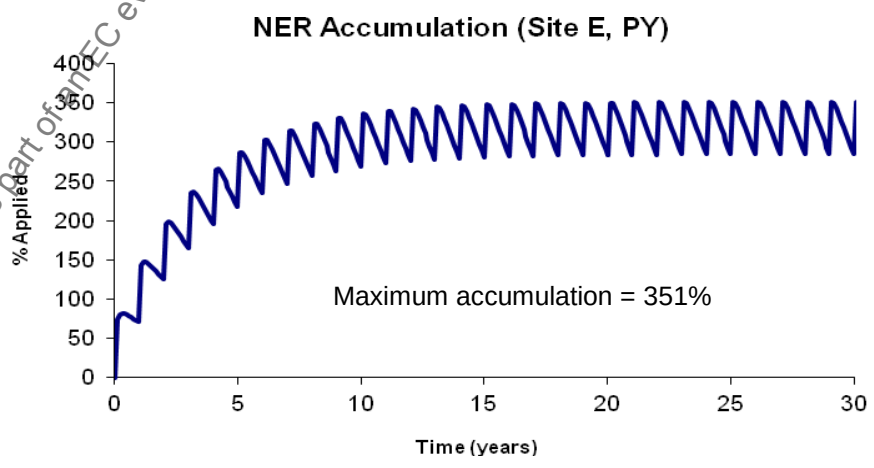
Measured and predicted vs time (for study duration)



Measured and predicted vs time (extrapolated to 400 days)



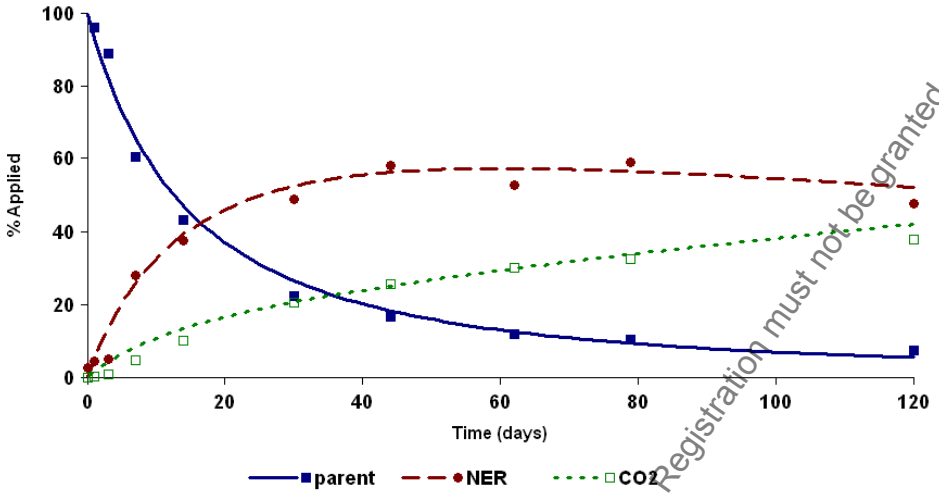
30 Year Accumulation



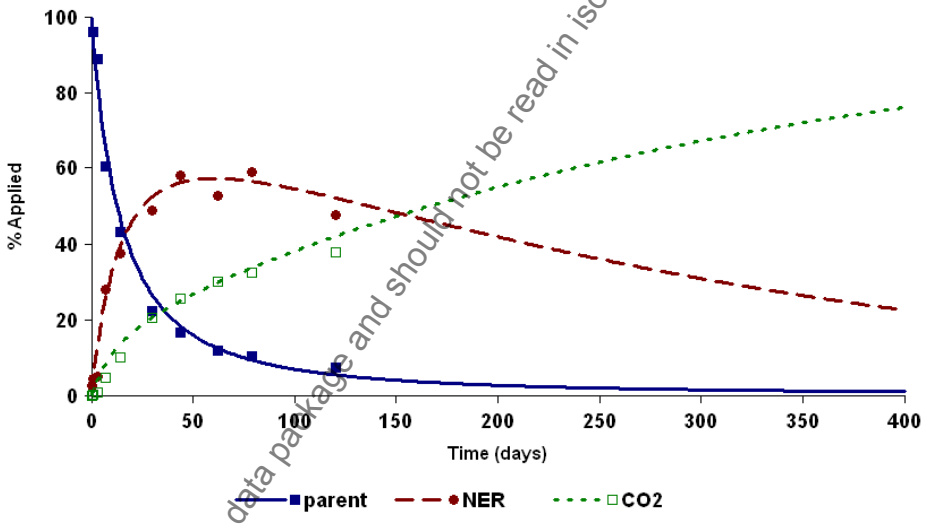
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Figure B.8.35 Prediction of unextracted residue and its accumulation in Site I2 Soil (PH Label, FOMC/SFO Model)

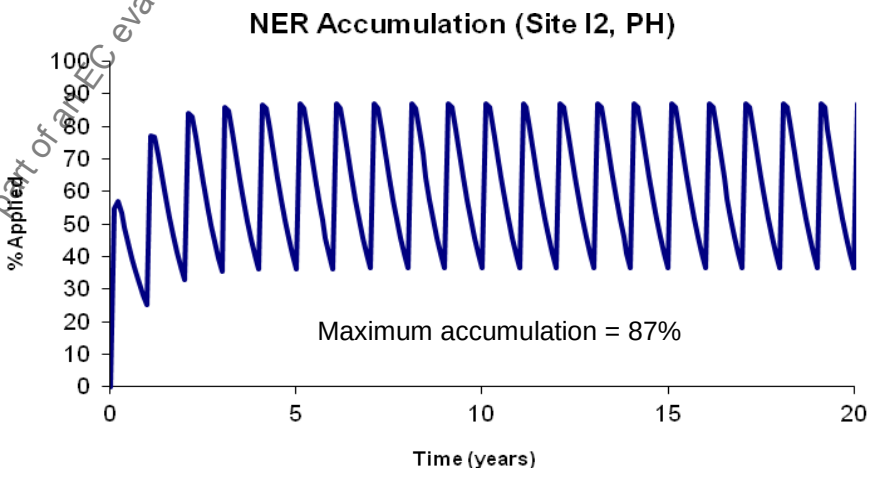
Measured and predicted vs time (for study duration)



Measured and predicted vs time (extrapolated to 400 days)



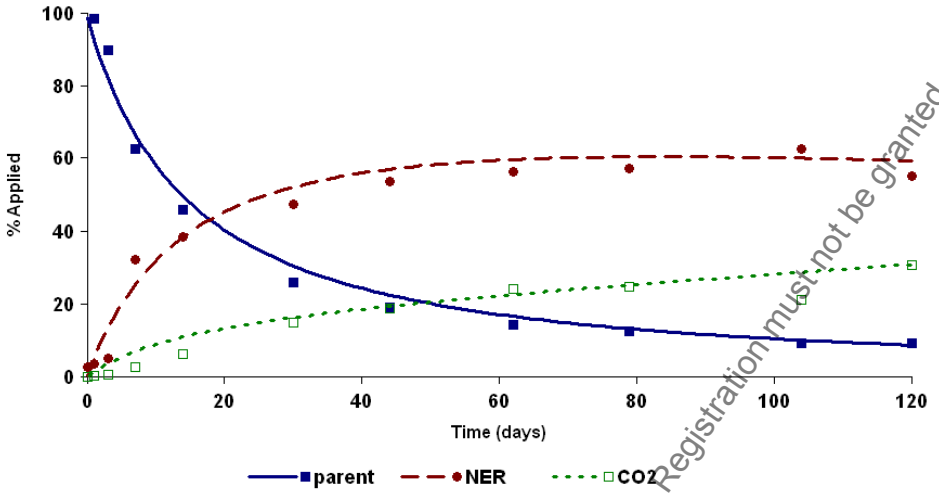
20 Year Accumulation



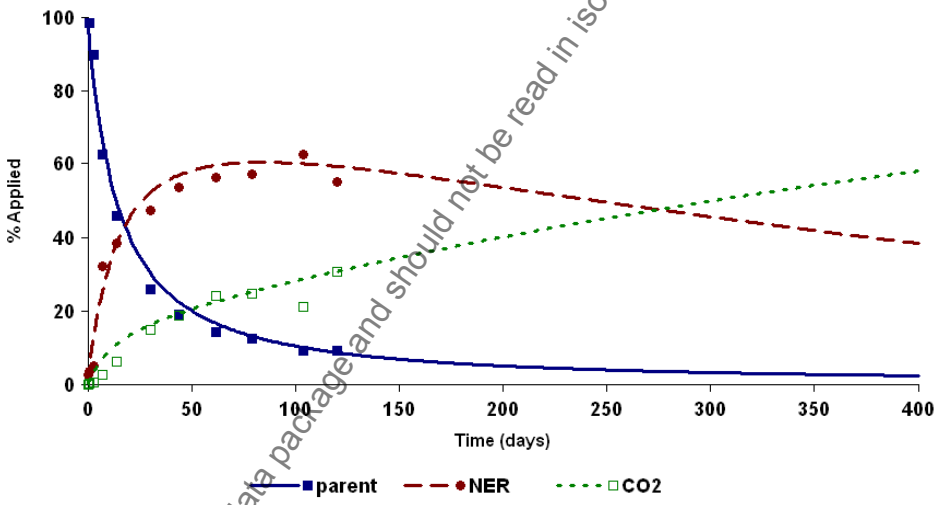
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Figure B.8.36 Prediction of unextracted residue and its accumulation in Site I2 Soil (PY Label, FOMC/SFO Model)

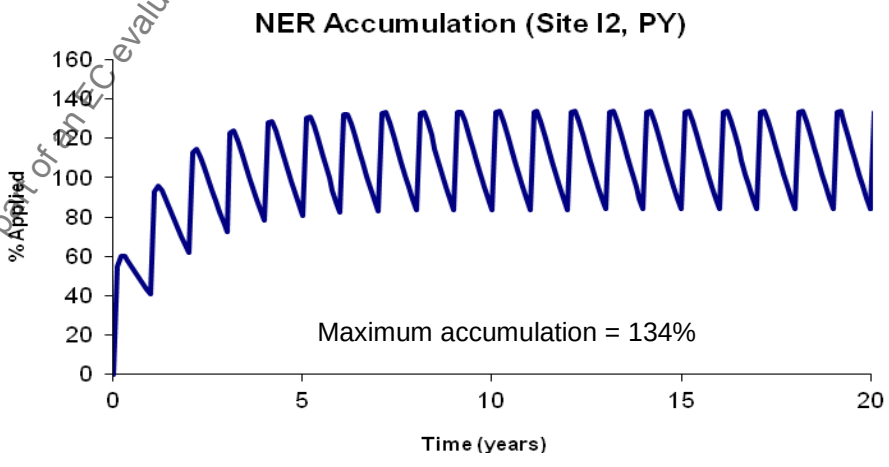
Measured and predicted vs time (for study duration)



Measured and predicted vs time (extrapolated to 400 days)



20 Year Accumulation



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The accumulation factors from these calculations are shown below.

Table B.8.58 Calculated accumulation factors for unextracted residue in soil

Soil	Label	Best Fit Model (Parent/NER)	Unextracted residue DT50		Accumulation Factor *
			(days)	(years)	
Yolo	PH	FOMC/SFO	345	0.9	1.48
	PY	nc	nc		
RefSol 03-G	PH	FOMC/SFO	361	1.0	1.54
	PY	FOMC/SFO	870	2.4	3.83
Site E	PH	FOMC/SFO	327	0.9	1.45
	PY	FOMC/SFO	855	2.3	3.51
Site I2	PH	FOMC/SFO	209	0.6	0.87
	PY	FOMC/SFO	362	1.0	1.34

* maximum predicted accumulation expressed as x initial application rate

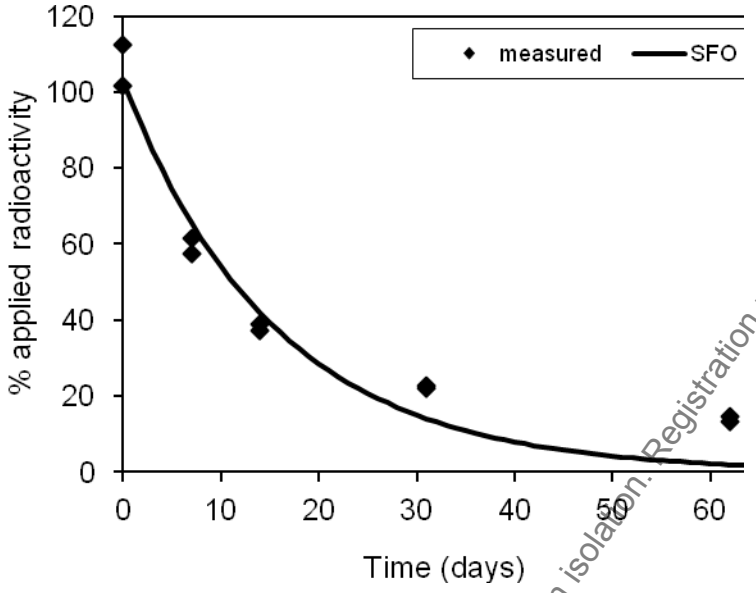
Jackson 2012 a&c, GHE-P-12808)

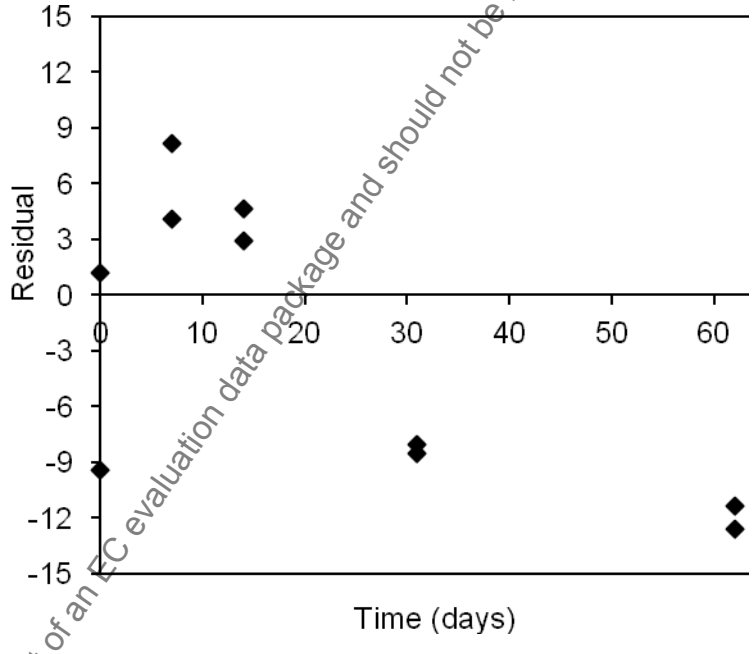
c) The degradation kinetics of XDE-729 methyl and its major metabolites under dark, aerobic conditions but either with sterile soils or at lower temperature (10ºC) were investigated as part of the route of degradation study described at section B.8.1.1b) above.

The study authors calculated degradation rates for the incubations, but in the case of the parent, did not add 0 DAT concentrations for metabolites and unextracted residues to the parent residue. In some cases, the additional radioactivity is significant, thus the RMS has recalculated kinetics for parent using FOCUS_DEGKIN v2.xls using the mass balance at 0 DAT as the initial concentration as this reflects the total parent, metabolite and unextracted residue at day 0. A relatively simple approach has been taken to obtain data suitable for comparison with the aerobic non-sterile endpoints at 20ºC. Kinetics for metabolite X11393729 under sterile conditions have not been calculated as it is clear from the sterile incubations that the metabolite is persistent leading the RMS to the conclusion that degradation of X11393729 is predominantly microbially mediated.

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Figure B.8.37 Visual and residual fits, SFO kinetics for XDE-729 methyl in sterile Yolo soil

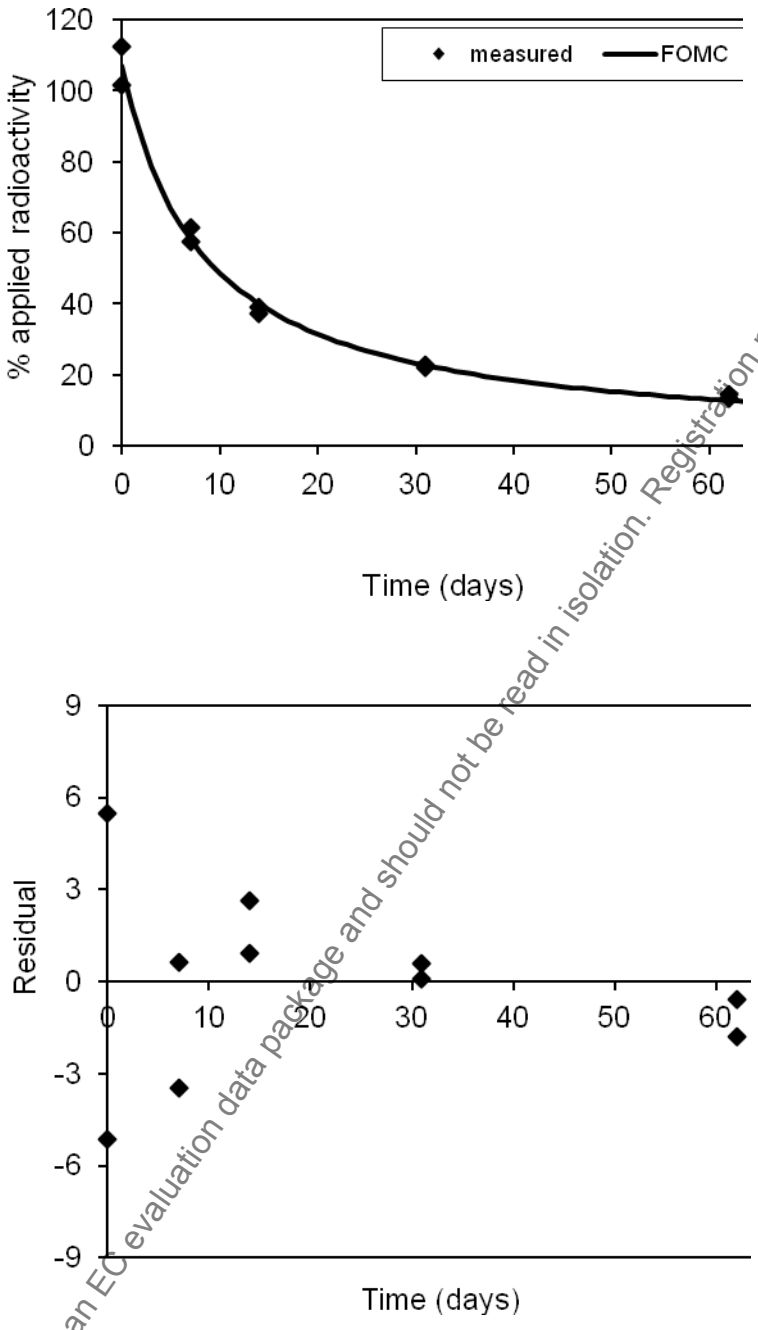




χ^2 = 12.4, k = 0.064, DT50 10.8 days, DT90 35.9 days

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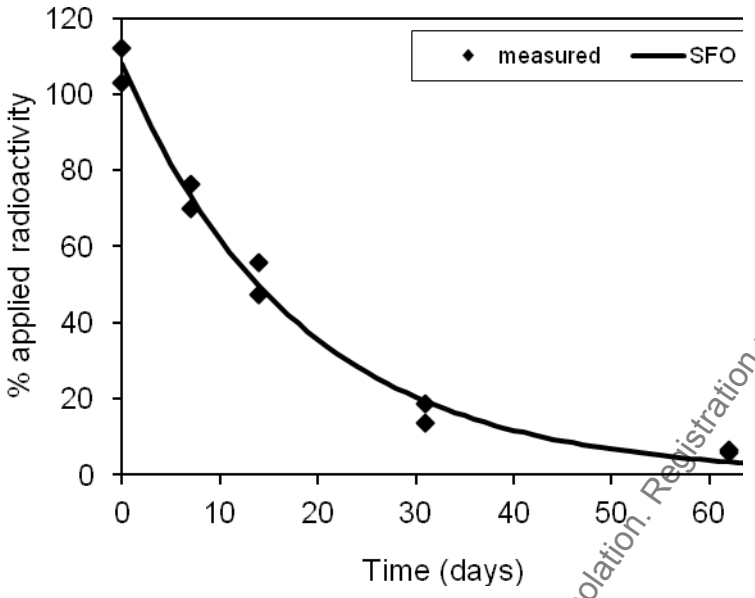
Figure B.8.38 Visual and residual fits, FOMC kinetics for XDE-729 methyl in sterile Yolo soil

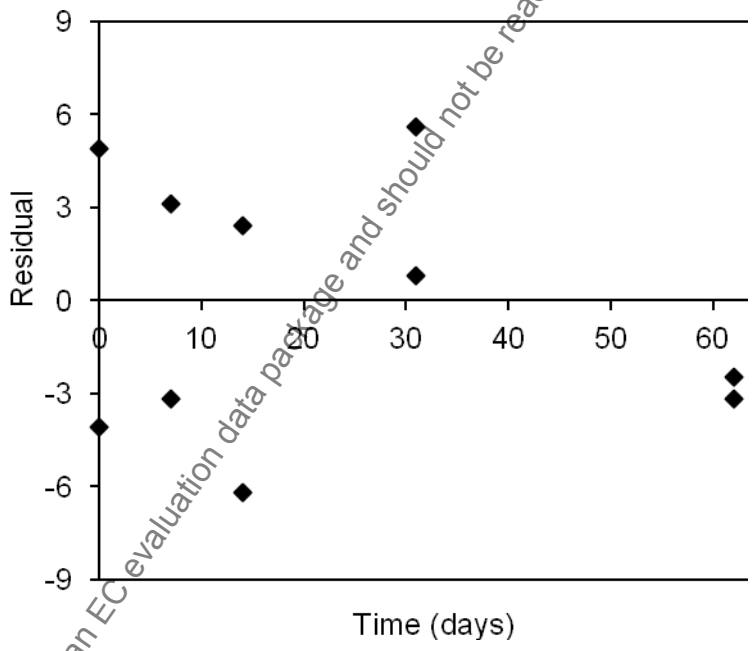


χ^2 = 2.2, α = 0.996, β = 8.3, DT50 8.3 days, DT90 75.1 days

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Figure B.8.39 Visual and residual fits, SFO kinetics for XDE-729 methyl in sterile RefSol 03-G soil



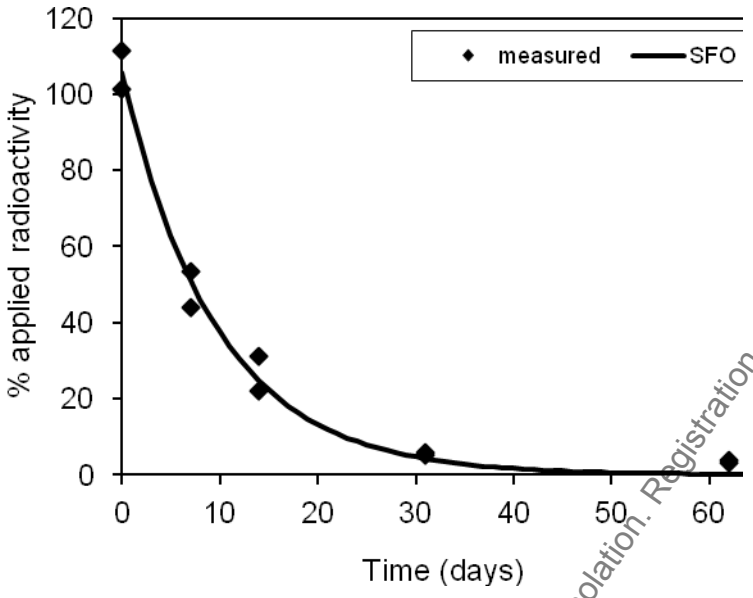


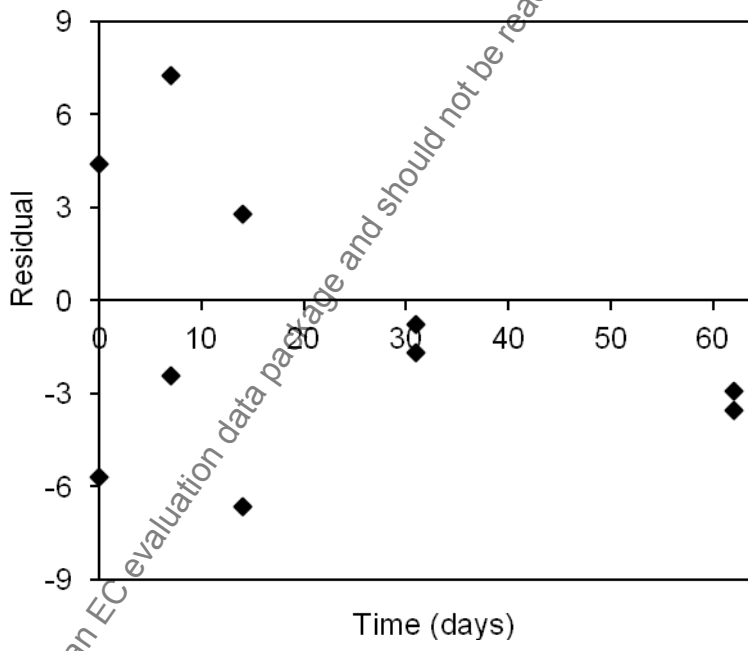
χ^2 = 3.3, k = 0.056, DT50 12.5 days, DT90 41.5 days

Note FOMC not shown as gave virtually same results with χ^2 = 3.7.

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Figure B.8.40 Visual and residual fits, SFO kinetics for XDE-729 methyl in sterile Site E soil



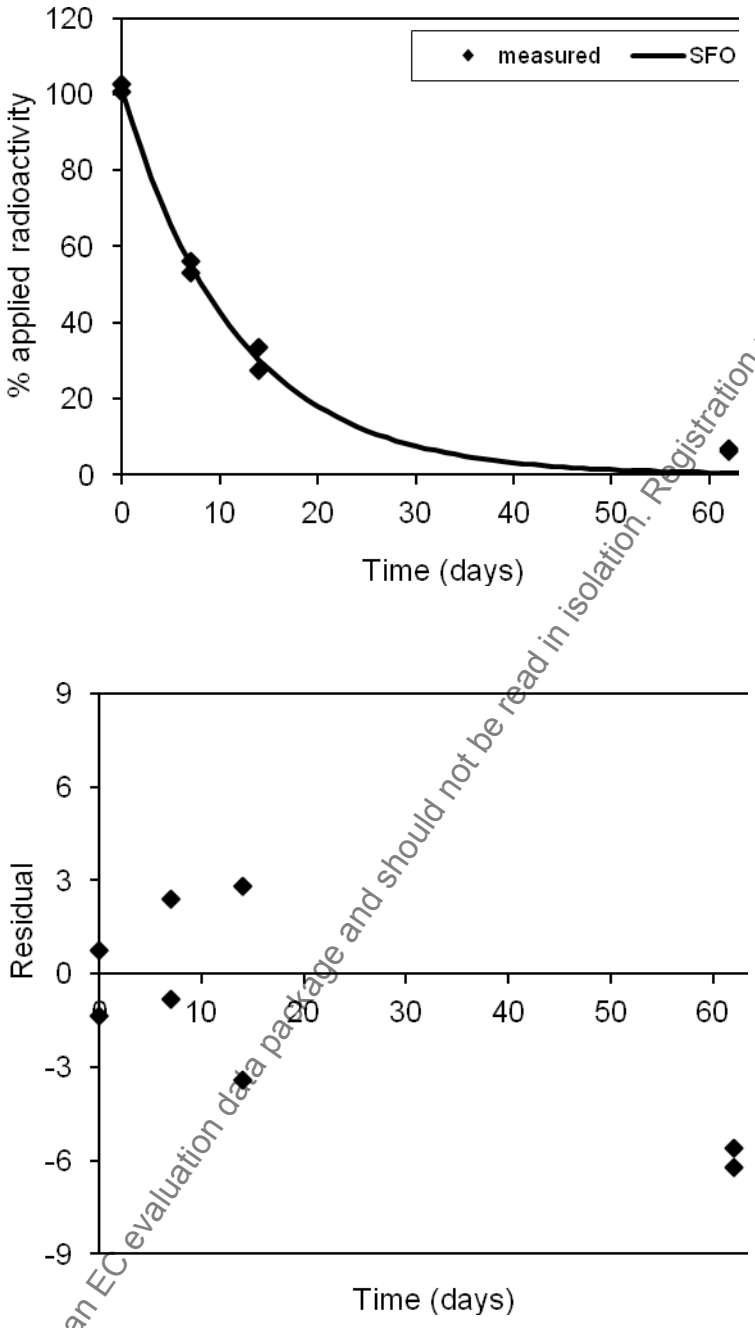


χ^2 = 4.4, k = 0.104, DT50 6.7 days, DT90 22.2 days

Note FOMC not shown as gave virtually same results with χ^2 = 5.0.

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Figure B.8.41 Visual and residual fits, SFO kinetics for XDE-729 methyl in sterile Site I2 soil



χ^2 = 5.1, k = 0.086, DT50 8.0 days, DT90 26.6 days

Note FOMC not shown as gave virtually same results with χ^2 = 6.3.

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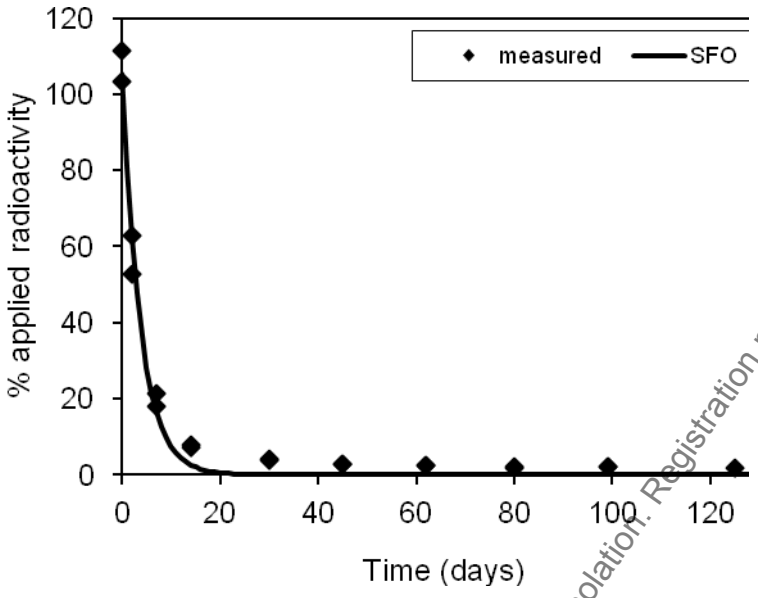
Table B.8.59 Best fit DT50 and DT90 for XDE-729 methyl in sterile soil

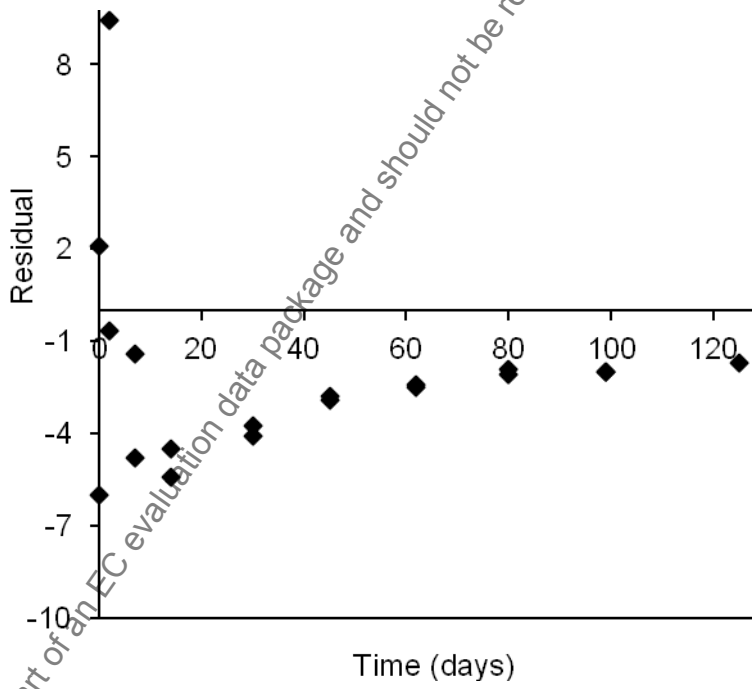
	DT50 (days)	DT90 (days)	Kinetics	χ^2
Yolo	8.3	75.1	FOMC	2.2
RefSol 03-G	12.5	41.5	SFO	3.3
Site E	6.7	22.2	SFO	4.4
Site I2	8.0	26.6	SFO	5.1

Kinetics at low temperature have also been calculated. As with the sterile incubations, the mass balance at day 0 has been used for the parent concentration at day 0 to account for metabolite formation and unextracted residues at day 0.

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Figure B.8.42 Visual and residual fits, SFO kinetics for XDE-729 methyl in non-sterile Site E soil at 10ºC

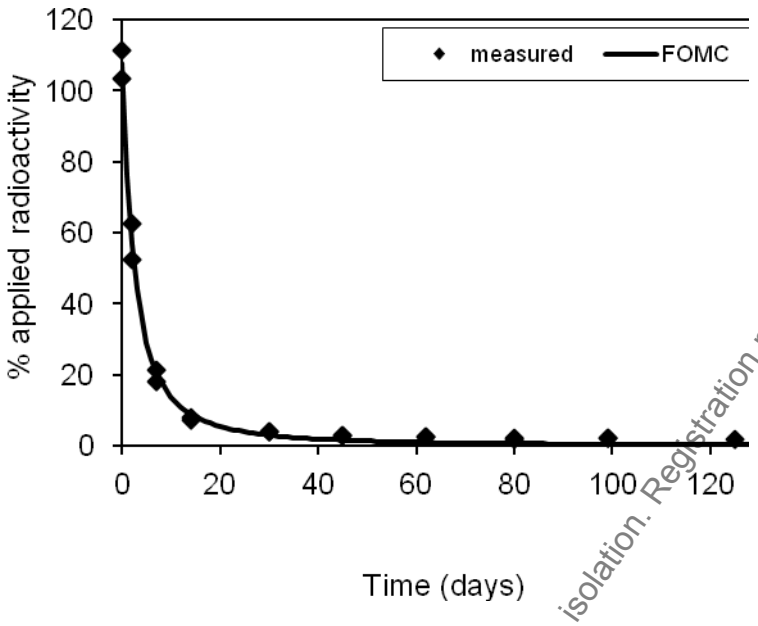


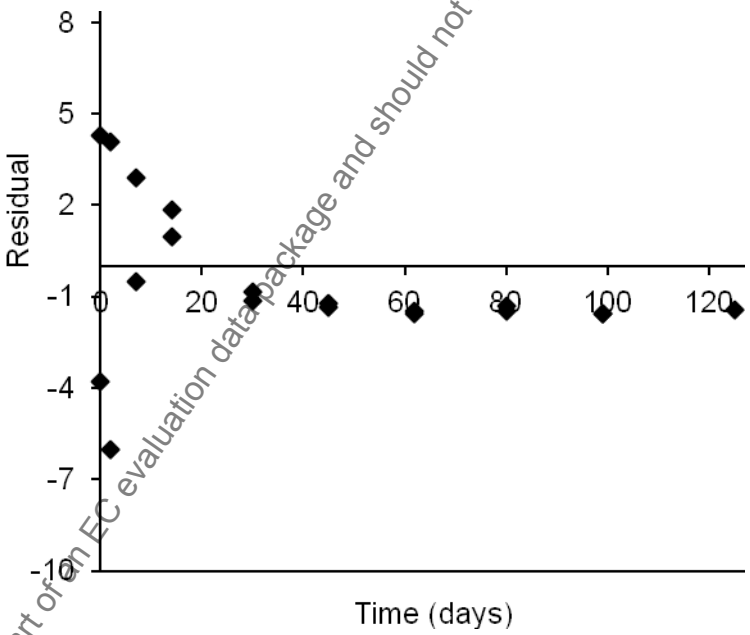


χ^2 = 11.6, k = 0.265, DT50 2.6 days, DT90 8.7 days

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Figure B.8.43 Visual and residual fits, FOMC kinetics for XDE-729 methyl in non-sterile Site E soil at 10ºC





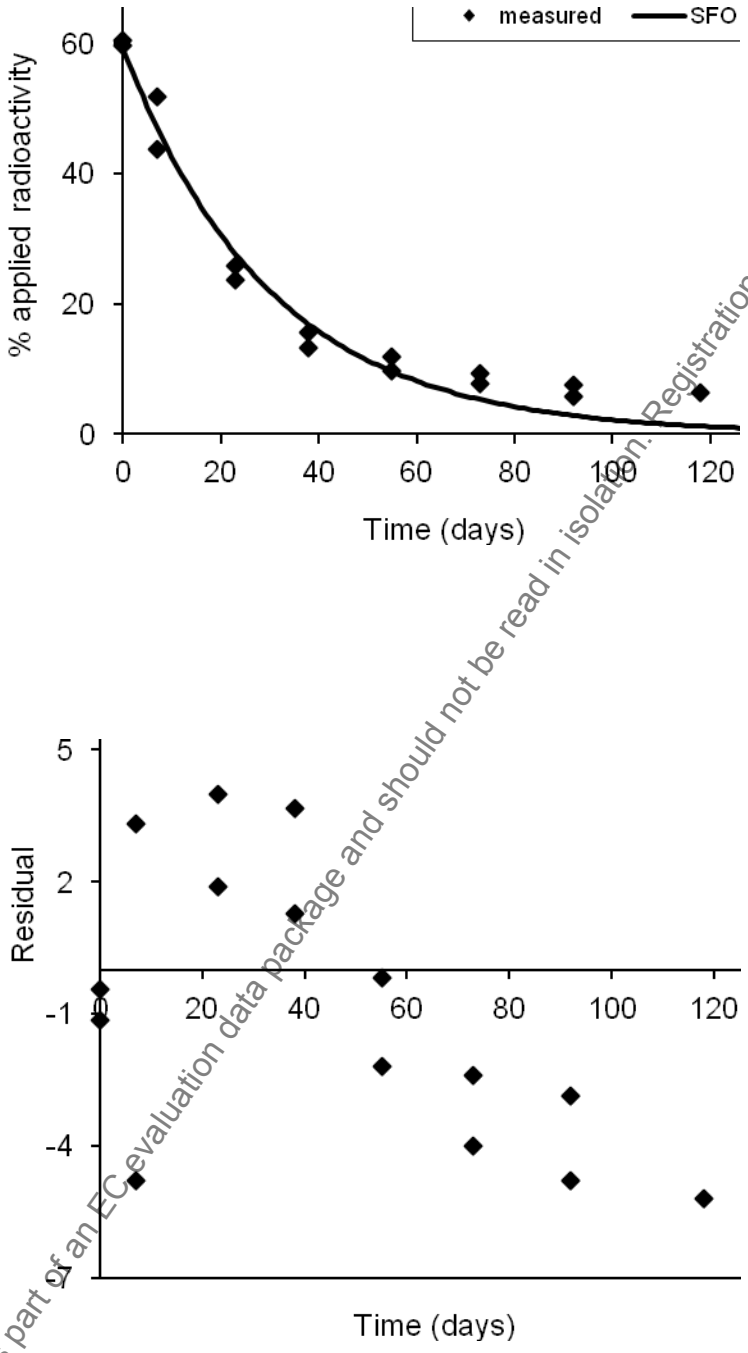
χ^2 = 4.9, α = 1.783, β = 4.6, DT50 2.2 days, DT90 12.2 days

The FOMC fits represent the best fit. As the values are only for comparison purposes, DFOP or HS kinetics have not been attempted. The FOMC DT50 and DT90 in the low temperature incubation are 2x those in the equivalent incubation at 20ºC.

For the purposes of comparison, a top down approach has been conducted for metabolite X11393729.

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Figure B.8.44 Visual and residual fits, SFO top down kinetics for X11393729 in non-sterile Site E soil at 10ºC



χ^2 = 10.0, k = 0.033, DT50 21.0 days, DT90 69.6 days

(Yoder and Boulton 2011)

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d) The rate of degradation of XDE-729 methyl and its main metabolites was also investigated under anaerobic conditions as described in section B.8.1.2. Kinetics of the active substance and metabolites X11393729 and X11449757 were calculated from the day of flooding and did not take into account the initial sample point at dosing, 2 days before flooding. At the point of flooding, significant degradation of the parent had been observed, with significant formation of X11393729 and, in some soils, X11449757. The study author applied the principles of FOCUS Degradation kinetics to the assessment.

The following results were obtained from the study author kinetic assessment using sequential fitting of parent followed by metabolites.

Table B.8.60 Rates of degradation calculated for XDE-729 methyl and its metabolites under anaerobic soil conditions from sequential fitting.

Sample ID	Model Type	DT50 (days)	DT90 (days)	Formation fraction	% error χ2 passes
XDE-729 methyl					
Yolo	DFOP	2.8	29	-	4.9
RefSol 03-G	SFO	1.6	5.5	-	10.3[1]
Site E	SFO	0.9	3.1	-	9.3[3]
Site I2	SFO	1.9	6.5	-	6.5[4]
X11393729					
Yolo	DFOP-SFO	77	257	0.9784	4.7
RefSol 03-G	SFO-SFO	21	70	2.3×10^{-14}	4.3[2]
Site E	SFO-SFO	14	46	0.8213	6.6
Site I2	SFO-SFO	106	352	1.0000	3.4
X11449757					
Yolo[5]	DFOP-SFO-SFO	92	304	0.6416	6.0
RefSol 03-G	SFO-SFO-SFO	165	549	0.9505	13.4
Site E	SFO-SFO-SFO	127	421	0.7011	10.1
Site I2[5]	SFO-SFO-SFO	>1000	>1000	0.7366	20.3

[1] FOMC fit had χ^2 of 2.5 and slightly better residuals, but rejected as β parameter confidence interval includes zero; [2] X11393729 formation maximum on day of flooding, and greater than parent concentration on day of flooding. Error associated with ff much greater than optimised ff, thus highly uncertain. [3] FOMC fit had χ^2 of 4.9 and slightly better residuals, but rejected as α and β parameter confidence intervals includes zero; [4] FOMC fit had χ^2 of 3.7 and slightly better residuals, but rejected as β parameter confidence interval includes zero; [5] Metabolite peak not reached by study end, thus parameters uncertain.

Top down fitting of metabolites was also attempted where possible. In all cases for X11449757, the peak metabolite formation was not reached by study end or was not sufficiently before study end for a decline to be seen. Thus, top down parameters could not be calculated for X11449757.

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Table B.8.61 Rates of degradation calculated for XDE-729 methyl anaerobic soil metabolites, top down SFO approach

Sample ID	DT50 (days)	DT90 (days)	% error $\chi 2$ passes
X11393729			
Yolo	90	299	6.3
RefSol 03-G	21	70	4.6
Site E	21	69	27.2
Site I2	100	334	3.8
X11449757			
Yolo[1]	-	-	-
RefSol 03-G[2]	-	-	-
Site E[2]	-	-	-
Site I2[1]	-	-	-

[1] Metabolite peak not reached by study end, not possible to calculate; [2] Insufficient data points after peak concentration to calculate top down parameters

The RMS can agree with the values calculated. As kinetic parameters from anaerobic soil studies have no standard place in EU environmental exposure assessment at present, and as the values are most likely to be used in relatively simple calculations, it is considered by the RMS that the parent DT50 and top-down DT50 for X11393729 should be used. For X11449757, given only limited or no apparent decline in the studies, the RMS proposes that a conservative DT50 ought to be used in simple soil exposure estimates, e.g. 1000 days.

B.8.1.5 Field studies

a) The magnitude of the DT50 and DT90 values for XDE-729 methyl do not trigger field dissipation studies, i.e. a laboratory DT50 of 60 days at 20ºC and pF 2 – 2.5 is required for the active substance to trigger field dissipation studies. One DT50 value for X11449757 exceeds the DT50 of 60 days which triggers field dissipation studies for parent substances. However, the Directive 91/414/EEC is unclear whether this trigger value applies to metabolites.

In spite of the fact that field dissipation studies are not triggered for XDE-729 methyl, the Applicant has conducted field dissipation studies at four European locations (Germany, UK, Spain, France). Two study reports were submitted, one addressing the results from applications made in the spring at the four sites, and one addressing applications made in the autumn at the same four sites. The studies were conducted in compliance SETAC (1995) guidelines and GLP.

All studies were bare soil studies and were applied at approximately the same dose (6.9 – 8.2 g/ha). Dose applied at each site was verified by measurements of spray solution before and after application. The soil surface at each site was cultivated prior to application to give a fine, firm seed bed. Dose verification was also provided by placing filter papers in petri dishes with in the plots. Filter papers were subsequently extracted and analysed. Weed control was conducted either manually or by application

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of glyphosate. Weather conditions at each site were recorded using on-site weather stations, recording daily average air and soil temperature (soil temperature recorded at 10cm depth)., daily volumetric soil moisture (at 10cm depth) and daily rainfall. Irrigation was applied as necessary in relation to long-term monthly rainfall. 'Missing' amounts were applied in the following month.

Field plots were divided into three sub-plots. At each sample time, six samples were taken from each sub-plot. Samples taken within the first two weeks after application were generally taken down to 30cm depth and subsequently down to 100cm. Soil cores were deep frozen after sampling.

Frozen cores from the top 30cm were subsequently divided into 10cm layers. For each 10cm layer, the six samples from each subplot were homogenised. Samples of soil (5 g) were weighed into 50 ml centrifuge tubes. Diatomaceous Earth was added to approximately 10 ml and the tubes were shaken vigorously to obtain a homogeneous mixture. Samples were added to 11-mL Accelerated Solvent Extraction cells with cellulose filters. The cells were extracted on an ASE 200 Accelerated Solvent Extractor using methanol/water (50/50, v/v) solution containing 0.1% (v/v) phosphoric acid. It is noted that this procedure does not include the 80:20 methanol:water or $CaCl_2$ initial extractions used in the laboratory aerobic degradation studies, but is otherwise similar. The RMS considers the absence of the initial extraction step is unlikely to significantly affect overall extraction in field studies in comparison with the laboratory studies.

Upon the completion of ASE extraction, extract weights were recorded and 5-mL aliquots were transferred into glass vials. An aliquot (40 µL) of a mixed internal standard solution (containing either the [M+4] or the [M+6] isotopes of XDE-729 methyl ester, X11393729 and X11449757) was added to each sample, which was then evaporated to about 1 ml under nitrogen at 40ºC. Vials were capped, sonicated and vortexed.

Extracts were analysed for XDE-729 methyl, X11393729 and X11449757 using HPLC-MS/MS. Claimed LOQ for each analyte was 0.05 µg/kg.

Specific details for each study are given below.

Spring application

Properties of the top 30 cm of each of the soils are given below.

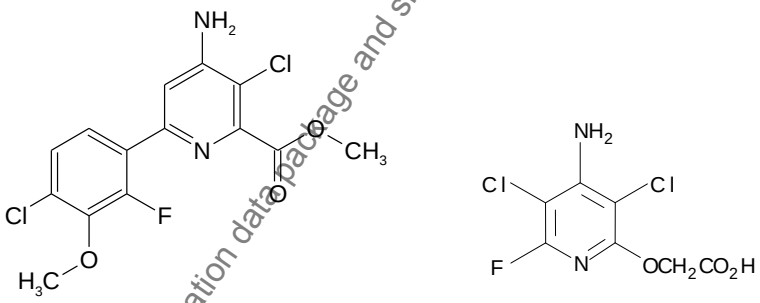
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Table B.8.62 Properties of field dissipation soils

Trial location:	Dollern, Niedersachsen, **Germany**	Melbourne, Derbyshire, **UK**	Carlet, Valencia**, Spain**	Barry-d'Islemade, Tarn-et-Garonne, **France**
Application date	29/4/2010	7/5/2010	18/5/2010	11/5/2010
% Sand:	74.9	26.9	36.5	44.9
% Silt:	16.5	50.4	35.9	36.3
% Clay:	8.7	22.8	27.7	18.9
USDA classification	Sandy loam	Silt loam	Clay loam	Loam
pH ($CaCl_2$)	5.73	6.94	7.71	5.52
pH (H_2O)	6.54	6.94	7.85	6.52
CEC [meq/100g]	7.3	11.4	10.7	7.9
OC [%]	1.4	1.2	0.67	< 0.3
Biomass (mg C/100g):	17.3	31.6	49.0	18.4

Site history of cropping and pesticide use for the previous three years was provided for each of the sites (for the UK site, the crop three years prior to the trial was not recorded, but from the range of substances applied, the RMS considers it likely that it was a cereal crop). It is noted that XDE-729 methyl is a member of the pyridine-carboxylic acid family of herbicides (HRAC class O, synthetic auxins). The German site was treated with fluroxypyr (a member of the same family of herbicides) two years before the year of the study. However, the RMS considers it unlikely that the results of this study would have been significantly affected by the use of fluroxypyr in a previous crop on the site as the structures are reasonably different.

Figure B.8.45 Structures of XDE-729 methyl (left) and fluroxypyr (right)



Procedural recovery information for the three analytes in soil is given below:
XDE-729 methyl at LOQ of 0.05 µg/kg, 67-121%, mean 94% (n=29), std dev 15%, recovery at 0.1-8 µg/kg 75 – 111%.
X11393729 at LOQ of 0.05 µg/kg 61-120%, mean 86% (n=29), std dev 18%, recovery at 0.1-8 µg/kg 71-104%.
X11449757 at LOQ of 0.05 µg/kg 21-124%, 21 apparently outlier according to Grubbs test therefore excluded, otherwise 60-124%, mean 89% (n=29), std dev 16%, recovery at 0.1-8 µg/kg 60-108%.

It is noted that in the guidance on pre-registration methods of analysis (SANCO/825/00), wider ranges of recovery of 60-120% may be acceptable for

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methods of analysis in soil with LOQ < 0.01 mg/kg. Procedural recoveries were generally considered to be acceptable for parent and X11393729 although some individual values were less than 70% or greater than 110%. However, the recoveries for X11449757 are more variable. The Applicant collated the residues data with procedural recovery information to indicate where recovery outside the expected range occurred. Overall, the RMS considers that the method is acceptable.

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Table B.8.63 Field soil residues from spring-applied field dissipation studies with XDE-729 methyl with procedural recovery data (low/high recoveries highlighted)

Germany

	XDE-729 Me			XDE-729 Acid			X-757		
DAT	Residue (ug/kg)	Fort. level (ug/kg)	% Rec	Residue (ug/kg)	Fort. level (ug/kg)	% Rec	Residue (ug/kg)	Fort. level (ug/kg)	% Rec
Pre	0	0.05	98	0	0.05	87	0	0.05	79
0	3.37	1	111	0.13	1	98	0.00	1	92
1	2.35	0.05	94	0.11	0.05	71	0.00	0.05	80
3	3.17	1	107	0.18	1	71	0.00	1	108
7	1.77	0.05	99	0.15	0.05	66	0.01	0.05	103
13	1.68			0.22			0.05		
29	1.20	0.05	111	0.19	0.05	73	0.14	0.05	78
60	0.36			0.09			0.17		
91	0.40	0.05	99	0.12	0.05	82	0.32	0.05	96
123	0.06			0.02			0.08		
182	0.15	0.05	109	0.04	0.05	84	0.12	0.05	98
237	0.38			0.09			0.14		
302	0.38	0.05	94	0.12	0.05	95	0.26	0.05	60
372	0.10	0.1	91	0.04	0.1	84	0.05	0.1	90

UK

	XDE-729 Me			XDE-729 Acid			X-757		
DAT	Residue (ug/kg)	Fort. level (ug/kg)	% Rec	Residue (ug/kg)	Fort. level (ug/kg)	% Rec	Residue (ug/kg)	Fort. level (ug/kg)	% Rec
Pre	0	0.05	120	0	0.05	120	0	0.05	99
0	1.11			0.56			0.04		
1	4.07	0.05	73	0.25	0.05	70	0.01	0.05	74
3	2.21	1	86	0.33	1	73	0.00	1	83
7	2.71	0.05	69	0.50	0.05	61	0.00	0.05	73
14	2.87			0.44			0.00		
28	2.28	0.05	96	0.47	0.05	71	0.01	0.05	88
62	1.07			0.51			0.05		
89	0.80	0.05	85	0.76	0.05	101	0.08	0.05	104
123	0.41			0.62			0.05		
183	0.34	0.05	96	0.54	0.05	95	0.04	0.05	103
243	0.31			0.39			0.04		
300	0.38	0.05	108	0.42	0.05	99	0.04	0.05	21
372	0.39	0.1	89	0.40	0.1	80	0.03	0.1	63

Spain

	XDE-729 Me			XDE-729 Acid			X-757		
DAT	Residue (ug/kg)	Fort. level (ug/kg)	% Rec	Residue (ug/kg)	Fort. level (ug/kg)	% Rec	Residue (ug/kg)	Fort. level (ug/kg)	% Rec
Pre	0	0.05	105	0	0.05	119	0	0.05	120
0	1.48			2.21			0.72		
1	5.14	0.05	81	0.88	0.05	72	0.14	0.05	124
3	4.26			0.60			0.10		
7	3.70	0.05	113	0.65	0.05	64	0.16	0.05	90
14	1.87			0.61			0.12		
27	1.75	0.05	72	1.02	0.05	63	0.19	0.05	105
58	0.53			0.65			0.13		
91	0.13	0.05	98	0.39	0.05	111	0.13	0.05	87
119	0.15			0.39			0.15		
181	0.08	0.05	72	0.15	0.05	76	0.05	0.05	90
240	0.05			0.12			0.02		
302	0.11	0.1	75	0.18	0.1	72	0.06	0.1	60
363	0.08	2	100	0.11	2	85	0.03	2	95

France

	XDE-729 Me			XDE-729 Acid			X-757		
DAT	Residue (ug/kg)	Fort. level (ug/kg)	% Rec	Residue (ug/kg)	Fort. level (ug/kg)	% Rec	Residue (ug/kg)	Fort. level (ug/kg)	% Rec
Pre	0	0.05	121	0	0.05	124	0	0.05	107
0	2.98			0.72			0.06		
1	1.95	0.05	102	0.26	0.05	63	0.08	0.05	78
3	2.60	1	92	0.51	1	78	0.22	1	87
7	1.10	0.05	98	0.39	0.05	88	0.18	0.05	81
15	1.57			0.51			0.32		
28	1.15	0.05	86	0.26	0.05	78	0.29	0.05	68
62	0.24			0.07			0.30		
92	0.11	0.05	85	0.06	0.05	82	0.26	0.05	83
122	0.08			0.05			0.26		
183	0.06	0.05	99	0.03	0.05	91	0.10	0.05	83
239	0.04	8	83	0.02	8	104	0.07	8	106
300	0.04	0.05	91	0.01	0.05	90	0.09	0.05	70
364	0.04	8	103	0.01	8	98	0.07	8	82

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Procedural recovery info for filter papers (for dose verification):
XDE-729 methyl at LOQ of 4 µg/kg 80-157%, mean 109% (n-5), std dev 30%
X11393729 at LOQ of 4 µg/kg 98-136%, mean 115% (n=5), std dev 18%
X11449757at LOQ of 4 µg/kg 70-106%, mean 95% (n=5), std dev 16%

Note that some samples were stored for more than 1 year between sampling and extraction with some up to 18 months. At the time of writing, interim storage stability data have been provided for storage up to 1 year which indicate stability of the stored frozen residue (see Volume 3, section B.7.7). The study is intended to demonstrate stability of residues in soil stored for up to 2 years.

Results of the petri dish residues to verify application dose are presented below.

Table B.8.64 Petri dish residues in XDE-729 methyl field dissipation studies, spring application

XDE-729 methyl (µg/sample)	X11393729 (µg/kg)	X11449757 (µg/kg)
Germany		
32	n.d.	n.d.
19	n.d.	n.d.
21	n.d.	n.d.
18	n.d.	n.d.
*	*	*
UK		
5.0	n.d.	n.d.
10	n.d.	n.d.
<LOQ (2.2)	n.d.	n.d.
< LOQ (3.2)	n.d.	n.d.
4.2	n.d.	n.d.
Spain**		
<LOQ (1.7)	n.d.	n.d.
<LOQ (2.6)	n.d.	n.d.
<LOQ (1.4)	n.d.	n.d.
<LOQ (1.0)	n.d.	n.d.
<LOQ (1.1)	n.d.	n.d.
France		
9.0	n.d.	n.d.
9.1	n.d.	n.d.
5.8	n.d.	n.d.
7.7	n.d.	n.d.
10	n.d.	n.d.

n.d. = not detectable (<LOD, i.e. <1.2 µg/sample); LOQ = 4 µg/sample
* = petri dish broken and could not be analysed
** = petri dishes covered by approx 30 g soil which was removed prior to extraction

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Residues results for the spring-applied sites are provided below. In some cases, reanalysis of soil from a specific subplot and soil layer was re-analysed. Whilst not specifically explained in the study, the Applicant clarified separately that re-analysis was conducted where an unexpectedly high or low residue was found.

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Table B.8.65 Results for German field dissipation study, spring appln XDE-729 methyl

Timing	Stratum [cm]	XDE-729 methyl [µg/kg]	XDE-729 acid [µg /kg]	X-757 [µg /kg]
2 DBA	0-10	n.d.	n.d.	n.d.
	10-20	< LOQ (0.02)	< LOQ (0.02)	n.d.
	20-30	n.d.	n.d.	n.d.
2 DBA	0-10	n.d.	n.d.	n.d.
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
2 DBA	0-10	n.d.	n.d.	n.d.
	10-20	n.d.	< LOQ (0.02)	n.d.
	20-30	n.d.	n.d.	n.d.
0 DAA	0-10	4.36	0.17	n.d.
	10-20	< LOQ (0.04)	n.d.	n.d.
	20-30	0.06	n.d.	n.d.
0 DAA	0-10	2.40	0.08	n.d.
	10-20	< LOQ (0.04)	n.d.	n.d.
	20-30	0.08	n.d.	n.d.
0 DAA	0-10	3.12	0.15	n.d.
	10-20	< LOQ (0.02)	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
1 DAA	0-10	2.27	0.12	n.d.
	10-20	n.d.	n.d.	n.d.
	20-30	n.d. 0.02	2.1 n.d.	n.d. n.d.
1 DAA	0-10	3.49	0.16	n.d.
	10-20	0.12	n.d.	n.d.
	20-30	< LOQ (0.02)	n.d.	n.d.
1 DAA	0-10	1.05	0.06	n.d.
	10-20	n.d.	n.d.	n.d.
	20-30	0.07	n.d.	n.d.

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Timing	Stratum [cm]	XDE-729 methyl [µg/kg]	XDE-729 acid [µg /kg]	X-757 [µg /kg]
3 DAA	0-10	2.70	0.18	n.d.
	10-20	n.d. n.d.	0.48 n.d.	n.d. n.d.
	20-30	n.d.	n.d.	n.d.
3 DAA	0-10	3.62	0.21	n.d.
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
3 DAA	0-10	3.19	0.15	n.d.
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
7 DAA	0-10	1.72	0.15	n.d.
	10-20	0.13	< LOQ (0.02)	n.d.
	20-30	< LOQ (0.02)	n.d.	n.d.
7 DAA	0-10	1.76	0.14	n.d.
	10-20	0.05	n.d.	n.d.
	20-30	< LOQ (0.02)	n.d.	n.d.
7 DAA	0-10	1.60	0.14	< LOQ (0.02)
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
13 DAA	0-10	1.28	0.15	< LOQ (0.04)
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
13 DAA	0-10	2.41	0.27	0.06
	10-20	< LOQ (0.03)	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
13 DAA	0-10	1.32	0.23	< LOQ (0.05)
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.

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Timing	Stratum [cm]	XDE-729 methyl [µg/kg]	XDE-729 acid [µg /kg]	X-757 [µg /kg]
29 DAA	0-10	1.55	0.23	0.21
	10-20	< LOQ (0.03)	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
29 DAA	0-10	1.07	0.17	0.11
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
29 DAA	0-10	0.96	0.18	0.11
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
60 DAA	0-10	0.29	0.06	0.14
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
60 DAA	0-10	0.34	0.08	0.15
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
60 DAA	0-10	0.46	0.13	0.21
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
91 DAA	0-10	0.68	0.19	0.57
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
91 DAA	0-10	0.37	0.11	0.27
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
91 DAA	0-10	0.14	0.05	0.12
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.

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Timing	Stratum [cm]	XDE-729 methyl [µg/kg]	XDE-729 acid [µg /kg]	X-757 [µg /kg]
123 DAA	0-10	0.06	< LOQ (0.03)	0.07
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
123 DAA	0-10	< LOQ (0.03)	n.d.	< LOQ (0.03)
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
123 DAA	0-10	0.09	< LOQ (0.04)	0.13
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
182 DAA	0-10	0.33	0.07	0.30
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
182 DAA	0-10	< LOQ (0.04)	n.d.	< LOQ (0.02)
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
182 DAA	0-10	0.09	< LOQ (0.04)	< LOQ (0.04)
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
237 DAA	0-10	0.74	0.14	0.25
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
237 DAA	0-10	0.26	0.09	0.16
	10-20	< LOQ (0.03)	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
237 DAA	0-10	0.11	0.05	n.d.
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.

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Timing	Stratum [cm]	XDE-729 methyl [µg/kg]	XDE-729 acid [µg /kg]	X-757 [µg /kg]
302 DAA	0-10	0.37	0.09	0.22
	10-20	< LOQ (0.03)	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
302 DAA	0-10	0.29	0.10	0.21
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
302 DAA	0-10	0.46	0.16	0.35
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
372 DAA	0-10	0.11	< LOQ (0.04)	0.06
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
372 DAA	0-10	0.09	< LOQ (0.04)	0.05
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
372 DAA	0-10	0.09	< LOQ (0.03)	< LOQ (0.03)
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.

DBA = days before application, DAA: days after application
n.d. = not detectable (below LOD, < 0.017 µg/kg), LOQ = 0.05 µg/kg

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Table B.8.66 Results for UK field dissipation study, spring appln XDE-729 methyl

Timing	Stratum [cm]	XDE-729 methyl [µg/kg]	XDE-729 acid [µg /kg]	X-757 [µg /kg]
0 DBA	0-10	n.d.	n.d.	n.d.
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
0 DBA	0-10	n.d.	n.d.	n.d.
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
0 DBA	0-10	n.d.	n.d.	n.d.
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
0 DAA	0-10	1.46	0.59	< LOQ (0.04)
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
0 DAA	0-10	1.30	0.74	0.06
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
0 DAA	0-10	0.58	0.36	< LOQ (0.02)
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
1 DAA	0-10	2.60	0.16	n.d.
	10-20	< LOQ (0.04) n.d.	2.40 n.d.	n.d. < LOQ (0.02)
	20-30	n.d.	n.d.	n.d.
1 DAA	0-10	5.12	0.28	n.d.
	10-20	n.d.	n.d.	n.d.
	20-30	0.09	n.d.	n.d.
1 DAA	0-10	4.41	0.31	n.d.
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.

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Timing	Stratum [cm]	XDE-729 methyl [µg/kg]	XDE-729 acid [µg /kg]	X-757 [µg /kg]
3 DAA	0-10	3.67	0.47	n.d.
	10-20	n.d.	< LOQ (0.03)	n.d.
	20-30	n.d.	< LOQ (0.03)	n.d.
3 DAA	0-10	1.45	0.20	n.d.
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
3 DAA	0-10	1.50	0.25	n.d.
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
7 DAA	0-10	2.27	0.40	n.d.
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
7 DAA	0-10	2.32	0.50	n.d.
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
7 DAA	0-10	3.55	0.60	n.d.
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
14 DAA	0-10	3.53	0.67	n.d.
	10-20	< LOQ (0.04)	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
14 DAA	0-10	2.01	0.30	n.d.
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
14 DAA	0-10	3.02	0.34	n.d.
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.

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Timing	Stratum [cm]	XDE-729 methyl [µg/kg]	XDE-729 acid [µg /kg]	X-757 [µg /kg]
28 DAA	0-10	2.18	0.48	n.d.
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
28 DAA	0-10	2.68	0.62	< LOQ (0.02)
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
28 DAA	0-10	1.95	0.30	n.d.
	10-20	< LOQ (0.02)	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
62 DAA	0-10	0.64	0.37	< LOQ (0.04)
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
62 DAA	0-10	1.00	0.62	0.05
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
62 DAA	0-10	1.58	0.55	0.07
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.

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Timing	Stratum [cm]	XDE-729 methyl [µg/kg]	XDE-729 acid [µg /kg]	X-757 [µg /kg]
89 DAA	0-10	n.d. 0.55	n.d. 0.76	n.d. 0.11
	10-20	n.d. n.d.	n.d. n.d.	n.d. n.d.
	20-30	n.d. n.d.	n.d. n.d.	n.d. n.d.
89 DAA	0-10	n.d. 1.33	n.d. 0.95	n.d. 0.09
	10-20	n.d. n.d.	n.d. < LOQ (0.02)	n.d. n.d.
	20-30	n.d. n.d.	n.d. n.d.	n.d. n.d.
89 DAA	0-10	n.d. 0.49	n.d. 0.56	n.d. 0.05
	10-20	n.d. n.d.	n.d. n.d.	n.d. n.d.
	20-30	n.d. < LOQ (0.02)	n.d. n.d.	n.d. n.d.
123 DAA	0-10	0.30	0.56	< LOQ (0.04)
	10-20	n.d.	< LOQ (0.04)	n.d.
	20-30	n.d.	n.d.	n.d.
123 DAA	0-10	0.26	0.41	< LOQ (0.04)
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
123 DAA	0-10	0.66	0.82	0.07
	10-20	n.d.	< LOQ (0.02)	n.d.
	20-30	n.d.	n.d.	n.d.

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Timing	Stratum [cm]	XDE-729 methyl [µg/kg]	XDE-729 acid [µg /kg]	X-757 [µg /kg]
183 DAA	0-10	0.24	0.41	< LOQ (0.04)
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
183 DAA	0-10	0.39	0.61	< LOQ (0.04)
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
183 DAA	0-10	0.40	0.57	0.05
	10-20	n.d.	< LOQ (0.03)	n.d.
	20-30	n.d.	n.d.	n.d.
243 DAA	0-10	0.22	0.31	< LOQ (0.03)
	10-20	n.d.	< LOQ (0.02)	n.d.
	20-30	n.d.	n.d.	n.d.
243 DAA	0-10	0.32	0.36	< LOQ (0.04)
	10-20	n.d.	< LOQ (0.02)	n.d.
	20-30	n.d.	n.d.	n.d.
243 DAA	0-10	0.38	0.44	< LOQ (0.04)
	10-20	n.d.	< LOQ (0.02)	n.d.
	20-30	n.d.	n.d.	n.d.
300 DAA	0-10	0.24	0.32	< LOQ (0.04)
	10-20	n.d.	< LOQ (0.04)	n.d.
	20-30	n.d.	n.d.	n.d.
300 DAA	0-10	0.46	0.38	< LOQ (0.04)
	10-20	n.d.	< LOQ (0.03)	n.d.
	20-30	n.d.	n.d.	< LOQ (0.02)
300 DAA	0-10	0.45	0.45	< LOQ (0.03)
	10-20	n.d.	< LOQ (0.03)	n.d.
	20-30	n.d.	n.d.	n.d.

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Timing	Stratum [cm]	XDE-729 methyl [µg/kg]	XDE-729 acid [µg /kg]	X-757 [µg /kg]
372 DAA	0-10	0.43	0.38	< LOQ (0.03)
	10-20	< LOQ (0.02)	< LOQ (0.04)	n.d.
	20-30	n.d.	n.d.	n.d.
372 DAA	0-10	0.31	0.37	< LOQ (0.03)
	10-20	< LOQ (0.02)	< LOQ (0.02)	n.d.
	20-30	n.d.	n.d.	n.d.
372 DAA	0-10	0.38	0.35	< LOQ (0.03)
	10-20	< LOQ (0.02)	< LOQ (0.03)	n.d.
	20-30	n.d.	n.d.	n.d.

DBA = days before application, DAA: days after application
n.d. = not detectable (below LOD, < 0.017 µg/kg), LOQ = 0.05 µg/kg

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Table B.8.67 Results for Spanish field dissipation study, spring appln XDE-729 methyl

Timing	Stratum [cm]	XDE-729 methyl [µg/kg]	XDE-729 acid [µg /kg]	X-757 [µg /kg]
1 DBA	0-10	n.d.	n.d.	n.d.
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
1 DBA	0-10	n.d.	n.d.	n.d.
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
1 DBA	0-10	n.d.	n.d.	n.d.
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
0 DAA	0-10	1.63	2.19	0.75
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
0 DAA	0-10	1.75	3.18	1.01
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
0 DAA	0-10	1.07	1.27	0.39
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
1 DAA	0-10	4.49	0.73	0.10
	10-20	< LOQ (0.02)	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
1 DAA	0-10	3.71	0.79	0.15
	10-20	< LOQ (0.03)	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
1 DAA	0-10	7.14	1.08	0.17
	10-20	< LOQ (0.02)	< LOQ (0.05)	n.d.
	20-30	n.d.	n.d.	n.d.

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Timing	Stratum [cm]	XDE-729 methyl [µg/kg]	XDE-729 acid [µg /kg]	X-757 [µg /kg]
3 DAA	0-10	5.51	0.80	0.13
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
3 DAA	0-10	2.30	0.34	0.06
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
3 DAA	0-10	4.98	0.67	0.10
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
7 DAA	0-10	3.02	0.33	< LOQ (0.03)
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
7 DAA	0-10	4.49	0.86	0.24
	10-20	< LOQ (0.02)	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
7 DAA	0-10	3.56	0.75	0.21
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.

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Timing	Stratum [cm]	XDE-729 methyl [µg/kg]	XDE-729 acid [µg /kg]	X-757 [µg /kg]
14 DAA	0-10	1.64	0.46	0.05
	10-20	0.07	< LOQ (0.03)	n.d.
	20-30	< LOQ (0.03)	n.d.	n.d.
	30-40	< LOQ (0.02)	n.d.	n.d.
14 DAA	0-10	1.85	0.79	0.24
	10-20	0.15	0.06	n.d.
	20-30	< LOQ (0.04)	< LOQ (0.02)	n.d.
	30-40	< LOQ (0.02)	n.d.	n.d.
14 DAA	0-10	1.70	0.42	0.07
	10-20	0.07	< LOQ (0.04)	n.d.
	20-30	< LOQ (0.03)	n.d.	n.d.
	30-40	n.d.	n.d.	n.d.
27 DAA	0-10	2.21	1.01	0.21
	10-20	0.60 0.35	0.27 0.32	0.07 < LOQ (0.02)
	20-30	0.09	< LOQ (0.03)	n.d.
	30-40	n.d.	n.d.	n.d.
27 DAA	0-10	1.77	0.98	0.15
	10-20	0.09	< LOQ (0.04)	n.d.
	20-30	n.d.	n.d.	n.d.
	30-40	n.d.	n.d.	n.d.
27 DAA	0-10	0.69	0.65	0.18
	10-20	n.d.	n.d.	n.d.
	20-30	0.06	< LOQ (0.02)	n.d.
	30-40	n.d.	n.d.	n.d.

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Timing	Stratum [cm]	XDE-729 methyl [µg/kg]	XDE-729 acid [µg /kg]	X-757 [µg /kg]
58 DAA	0-10	0.56	0.54	0.13
	10-20	< LOQ (0.05)	< LOQ (0.04)	n.d.
	20-30	< LOQ (0.03)	n.d.	n.d.
58 DAA	0-10	0.49	0.45	0.10
	10-20	< LOQ (0.03)	< LOQ (0.02)	n.d.
	20-30	n.d.	n.d.	n.d.
58 DAA	0-10	n.d. 0.41	n.d. 0.89	n.d. 0.17
	10-20	< LOQ (0.02)	< LOQ (0.02)	n.d.
	20-30	n.d.	n.d.	n.d.
91 DAA	0-10	< LOQ (0.03)	0.06	n.d.
	10-20	n.d.	< LOQ (0.03)	n.d.
	20-30	n.d.	n.d.	n.d.
91 DAA	0-10	0.19	0.45	0.17
	10-20	n.d.	< LOQ (0.03)	n.d.
	20-30	n.d.	n.d.	n.d.
91 DAA	0-10	0.18	0.56	0.22
	10-20	n.d.	< LOQ (0.03)	n.d.
	20-30	n.d.	n.d.	n.d.
119 DAA	0-10	0.13	0.35	0.14
	10-20	n.d.	< LOQ (0.03)	n.d.
	20-30	n.d.	n.d.	n.d.
119 DAA	0-10	0.14	0.36	0.15
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
119 DAA	0-10	0.17	0.43	0.15
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.

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Timing	Stratum [cm]	XDE-729 methyl [µg/kg]	XDE-729 acid [µg /kg]	X-757 [µg /kg]
181 DAA	0-10	0.07	0.17	0.05
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
181 DAA	0-10	0.07	0.13	< LOQ (0.04)
	10-20	< LOQ (0.02)	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
181 DAA	0-10	0.08	0.15	< LOQ (0.05)
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
240 DAA	0-10	< LOQ (0.04)	0.10	< LOQ (0.03)
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
240 DAA	0-10	0.05	0.12	< LOQ (0.02)
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
240 DAA	0-10	0.06	0.13	< LOQ (0.02)
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
302 DAA	0-10	0.11	0.14	< LOQ (0.04)
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
302 DAA	0-10	0.08	0.23	0.07
	10-20	n.d.	n.d.	< LOQ (0.02)
	20-30	n.d.	n.d.	n.d.
302 DAA	0-10	0.12	0.16	< LOQ (0.05)
	10-20	< LOQ (0.02)	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.

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Timing	Stratum [cm]	XDE-729 methyl [µg/kg]	XDE-729 acid [µg /kg]	X-757 [µg /kg]
363 DAA	0-10	< LOQ (0.04)	< LOQ (0.04)	< LOQ (0.03)
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
363 DAA	0-10	0.09	0.12	< LOQ (0.03)
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
363 DAA	0-10	0.12	0.16	0.04
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.

DBA = days before application, DAA: days after application; n.d. = not detectable (below LOD, < 0.017 µg/kg), LOQ = 0.05 µg/kg

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Table B.8.68 Results for French field dissipation study, spring appln XDE-729 methyl

Timing	Stratum [cm]	XDE-729 methyl [µg/kg]	XDE-729 acid [µg /kg]	X-757 [µg /kg]
0 DBA	0-10	n.d.	n.d.	n.d.
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
0 DBA	0-10	n.d.	n.d.	n.d.
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
0 DBA	0-10	n.d.	n.d.	n.d.
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
0 DAA	0-10	2.51	0.69	0.08
	10-20	< LOQ (0.02)	n.d.	n.d.
	20-30	0.09	< LOQ (0.03)	n.d.
0 DAA	0-10	3.03	0.82	0.06
	10-20	< LOQ (0.02)	n.d.	n.d.
	20-30	< LOQ (0.02)	n.d.	n.d.
0 DAA	0-10	3.14	0.62	< LOQ (0.04)
	10-20	< LOQ (0.03)	n.d.	n.d.
	20-30	0.08	n.d.	n.d.
1 DAA	0-10	1.02	0.13	< LOQ (0.04)
	10-20	n.d.	n.d.	n.d.
	20-30	< LOQ (0.02)	n.d.	n.d.
1 DAA	0-10	2.31	0.19	< LOQ (0.05)
	10-20	< LOQ (0.02)	n.d.	n.d.
	20-30	< LOQ (0.02)	n.d.	n.d.
1 DAA	0-10	2.40	0.45	0.14
	10-20	< LOQ (0.03)	n.d.	n.d.
	20-30	< LOQ (0.03)	n.d.	n.d.

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Timing	Stratum [cm]	XDE-729 methyl [µg/kg]	XDE-729 acid [µg /kg]	X-757 [µg /kg]
3 DAA	0-10	1.31	0.34	0.14
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
3 DAA	0-10	2.17	0.31	0.14
	10-20	< LOQ (0.04)	n.d.	n.d.
	20-30	< LOQ (0.03)	n.d.	n.d.
3 DAA	0-10	4.25	0.89	0.37
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
7 DAA	0-10	1.04	0.29	0.17
	10-20	< LOQ (0.02)	n.d.	n.d.
	20-30	< LOQ (0.02)	n.d.	n.d.
7 DAA	0-10	1.50	0.54	0.22
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
7 DAA	0-10	0.67	0.31	0.15
	10-20	< LOQ (0.04)	< LOQ (0.02)	n.d.
	20-30	n.d.	n.d.	n.d.
15 DAA	0-10	2.07	0.58	0.18
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
15 DAA	0-10	0.81	0.25	0.25
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
15 DAA	0-10	1.83	0.69	0.52
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.

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Timing	Stratum [cm]	XDE-729 methyl [µg/kg]	XDE-729 acid [µg /kg]	X-757 [µg /kg]
28 DAA	0-10	1.45	0.30	0.33
	10-20	< LOQ (0.04)	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
28 DAA	0-10	0.54	0.21	0.27
	10-20	< LOQ (0.03)	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
28 DAA	0-10	1.33	0.27	0.26
	10-20	< LOQ (0.03)	n.d.	n.d.
	20-30	< LOQ (0.02)	n.d.	n.d.
62 DAA	0-10	0.12	< LOQ (0.04)	0.31
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
62 DAA	0-10	0.18	0.07	0.30
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
62 DAA	0-10	0.42	0.11	0.28
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
92 DAA	0-10	0.08	0.05	0.25
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
92 DAA	0-10	0.15	0.07	0.34
	10-20	0.02	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
92 DAA	0-10	0.07	0.06	0.18
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.

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Timing	Stratum [cm]	XDE-729 methyl [µg/kg]	XDE-729 acid [µg /kg]	X-757 [µg /kg]
122 DAA	0-10	< LOQ (0.05)	< LOQ (0.03)	0.11
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
122 DAA	0-10	0.08	< LOQ (0.05)	0.35
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
122 DAA	0-10	0.10	0.07	0.32
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
183 DAA	0-10	0.05	< LOQ (0.03)	0.08
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
183 DAA	0-10	0.05	< LOQ (0.04)	0.12
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
183 DAA	0-10	0.07	< LOQ (0.03)	0.10
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
239 DAA	0-10	< LOQ (0.04)	< LOQ (0.02)	0.06
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
239 DAA	0-10	< LOQ (0.03)	< LOQ (0.02)	0.06
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
239 DAA	0-10	< LOQ (0.05)	< LOQ (0.03)	0.10
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.

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Timing	Stratum [cm]	XDE-729 methyl [µg/kg]	XDE-729 acid [µg /kg]	X-757 [µg /kg]
300 DAA	0-10	< LOQ (0.03)	n.d.	0.07
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	< LOQ (0.02)
300 DAA	0-10	< LOQ (0.04)	< LOQ (0.02)	0.09
	10-20	n.d.	n.d.	< LOQ (0.02)
	20-30	n.d.	n.d.	n.d.
300 DAA	0-10	< LOQ (0.04)	n.d.	0.09
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
364 DAA	0-10	< LOQ (0.04)	n.d.	0.10
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
364 DAA	0-10	< LOQ (0.03)	n.d.	0.04
	10-20	< LOQ (0.03)	< LOQ (0.03)	n.d.
	20-30	n.d.	n.d.	< LOQ (0.02)
364 DAA	0-10	< LOQ (0.03)	n.d.	0.05
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.

DBA = days before application, DAA: days after application; n.d. = not detectable (below LOD, < 0.017 µg/kg), LOQ = 0.05 µg/kg

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Autumn applied study

Properties of the top 30 cm of each of the soils are given below.

Table B.8.69 Properties of field dissipation soils

Trial location:	Dollern, Niedersachsen, **Germany**	Melbourne, Derbyshire, **UK**	Carlet, Valencia**, Spain**	Barry-d'Islemade, Tarn-et-Garonne, **France**
Application date	19/10/2010	15/11/2010	26/10/2010	16/11/2010
% Sand:	73.4	36.1	36.6	57.8
% Silt:	19.4	43.2	35.0	26.2
% Clay:	7.3	20.7	28.5	16.1
USDA classification	Sandy loam	Loam	Clay loam	Sandy loam
pH ($CaCl_2$)	6.34	6.63	7.61	5.25
pH (H_2O)	6.36	6.91	8.49	6.41
CEC [meq/100g]	7.4	12.3	10.6	6.1
OC [%]	1.74	1.5	1.3	0.55
Biomass (mg C/100g):	16.7	31.1	29.4	13.5

Site history of cropping and pesticide use was essentially the same as with the spring applied trials.

Procedural recovery information for the three analytes in soil is given below:
XDE-729 methyl at LOQ of 0.05 µg/kg, 73-119%, mean 97% (n=28), std dev 16%, recovery at 0.1-8 µg/kg 71 – 105%.
X11393729 at LOQ of 0.05 µg/kg 52-154%, mean 88% (n=28; one value of 154% excluded as outlier according to Grubb's test), std dev 14%, recovery at 0.1-8 µg/kg 70-208%, value of 208% excluded, otherwise 70-98%.
X11449757 at LOQ of 0.05 µg/kg 39-105%, mean 72% (n=28), std dev 15%, recovery at 0.1-8 µg/kg 87-98%.

Procedural recoveries were considered generally acceptable for XDE-729 methyl. However, there were a number of instances for X11393729 and X11449757 where procedural recoveries were well outside the normally accepted range of 70-110% for individual recovery values. As stated in the section for the spring-applied study, the applicant quoted the guidance on pre-registration analysis to justify a wider range of recovery as being acceptable for methods with LOQ <0.01 mg/kg. The Applicant collated the residues data with procedural recovery information to indicate where recovery outside the expected range occurred. Overall, the RMS considers that the method is acceptable, particularly for the German, UK and Spanish sites. It is noticeable that the French site experienced particularly low recoveries at 7 DAT for each analyte, for X11449757 at 181 DAT and a very high recovery for a fortification of 8 µg/kg at 233 DAT for X11393729. However, within the context of the study as a whole, it is considered that the results can be accepted.

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Table B.8.70 Field soil residues from spring-applied field dissipation studies with XDE-729 methyl with procedural recovery data (low/high recoveries highlighted)

Germany

	XDE-729 Me			XDE-729 Acid			X-757		
DAT	Residue (ug/kg)	Fort. level (ug/kg)	% Rec	Residue (ug/kg)	Fort. level (ug/kg)	% Rec	Residue (ug/kg)	Fort. level (ug/kg)	% Rec
Pre	0	0.05	78	0	0.05	71	0	0.05	73
0	2.97	1	71	0.35	1	70	0.01	1	93
1	3.78	0.05	118	0.42	0.05	115	0.01	0.05	106
3	1.81	1	105	0.54	1	85	0.03	1	87
7	1.50	0.05	102	0.80	0.05	91	0.06	0.05	73
15	0.85			0.82			0.09		
30	0.48	0.05	96	0.82	0.05	87	0.12	0.05	60
62	0.83			1.39			0.18		
90	0.55	0.05	96	1.18	0.05	83	0.17	0.05	73
118	0.41			1.04			0.17		
178	0.28	0.05	103	1.03	0.05	103	0.17	0.05	105
240	0.07			0.21			0.11		
302	0.11	0.05	105	0.17	0.05	105	0.09	0.05	77
367	0.04			0.10			0.05		

UK

	XDE-729 Me			XDE-729 Acid			X-757		
DAT	Residue (ug/kg)	Fort. level (ug/kg)	% Rec	Residue (ug/kg)	Fort. level (ug/kg)	% Rec	Residue (ug/kg)	Fort. level (ug/kg)	% Rec
Pre	0	0.05	84	0	0.05	95	0	0.05	84
0	4.02			0.42			0.00		
1	4.20	0.05	82	0.42	0.05	81	0.00	0.05	68
3	3.48			0.66			0.00		
7	3.36	0.05	103	1.50	0.05	78	0.05	0.05	67
14	2.03			1.43			0.05		
29	1.55	0.05	101	1.53	0.05	80	0.05	0.05	62
60	1.02			1.47			0.05		
91	0.34	0.05	119	1.12	0.05	110	0.04	0.05	91
122	0.41			1.39			0.05		
180	0.21	0.05	106	1.03	0.05	98	0.08	0.05	86
238	0.12			0.53			0.06		
303	0.09	0.05	93	0.39	0.05	85	0.05	0.05	63
367	0.07			0.36			0.05		

Spain

	XDE-729 Me			XDE-729 Acid			X-757		
DAT	Residue (ug/kg)	Fort. level (ug/kg)	% Rec	Residue (ug/kg)	Fort. level (ug/kg)	% Rec	Residue (ug/kg)	Fort. level (ug/kg)	% Rec
Pre	0	0.05	108	0	0.05	103	0	0.05	72
0	4.89	8	92	0.50			0.01		
1	3.47	0.05	109	0.87	0.05	84	0.06	0.05	71
3	4.15			0.92			0.06		
7	3.38	0.05	84	1.13	0.05	"154"	0.10	0.05	91
14	1.82			0.52			0.05		
29	1.12	0.05	118	0.67	0.05	97	0.06	0.05	67
58	0.68			0.97			0.05		
90	0.56	0.05	106	0.74	0.05	95	0.05	0.05	61
120	0.43			0.60			0.04		
182	0.24	0.05	73	0.42	0.05	69	0.02	0.05	76
240	0.11			0.29			0.02		
301	0.12	0.05	81	0.22	0.05	93	0.01	0.05	57
365	0.06			0.15			0.00		

France

	XDE-729 Me			XDE-729 Acid			X-757		
DAT	Residue (ug/kg)	Fort. level (ug/kg)	% Rec	Residue (ug/kg)	Fort. level (ug/kg)	% Rec	Residue (ug/kg)	Fort. level (ug/kg)	% Rec
Pre	0	0.05	110	0	0.05	90	0	0.05	85
0	2.40	1	100	0.61	1	98	0.03	1	89
1	1.89	0.05	111	0.84	0.05	90	0.05	0.05	60
3	1.35			1.18			0.18		
7	0.43	0.05	58	0.38	0.05	52	0.10	0.05	39
14	0.36			0.43			0.14		
31	0.46	0.05	88	0.76	0.05	77	0.39	0.05	60
57	0.36			0.42			0.36		
90	0.21	0.05	97	0.39	0.05	84	0.35	0.05	76
119	0.09			0.16			0.21		
181	0.05	0.05	75	0.04	0.05	64	0.11	0.05	47
239	0.01	8	94	0.02	8	"208"	0.05	8	98
303	0.00	0.05	115	0.01	0.05	103	0.04	0.05	60
366	0.00			0.01			0.01		

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Procedural recoveries for filter papers analysis (for dose verification) are given below:
XDE-729 methyl at LOQ of 4 µg/kg 101-105%, mean 103% (n=3), std dev 2.1%
X11393729 at LOQ of 4 µg/kg 72-88%, mean 82% (n=3), std dev 8.5%
X11449757 at LOQ of 4 µg/kg 70-82%, mean 75% (n=3), std dev 6.4%

As with the spring applied study, sample storage was routinely well over 1 year from sampling to analysis. As stated previously for the spring applied study, at the time of writing, an interim study has demonstrated stability of stored frozen residues for 12 months. The final study is intended to address frozen storage stability for 24 months.

Results of the petri dish residues to verify application dose are presented below.

Table B.8.71 Petri dish residues in XDE-729 methyl field dissipation studies, autumn application

XDE-729 methyl (µg/sample)	X11393729 (µg/kg)	X11449757 (µg/kg)
Germany		
5	n.d.	n.d.
6	n.d.	n.d.
5	n.d.	n.d.
6	n.d.	n.d.
5	n.d.	n.d.
UK		
<LOQ (3.0)	n.d.	n.d.
7	n.d.	n.d.
5	n.d.	n.d.
4	n.d.	n.d.
4	n.d.	n.d.
Spain		
7	n.d.	n.d.
6	n.d.	n.d.
6	n.d.	n.d.
8	n.d.	n.d.
<LOQ (3.0)	n.d.	n.d.
France		
<LOQ (3.8)	n.d.	n.d.
<LOQ (3.1)	n.d.	n.d.
6	n.d.	n.d.
6	n.d.	n.d.
<LOQ (3.0)	n.d.	n.d.

n.d. = not detectable (<LOD, i.e. <1.2 µg/sample); LOQ = 4 µg/sample

Residues results for the autumn-applied sites are provided below.

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Table B.8.72 Results for German field dissipation study, autumn appln XDE-729 methyl

Timing	Stratum [cm]	XDE-729 methyl [µg/kg]	XDE-729 acid [µg /kg]	X-757 [µg /kg]
1 DBA	0-10	n.d.	n.d.	< LOQ (0.04)
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
1 DBA	0-10	n.d.	n.d.	n.d.
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
1 DBA	0-10	n.d.	n.d.	n.d.
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
0 DAA	0-10	1.91	0.24	n.d.
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
0 DAA	0-10	2.99	0.34	n.d.
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
0 DAA	0-10	4.02	0.44	n.d.
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	< LOQ (0.03)	< LOQ (0.03)
1 DAA	0-10	5.43	0.65	< LOQ (0.02)
	10-20	n.d.	n.d.	n.d.
	20-30	< LOQ (0.04)	n.d.	n.d.
1 DAA	0-10	2.65	0.29	n.d.
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
1 DAA	0-10	3.22	0.33	n.d.
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.

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Timing	Stratum [cm]	XDE-729 methyl [µg/kg]	XDE-729 acid [µg /kg]	X-757 [µg /kg]
3 DAA	0-10	1.83	0.60	< LOQ (0.03)
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
3 DAA	0-10	1.46	0.46	< LOQ (0.02)
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
3 DAA	0-10	2.14	0.56	< LOQ (0.04)
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
7 DAA	0-10	1.32	0.82	0.07
	10-20	< LOQ (0.03)	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
7 DAA	0-10	1.75	0.95	0.07
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
7 DAA	0-10	1.40	0.64	< LOQ (0.05)
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
15 DAA	0-10	1.27	1.32	0.15
	10-20	0.07	0.06	n.d.
	20-30	n.d.	n.d.	n.d.
15 DAA	0-10	0.86	0.74	0.08
	10-20	0.09	< LOQ (0.05)	n.d.
	20-30	n.d.	n.d.	n.d.
15 DAA	0-10	0.25	0.28	< LOQ (0.03)
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.

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Timing	Stratum [cm]	XDE-729 methyl [µg/kg]	XDE-729 acid [µg /kg]	X-757 [µg /kg]
30 DAA	0-10	1.00	1.49	0.15
	10-20	n.d.	n.d.	< LOQ (0.02)
	20-30	n.d.	n.d.	n.d.
30 DAA	0-10	0.29	0.61	0.09
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
30 DAA	0-10	0.14	0.35	0.07
	10-20	n.d.	n.d.	< LOQ (0.02)
	20-30	n.d.	n.d.	n.d.
62 DAA	0-10	1.17	1.59	0.13
	10-20	n.d.	0.07	< LOQ (0.02)
	20-30	n.d.	< LOQ (0.03)	< LOQ (0.02)
62 DAA	0-10	0.63	0.99	0.12
	10-20	n.d.	< LOQ (0.03)	< LOQ (0.02)
	20-30	n.d.	< LOQ (0.03)	< LOQ (0.02)
62 DAA	0-10	0.70	1.44	0.20
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
90 DAA	0-10	0.65	1.56	0.19
	10-20	n.d.	< LOQ (0.03)	n.d.
	20-30	n.d. (0.12[1])	n.d.	n.d.
90 DAA	0-10	0.28	0.76	0.13
	10-20	n.d.	< LOQ (0.02)	n.d.
	20-30	n.d.	n.d.	n.d.
90 DAA	0-10	0.72	1.13	0.20
	10-20	n.d.	< LOQ (0.03)	n.d.
	20-30	n.d.	n.d.	n.d.

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Timing	Stratum [cm]	XDE-729 methyl [µg/kg]	XDE-729 acid [µg /kg]	X-757 [µg /kg]
118 DAA	0-10	0.56	1.07	0.12
	10-20	n.d.	0.17	< LOQ (0.03)
	20-30	n.d. (<LOQ, 0.02[1])	< LOQ (0.04) (0.07[1])	n.d.
118 DAA	0-10	0.33	0.76	0.15
	10-20	< LOQ (0.03)	0.09	< LOQ (0.02)
	20-30	n.d.	n.d.	n.d.
118 DAA	0-10	0.32	0.89	0.19
	10-20	n.d.	0.09	n.d.
	20-30	n.d.	n.d.	n.d.
178 DAA	0-10	0.28	1.06	0.15
	10-20	n.d.	0.14	n.d.
	20-30	n.d.	< LOQ (0.04)	n.d.
178 DAA	0-10	0.32	0.82	0.14
	10-20	n.d.	0.06	n.d.
	20-30	n.d.	n.d.	n.d.
178 DAA	0-10	0.24	0.87	0.21
	10-20	n.d.	0.08	n.d.
	20-30	n.d.	< LOQ (0.02)	n.d.
240 DAA	0-10	0.08	0.09	0.05
	10-20	n.d.	0.10	< LOQ (0.04)
	20-30	n.d.	n.d.	n.d.
240 DAA	0-10	0.07	0.19	0.10
	10-20	n.d.	< LOQ (0.04)	< LOQ (0.02)
	20-30	n.d.	< LOQ (0.03)	< LOQ (0.02)
240 DAA	0-10	0.05	0.12	0.08
	10-20	n.d.	< LOQ (0.05)	< LOQ (0.03)
	20-30	n.d.	n.d.	n.d.

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Timing	Stratum [cm]	XDE-729 methyl [µg/kg]	XDE-729 acid [µg /kg]	X-757 [µg /kg]
302 DAA	0-10	0.07	0.18	0.06
	10-20	n.d.	< LOQ (0.02)	n.d.
	20-30	n.d.	n.d.	n.d.
302 DAA	0-10	0.14	0.18	0.09
	10-20	n.d.	n.d.	< LOQ (0.02)
	20-30	n.d.	n.d.	n.d.
302 DAA	0-10	0.10	0.11	0.07
	10-20	< LOQ (0.02)	< LOQ (0.03)	< LOQ (0.02)
	20-30	n.d.	n.d.	n.d.
367 DAA	0-10	< LOQ (0.05)	0.12	< LOQ (0.04)
	10-20	n.d.	n.d.	< LOQ (0.02)
	20-30	n.d.	n.d.	n.d.
367 DAA	0-10	< LOQ (0.03)	0.08	< LOQ (0.03)
	10-20	n.d.	< LOQ (0.02)	n.d.
	20-30	n.d.	n.d.	n.d.
367 DAA	0-10	< LOQ (0.03)	0.09	< LOQ (0.04)
	10-20	n.d.	n.d.	< LOQ (0.02)
	20-30	n.d.	n.d.	n.d.

DBA = days before application, DAA: days after application;
n.d. = not detectable (below LOD, < 0.017 µg/kg), LOQ = 0.05 µg/kg
[1] Apparently anomalous result, re-analysed and found to be not detectable

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Table B.8.73 Results for UK field dissipation study, autumn appln XDE-729 methyl

Timing	Stratum [cm]	XDE-729 methyl [µg/kg]	XDE-729 acid [µg /kg]	X-757 [µg /kg]
0 DBA	0-10	n.d.	n.d.	n.d.
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
0 DBA	0-10	n.d.	n.d.	n.d.
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
0 DBA	0-10	n.d.	n.d.	n.d.
	10-20	n.d.	n.d.	< LOQ (0.02)
	20-30	n.d.	n.d.	n.d.
0 DAA	0-10	2.26	0.29	n.d.
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
0 DAA	0-10	5.88	0.50	n.d.
	10-20	n.d.	n.d.	n.d.
	20-30	< LOQ (0.02)	n.d.	n.d.
0 DAA	0-10	3.89	0.46	n.d.
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
1 DAA	0-10	3.02	0.33	n.d.
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
1 DAA	0-10	2.35	0.23	n.d.
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
1 DAA	0-10	7.21	0.71	n.d.
	10-20	< LOQ (0.02)	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.

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Timing	Stratum [cm]	XDE-729 methyl [µg/kg]	XDE-729 acid [µg /kg]	X-757 [µg /kg]
3 DAA	0-10	2.57	0.56	n.d.
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
3 DAA	0-10	2.51	0.51	n.d.
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
3 DAA	0-10	5.35	0.90	n.d.
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
7 DAA	0-10	4.15	1.93	0.05
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
7 DAA	0-10	3.80	1.47	< LOQ (0.05)
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
7 DAA	0-10	2.14	1.09	< LOQ (0.04)
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
14 DAA	0-10	2.42	1.65	0.06
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
14 DAA	0-10	2.64	1.72	0.05
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
14 DAA	0-10	1.04	0.93	< LOQ (0.03)
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.

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Timing	Stratum [cm]	XDE-729 methyl [µg/kg]	XDE-729 acid [µg /kg]	X-757 [µg /kg]
29 DAA	0-10	1.35	1.64	0.05
	10-20	n.d.	< LOQ (0.03)	n.d.
	20-30	n.d.	n.d.	n.d.
29 DAA	0-10	1.64	1.53	< LOQ (0.05)
	10-20	0.07	0.08	n.d.
	20-30	n.d.	n.d.	n.d.
29 DAA	0-10	1.59	1.30	0.05
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
60 DAA	0-10	1.21	1.53	0.05
	10-20	n.d.	< LOQ (0.04)	n.d.
	20-30	n.d.	n.d.	n.d.
60 DAA	0-10	0.86	1.46	< LOQ (0.05)
	10-20	< LOQ (0.02)	0.07	n.d.
	20-30	n.d.	n.d.	n.d.
60 DAA	0-10	0.94	1.26	< LOQ (0.05)
	10-20	< LOQ (0.02)	0.06	n.d.
	20-30	n.d.	n.d.	n.d.
91 DAA	0-10	0.34	1.03	< LOQ (0.04)
	10-20	n.d.	0.05	n.d.
	20-30	n.d.	< LOQ (0.02)	n.d.
91 DAA	0-10	0.25	1.24	< LOQ (0.04)
	10-20	n.d.	0.06	n.d.
	20-30	n.d.	n.d.	n.d.
91 DAA	0-10	0.43	0.96	< LOQ (0.04)
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.

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Timing	Stratum [cm]	XDE-729 methyl [µg/kg]	XDE-729 acid [µg /kg]	X-757 [µg /kg]
122 DAA	0-10	0.39	1.27	< LOQ (0.04)
	10-20	n.d.	0.09	n.d.
	20-30	n.d.	< LOQ (0.02)	n.d.
122 DAA	0-10	0.29	1.24	< LOQ (0.05)
	10-20	n.d.	0.10	n.d.
	20-30	n.d.	n.d.	n.d.
122 DAA	0-10	0.56	1.39	< LOQ (0.05)
	10-20	n.d.	0.07	< LOQ (0.02)
	20-30	n.d.	n.d.	n.d.
180 DAA	0-10	0.23	1.36	0.06
	10-20	n.d.	< LOQ (0.05)	n.d.
	20-30	n.d.	n.d.	n.d.
180 DAA	0-10	0.15	0.69	0.05
	10-20	n.d.	< LOQ (0.05)	n.d.
	20-30	n.d.	n.d.	n.d.
180 DAA	0-10	0.24	0.93	0.07
	10-20	n.d.	n.d.	< LOQ (0.04)
	20-30	n.d.	n.d.	< LOQ (0.03)
238 DAA	0-10	0.10	0.55	0.06
	10-20	n.d.	< LOQ (0.04)	n.d.
	20-30	n.d.	n.d.	n.d.
238 DAA	0-10	0.14	0.54	0.05
	10-20	n.d.	< LOQ (0.03)	n.d.
	20-30	n.d.	n.d.	n.d.
238 DAA	0-10	0.11	0.46	0.08
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.

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Timing	Stratum [cm]	XDE-729 methyl [µg/kg]	XDE-729 acid [µg /kg]	X-757 [µg /kg]
303 DAA	0-10	0.12	0.62	< LOQ (0.04)
	10-20	n.d.	< LOQ (0.03)	n.d.
	20-30	n.d.	n.d.	n.d.
303 DAA	0-10	0.09	0.26	0.05
	10-20	n.d.	< LOQ (0.02)	< LOQ (0.02)
	20-30	n.d.	n.d.	n.d.
303 DAA	0-10	0.07	0.23	0.03
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
367 DAA	0-10	0.10	0.64	< LOQ (0.04)
	10-20	n.d.	< LOQ (0.03)	< LOQ (0.02)
	20-30	n.d.	n.d.	< LOQ (0.02)
367 DAA	0-10	< LOQ (0.05)	0.17	< LOQ (0.04)
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
367 DAA	0-10	< LOQ (0.05)	0.24	< LOQ (0.03)
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.

DBA = days before application, DAA: days after application
n.d. = not detectable (below LOD, ca. 0.017 µg/kg), LOQ = 0.05 µg/kg

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Table B.8.74 Results for Spanish field dissipation study, autumn appln XDE-729 methyl

Timing	Stratum [cm]	XDE-729 methyl [µg/kg]	XDE-729 acid [µg /kg]	X-757 [µg /kg]
1 DBA	0-10	n.d.	n.d.	n.d.
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
1 DBA	0-10	n.d.	n.d.	n.d.
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
1 DBA	0-10	n.d.	n.d.	n.d.
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
0 DAA	0-10	5.99	0.45	n.d.
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
0 DAA	0-10	4.59	0.71	0.03
	10-20	< LOQ (0.03)	n.d.	n.d.
	20-30	< LOQ (0.04)	n.d.	n.d.
0 DAA	0-10	4.00	0.34	n.d.
	10-20	n.d.	n.d.	n.d.
	20-30	< LOQ (0.02)	n.d.	n.d.
1 DAA	0-10	3.09	0.79	0.06
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
1 DAA	0-10	3.15	0.99	0.06
	10-20	< LOQ (0.03)	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
1 DAA	0-10	4.07	0.82	0.06
	10-20	< LOQ (0.03)	n.d.	n.d.
	20-30	< LOQ (0.03)	n.d.	n.d.

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Timing	Stratum [cm]	XDE-729 methyl [µg/kg]	XDE-729 acid [µg /kg]	X-757 [µg /kg]
3 DAA	0-10	3.67	0.76	0.04
	10-20	n.d.	n.d.	n.d.
	20-30	< LOQ (0.03)	n.d.	n.d.
3 DAA	0-10	4.68	1.10	0.07
	10-20	< LOQ (0.04)	n.d.	n.d.
	20-30	< LOQ (0.03)	n.d.	n.d.
3 DAA	0-10	3.96	0.90	0.06
	10-20	< LOQ (0.02)	n.d.	n.d.
	20-30	< LOQ (0.02)	n.d.	n.d.
7 DAA	0-10	3.53	0.90	0.08
	10-20	n.d.	n.d.	n.d.
	20-30	< LOQ (0.02)	n.d.	n.d.
7 DAA	0-10	4.20	1.33	0.10
	10-20	n.d.	n.d.	< LOQ (0.02)
	20-30	< LOQ (0.02)	n.d.	< LOQ (0.02)
7 DAA	0-10	2.36	1.15	0.05
	10-20	n.d.	n.d.	< LOQ (0.02)
	20-30	< LOQ (0.02)	n.d.	n.d.
14 DAA	0-10	1.87	0.43	0.06
	10-20	< LOQ (0.04)	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
14 DAA	0-10	1.76	0.61	< LOQ (0.03)
	10-20	0.08	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
14 DAA	0-10	1.68	0.51	0.05
	10-20	< LOQ (0.03)	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.

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Timing	Stratum [cm]	XDE-729 methyl [µg/kg]	XDE-729 acid [µg /kg]	X-757 [µg /kg]
29 DAA	0-10	1.02	0.51	< LOQ (0.04)
	10-20	< LOQ (0.04)	< LOQ (0.02)	n.d.
	20-30	n.d.	n.d.	n.d.
29 DAA	0-10	0.99	0.70	0.06
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
29 DAA	0-10	1.25	0.75	0.07
	10-20	0.07	< LOQ (0.04)	n.d.
	20-30	n.d.	n.d.	n.d.
58 DAA	0-10	0.92	0.98	< LOQ (0.04)
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
58 DAA	0-10	0.48	0.88	0.06
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
58 DAA	0-10	0.65	1.04	0.06
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
90 DAA	0-10	0.50	0.70	< LOQ (0.04)
	10-20	< LOQ (0.03)	< LOQ (0.03)	n.d.
	20-30	n.d.	n.d.	n.d.
90 DAA	0-10	0.71	0.91	0.08
	10-20	< LOQ (0.02)	< LOQ (0.02)	n.d.
	20-30	< LOQ (0.02)	n.d.	n.d.
90 DAA	0-10	0.37	0.57	< LOQ (0.04)
	10-20	< LOQ (0.02)	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.

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Timing	Stratum [cm]	XDE-729 methyl [µg/kg]	XDE-729 acid [µg /kg]	X-757 [µg /kg]
120 DAA	0-10	0.73	0.64	< LOQ (0.03)
	10-20	< LOQ (0.03)	< LOQ (0.02)	n.d.
	20-30	n.d.	n.d.	n.d.
120 DAA	0-10	0.32	0.53	< LOQ (0.04)
	10-20	< LOQ (0.02)	< LOQ (0.03)	n.d.
	20-30	n.d.	n.d.	n.d.
120 DAA	0-10	0.20	0.59	< LOQ (0.04)
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
182 DAA	0-10	0.53	0.78	< LOQ (0.02)
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
182 DAA	0-10	0.07	0.30	< LOQ (0.02)
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
182 DAA	0-10	0.12	0.19	< LOQ (0.02)
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
240 DAA	0-10	0.16	0.60	< LOQ (0.02)
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
240 DAA	0-10	0.09	0.14	< LOQ (0.03)
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
240 DAA	0-10	0.07	0.13	< LOQ (0.02)
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.

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Timing	Stratum [cm]	XDE-729 methyl [µg/kg]	XDE-729 acid [µg /kg]	X-757 [µg /kg]
301 DAA	0-10	0.13	0.35	< LOQ (0.04)
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
301 DAA	0-10	0.20	0.20	n.d.
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
301 DAA	0-10	< LOQ (0.02)	0.11	n.d.
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
365 DAA	0-10	< LOQ (0.03)	0.07	n.d.
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
365 DAA	0-10	< LOQ (0.04)	0.16	n.d.
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
365 DAA	0-10	0.10	0.21	n.d.
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.

DBA = days before application, DAA: days after application
n.d. = not detectable (below LOD, < 0.017 µg/kg), LOQ = 0.05 µg/kg

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Table B.8.75 Results for French field dissipation study, autumn appln XDE-729 methyl

Timing	Stratum [cm]	XDE-729 methyl [µg/kg]	XDE-729 acid [µg /kg]	X-757 [µg /kg]
1 DBA	0-10	n.d.	n.d.	n.d.
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
1 DBA	0-10	n.d.	n.d.	n.d.
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
1 DBA	0-10	n.d.	n.d.	n.d.
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
0 DAA	0-10	2.76	0.42	< LOQ (0.02)
	10-20	n.d.	0.06	n.d.
	20-30	n.d.	n.d.	n.d.
0 DAA	0-10	2.07	0.32	n.d.
	10-20	0.10	< LOQ (0.02)	n.d.
	20-30	n.d.	n.d.	n.d.
0 DAA	0-10	1.95	0.92	0.06
	10-20	0.11	< LOQ (0.05)	n.d.
	20-30	0.22 (0.19[1])	< LOQ (0.04)	n.d.
1 DAA	0-10	1.86	0.59	0.04
	10-20	0.05	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
1 DAA	0-10	1.71	1.22	0.06
	10-20	0.08	n.d.	n.d.
	20-30	0.06 (0.09[1])	< LOQ (0.03)	n.d.
1 DAA	0-10	1.91	0.69	0.04
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.

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Timing	Stratum [cm]	XDE-729 methyl [µg/kg]	XDE-729 acid [µg /kg]	X-757 [µg /kg]
3 DAA	0-10	1.70	1.18	0.17
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
3 DAA	0-10	1.44	0.90	0.16
	10-20	n.d.	n.d.	n.d.
	20-30	< LOQ (0.04)	< LOQ (0.02)	n.d.
3 DAA	0-10	0.86	1.43	0.20
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
7 DAA	0-10	0.58	0.32	0.10
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
7 DAA	0-10	0.41	0.33	0.08
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
7 DAA	0-10	0.31	0.48	0.13
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
14 DAA	0-10	0.55	0.27	0.14
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
14 DAA	0-10	0.38	0.49	0.16
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
14 DAA	0-10	0.16	0.53	0.13
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.

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Timing	Stratum [cm]	XDE-729 methyl [µg/kg]	XDE-729 acid [µg /kg]	X-757 [µg /kg]
31 DAA	0-10	0.45	0.60	0.39
	10-20	n.d.	0.08	< LOQ (0.03)
	20-30	n.d.	0.07 (0.06[1])	n.d. (<LOQ, 0.03[1])
31 DAA	0-10	0.61	0.87	0.40
	10-20	n.d.	< LOQ (0.03)	n.d.
	20-30	n.d.	< LOQ (0.02)	n.d.
31 DAA	0-10	0.33	0.59	0.33
	10-20	n.d.	< LOQ (0.02)	n.d.
	20-30	n.d.	n.d.	n.d.
57 DAA	0-10	0.66	0.47	0.48
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
57 DAA	0-10	0.23	0.40	0.31
	10-20	n.d.	n.d.	< LOQ (0.02)
	20-30	n.d.	n.d.	n.d.
57 DAA	0-10	0.20	0.38	0.27
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
90 DAA	0-10	0.32	0.47	0.43
	10-20	< LOQ (0.02)	0.07	0.05
	20-30	n.d.	< LOQ (0.02)	< LOQ (0.03)
90 DAA	0-10	0.16	0.32	0.27
	10-20	n.d.	0.02	n.d.
	20-30	n.d.	n.d.	< LOQ (0.02)
90 DAA	0-10	0.13	0.26	0.25
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.

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Timing	Stratum [cm]	XDE-729 methyl [µg/kg]	XDE-729 acid [µg /kg]	X-757 [µg /kg]
119 DAA	0-10	0.13	0.19	0.28
	10-20	n.d.	n.d.	< LOQ (0.03)
	20-30	n.d.	n.d.	< LOQ (0.02)
119 DAA	0-10	0.06	0.12	0.12
	10-20	n.d.	< LOQ (0.02)	< LOQ (0.03)
	20-30	n.d.	n.d.	n.d.
119 DAA	0-10	0.07	0.15	0.15
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
181 DAA	0-10	0.07	< LOQ (0.04)	0.18
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	< LOQ (0.02)
181 DAA	0-10	0.06	0.05	0.07
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
181 DAA	0-10	< LOQ (0.02)	< LOQ (0.02)	0.07
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
239 DAA	0-10	< LOQ (0.02)	< LOQ (0.02)	< LOQ (0.04)
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
239 DAA	0-10	n.d.	< LOQ (0.02)	0.06
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
239 DAA	0-10	< LOQ (0.02)	< LOQ (0.02)	0.06
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.

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Timing	Stratum [cm]	XDE-729 methyl [µg/kg]	XDE-729 acid [µg /kg]	X-757 [µg /kg]
303 DAA	0-10	n.d.	< LOQ (0.02)	0.06
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
303 DAA	0-10	n.d.	n.d.	n.d.
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
303 DAA	0-10	n.d.	n.d.	0.05
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
366 DAA	0-10	n.d.	< LOQ (0.02)	< LOQ (0.03)
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
366 DAA	0-10	n.d.	n.d.	n.d.
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.
366 DAA	0-10	n.d.	n.d.	n.d.
	10-20	n.d.	n.d.	n.d.
	20-30	n.d.	n.d.	n.d.

DBA = days before application, DAA = days after application; n.d. = not detectable (below LOD, < 0.017 µg/kg), LOQ = 0.05 µg/kg [1] = original result, subsequently re-analysed

The RMS has calculated maximum observed molar formation for both metabolites in all these studies. The peak residues of parent have been used in these calculations, and in some cases this does not occur at time 0. Given that reasonable amounts of metabolites were seen even at the first sampling time, the peak residue of parent has been calculated by adding all the analytes together at the sample time where the peak occurs; the metabolite residues were corrected for molecular weight difference before adding to parent residue. In some cases, the peak was not calculated to be measured until 1 day after treatment, but in one case, the peak was calculated to be measured at 7 days after application.

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Table B.8.76 Average peak calculated concentrations of XDE-729 methyl and maximum observed molar formation of metabolites X11393729 and X11449757.

Site	Peak concentration of parent (DAT)	Molar observed formation of X11393729 (%, DAT)	Molar observed formation of X11449757 (%, DAT)
Germany Spring	3.51 µg/kg (0 DAT)	6.5% (13 DAT)	9.9% (91 DAT)
UK Spring	4.34 µg/kg (1 DAT)	18.3% (89 DAT)	2.0% (89 DAT)
Spain Spring	6.21 µg/kg (1 DAT)	37.1% (0 DAT); 17.1% (27 DAT)	12.6% (0 DAT); 3.3% (27 DAT)
France Spring	3.79 µg/kg (0 DAT)	14.0% (3 & 15 DAT)	9.2% (15 DAT)
Germany Autumn	4.23 µg/kg (1 DAT)	34.3% (62 DAT)	4.6% (62 DAT)
UK Autumn	4.97 µg/kg (7 DAT)	32.1% (29 DAT)	1.8% (180 DAT)
Spain Autumn	5.42 µg/kg (0 DAT)	21.7% (7 DAT)	2.0% (7 DAT)
France Autumn	3.07 µg/kg (0 DAT)	40.1% (3 DAT)	13.8% (31 DAT)

The RMS notes that the apparent maximum formation of X11393729 appears to be lower in the field studies than in the laboratory under aerobic conditions (maximum formation in lab 38.2 – 72.7% AR at 3 – 7 DAT). The maximum formation of X11449757 appears to be often within the range of that seen in the laboratory (2.7 – 17.4% AR at 3-14 DAT). It is also noticeable that the time of maximum observed formation is later in the field than in the lab. The RMS considers that this may be due to the apparently slower degradation/dissipation of XDE-729 methyl in the field compared to laboratory conditions.

(Kellner 2012 a & b)

b) A kinetic assessment was conducted on the results of the field dissipation studies to obtain persistence values for comparison against regulatory triggers and to potentially obtain degradation parameters suitable for use in exposure modelling.

The results of the field dissipation studies suggested that there was essentially minimal or no movement of residues of parent, X11393729 and X11449757 below the 30 cm soil layer. For this reason, the residues from the top 30cm layer at each sample time were combined to give a total residue at that sample time.

The study author initially considered that the residues of X11449757 were too low to generate meaningful results and were therefore excluded from kinetic analysis. However, the RMS notes that in terms of molar observed formation, the levels were greater than 5% at three sites and approaching 5% in one other. RMS experience suggests that kinetic assessments are often attempted for metabolites at such relatively low levels, although it recognised that with such low residues the statistical assessments often suggest relatively high uncertainty over optimised parameters. After discussion with the Applicant, X11449757 was included in kinetic assessment of normalised data.

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It was noted that in all cases, there were residues of metabolite X11393729 present at the day 0 sample time (and of X11449757 in some trials), suggesting that degradation of the parent had already occurred. Therefore, day 0 metabolite concentrations were added back to the parent residue levels.

For the assessment of un-normalised data, it was noted by the RMS that in attempting to comply with FOCUS Degradation Kinetics advice on treatment of day 0 residues, i.e. adding any metabolite residues at day zero to the parent concentration, the study author had neglected to account for the fact that as the residues of all analytes are measured in mg/kg, the metabolite residues have to be corrected for molecular weight difference from the parent substance. In most cases, the difference in residues before and after molecular weight correction are not that different. In addition, the effect of having a higher initial parent residue is generally to lead to a steeper initial curve which generally leads to a faster degradation rate. Thus, in this case, the slightly lower initial parent residue is expected to lead to a slower degradation rate for the parent.

For kinetic calculations using normalised data, the metabolite residues were corrected for molecular weight differences, this being appropriate as the FOCUS exposure models which will use the kinetic parameters expressly take into account molecular weight differences between parent and metabolites.

Dissipation rates for parent were calculated at ambient temperatures; dissipation rates were also attempted to be calculated for metabolite X11393729. Temperature and moisture correction was also performed to obtain field degradation rates adjusted to 20ºC and pF2 for the purpose of input parameters for environmental exposure modelling and comparison to the laboratory derived degradation rates. Soil temperature and moisture data, both from 10cm depth, were available from the sites at daily resolution. Some 'gaps' in soil temperature data (up to 11 days in one instance) were noted, and a surrogate temperature was interpolated for the period of no data by reference to the temperatures before and after the data gap. As these instances were not common, the RMS considers that this procedure was acceptable and unlikely to have a major influence on the outcome of the kinetic calculations. A Q10 of 2.58 was used for temperature correction purposes, and the Walker exponent (B) was set to 0.7 for moisture normalisation purposes. Whilst measured moisture content data were available, there was no measurement of moisture content at pF2 for the field sites. Therefore the default soil moisture contents at pF2 as given in FOCUS Groundwater Guidance were used to calculate the difference in measured and reference soil moisture.

Details of temperature and moisture corrected day lengths are given below.

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Table B.8.77 Temperature and moisture corrected day lengths for German field site

Spring			Autumn		
Actual DAT	**Temp. Corrected**	**Temp + Moist Corrected**	**Actual DAT**	**Temp. Corrected**	**Temp + Moist Corrected**
1	0.5	0.5	1	0.4	0.4
3	1.5	1.5	3	1.1	1.1
7	3.1	3.1	7	2.4	2.4
13	5.3	5.3	15	5.3	5.3
29	13	13	30	10	10
60	32	30	62	17	17
91	61	54	90	22	22
123	83	75	118	28	28
182	112	104	178	42	42
237	126	119	240	74	71
302	139	131	302	114	104
372	160	152	367	155	145

Table B.8.78 Temperature and moisture corrected day lengths for UK field site

Spring			Autumn		
Actual DAT	**Temp. Corrected**	**Temp + Moist Corrected**	**Actual DAT**	**Temp. Corrected**	**Temp + Moist Corrected**
1	0.4	0.3	1	0.2	0.2
3	1.1	0.9	3	0.6	0.6
7	2.5	2.1	7	1.7	1.7
14	5.9	4.4	14	3.1	3.1
28	14	12	29	6	6
62	38	30	60	11	11
89	59	48	91	18	18
123	82	65	122	26	26
183	110	92	180	51	49
243	122	103	238	87	78
300	135	118	303	133	115
372	164	143	367	163	140

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Table B.8.79 Temperature and moisture corrected day lengths for Spanish field site

Spring			Autumn		
Actual DAT	Temp. Corrected	Temp + Moist Corrected	Actual DAT	Temp. Corrected	Temp + Moist Corrected
1	0.5	0.4	1	0.8	0.8
3	1.4	1.1	3	2.3	2.2
7	3.6	3.0	7	5.3	5.3
14	8.1	6.8	14	11	11
27	18	16	29	20	20
58	50	43	58	35	34
91	88	73	90	50	49
119	114	98	120	63	62
181	157	138	182	113	102
240	186	167	240	191	134
302	218	197	301	334	181
363	277	239	365	442	225

Table B.8.80 Temperature and moisture corrected day lengths for French field site

Spring			Autumn		
Actual DAT	Temp. Corrected	Temp + Moist Corrected	Actual DAT	Temp. Corrected	Temp + Moist Corrected
1	1.0	0.7	1	0.4	0.4
3	2.2	1.7	3	1.0	1.0
7	4.3	3.3	7	2.4	2.4
15	12	8.4	14	4.1	4.1
28	26	18	31	8.0	8.0
62	70	53	57	14	14
92	114	89	90	22	22
122	155	121	119	32	32
183	195	154	181	76	71
239	210	167	239	150	145
300	227	183	303	241	235
364	268	210	366	292	282

For the normalised kinetic calculations, the actual sample times were replaced by the normalised sample times. Kinetic optimisations for un-normalised data were performed using KinGUI v 1.1; kinetic optimisation on normalised data were conducted using the software CAKE v 1.4.

It is noted by the RMS that in order to normalise field dissipation data to standard laboratory conditions, i.e. to use the kinetic endpoints as modelling input parameters, the impact of other dissipation losses on the results except bulk soil matrix degradation must be excluded. This includes processes such as volatilisation, plant uptake, soil photolysis and leaching. FOCUS Degradation Kinetics Guidance provides a checklist to help determine whether such losses can be excluded and whether the study results can be subject to normalisation procedures. The Applicant performed these checks in relation to plant uptake, volatilisation and leaching. In relation to all three analytes in the study, it is noted that they are relatively soluble with vapour pressures of 10^{-5} Pa or

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lower at 20ºC and thus would not be expected to be particularly volatile. The studies used bare soil plots, thus plant uptake would not be expected to be an issue.

In relation to leaching, the applicant indicated the following,

"Out of a total of 312 samples (8 trials x 13 time points x 3 replicates), there were only eight samples which gave residues above the LOQ of 0.05 µg/kg in the bottom layer. All but one of these were due to detections of parent XDE-729 Methyl in the Day 0 or Day 1 samples, which is most likely due to some minor contamination of the lower horizon ("smearing") which is very common for the early sample timings of TFD studies. The only other quantifiable residue was a low detection of XDE-729 Acid (0.07 µg equiv./kg) just above the LOQ in one of the Day 30 samples from the France, Autumn trial. Note that the initial residues in soil immediately after application were generally in the range of 3-5 µg/kg, therefore the LOQ represents only about 1% of the total residue after application. Overall, it can be concluded that XDE-729 Methyl or its metabolites are unlikely to have leached below the lowest horizon that was analysed."

The RMS has scrutinised the results of the field dissipation studies for residues in the deepest analysed layer. In the majority of cases, the lowest analysed depth was 20-30cm, but in the Spain Spring applied study, analysis was conducted on the 30-40cm layer at two sample times, 14 and 27 DAA. In the majority of cases, residues in the lowest analysed layer were <LOQ. In practice this meant less than 1% of the average calculated maximum parent residue. In the case of the France Autumn applied study which had the lowest peak average residue for parent, the LOQ equated to 1.6% of the dose. In some instances, residues of parent >LOQ were found in the lowest sampled horizon, but these appeared to be mainly related to samples very soon after application e.g. Germany Spring, residues up to 2.3% of average peak dose in individual replicate plots at 0 DAT and up to 2% on 1 DAT; UK Spring, one instance of 2.1% of peak average dose at 1 DAA; France Spring, 0.5 – 2.4% at 0 DAA; France Autumn, 7.2% of average peak dose in replicate at 0 DAA, up to 2.0% in one replicate on 1 DAA. These instances are likely to related to contamination of the lowest layer rather than representing leaching or macroporous flow. In addition, in the France Autumn study at 31 DAA, there was a single instance of X11393729 being found at 2.3% of the peak average parent residue in a single replicate in the 20-30cm layer. No other replicates had residues >LOQ at this time and the sample times adjacent to this had no residues >LOQ at this depth. As such, the RMS considers that the dissipation seen in the studies was not unacceptably influenced by leaching and can agree with the Applicants conclusion.

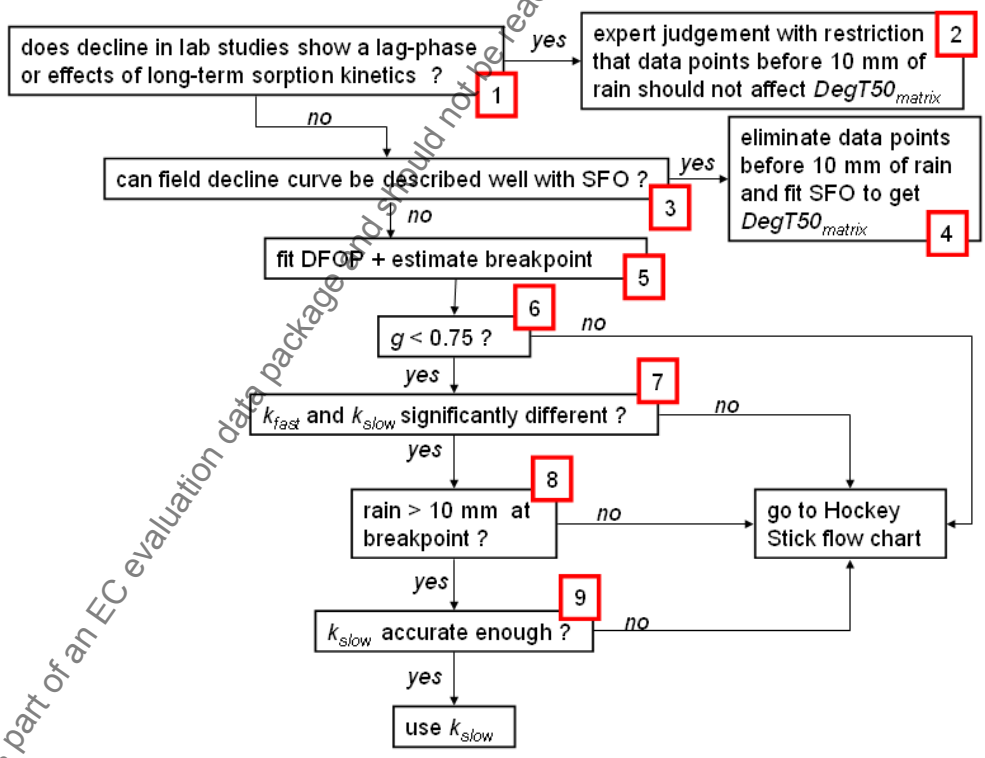
In the laboratory soil photolysis study, there appeared to be little influence of artificial sunlight in relation to the dark control. However, it is noted that XDE-729 methyl is demonstrated to be photolabile in the aqueous photolysis test (see Section B.8.4.2) with extremely rapid degradation in both pure and sterile natural water under artificial sunlight conditions. Whilst there was no apparent effect of irradiation in the soil photolysis study, given the results of the aqueous photolysis study, some uncertainty as to whether soil surface photolysis is possible has to be considered. A recent EFSA PPR Panel opinion on derivation of soil DegT50 values from laboratory and field dissipation studies (Guidance for evaluating laboratory and field dissipation studies to obtain DegT50 values of plant protection products in soil. EFSA Journal

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2010;8(12):1936. [67 pp.]. doi:10.2903/j.efsa.2010.1936) suggests a methodology for attempting to exclude surface processes. Following discussions between the RMS and Applicant, the Applicant attempted to use this methodology on the four field data sets. The RMS considered it might be appropriate to use this Opinion because, whilst the laboratory aerobic degradation study suggested rapid degradation by hydrolysis to the acid metabolite, the Applicant indicated that degradation was slower in the field study. In addition, whilst the soil photolysis study suggested little if any photolysis under laboratory conditions, the RMS considered there was the possibility of a photolytic influence given the results of the aqueous photolysis study (see section B.8.4.2).

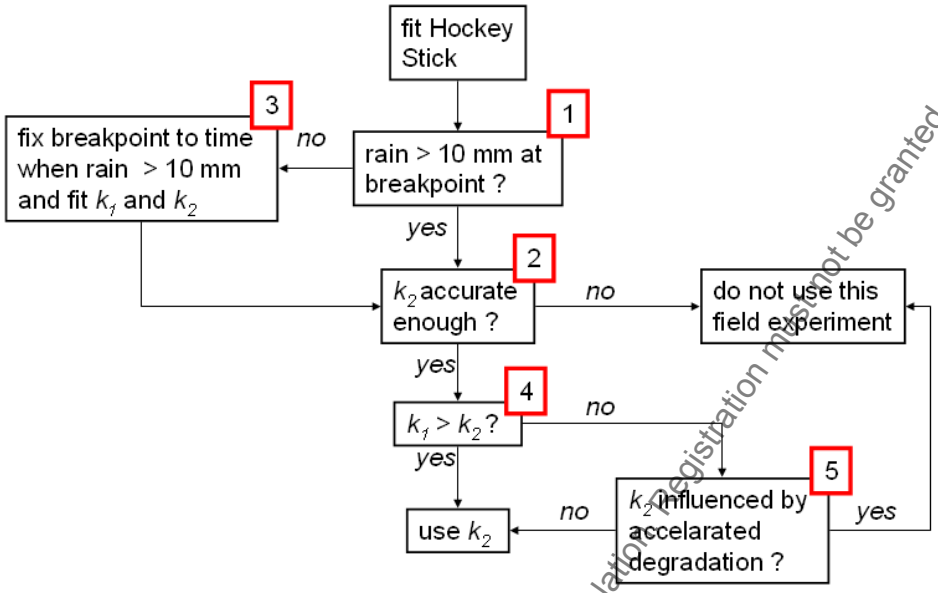
The RMS is aware that this Opinion is not accepted as guidance in the EU at the time of writing (October 2013). The Applicants assessment was also produced without reference to the draft EFSA guidance document on this subject which was undergoing a public consultation at the time (summer 2013); The Applicant had discussed this aspect with the RMS and it was decided that it would be better to use the published 2010 opinion rather than the 2103 draft guidance document.. The EFSA opinion introduces the following flow charts to describe the procedure to obtain DegT50 from normalised field dissipation study data.

Figure B.8.46 Procedure to obtain DegT50 from normalised field dissipation study datasets using SFO or DFOP (taken from EFSA Journal 2010;8(12):1936)



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Figure B.8.47 Procedure to obtain DegT50 from normalised field dissipation study datasets using HS (taken from EFSA Journal 2010;8(12):1936)



Following the normalisation procedure, the Applicant adjusted the residues data for the three analytes. Residues values for each analyte were summed over the whole analysed soil depth (usually 0-30 cm, but 0-40 cm for a few sample times). Concentrations of X11393729 and X11449757 were converted to molar equivalents using the following correction factors.

Table B.8.81 Molar correction factors for metabolites of XDE-729 methyl

Compound	Molecular weight	Correction factor
XDE-729 Methyl	345	1
X11393729	331	1.042
X11449757	317	1.088

For all datasets, any residues of X11393729 and X11449757 detected in day 0 samples were added to the XDE-729 methyl residues and the metabolite day 0 residues set to zero. All subsequent fitting was performed on triplicate residues values. In taking account the EFSA 2010 guidance on DegT50 estimation, the Applicant calculated true time and normalised time at which 10mm of rain had occurred after treatment, together with the time of the first sample time after 10mm rainfall had occurred and the number of sample points following 10mm rainfall. These are shown below.

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Table B.8.82 Summary of rainfall data at start of XDE-729 methyl field dissipation trials

Trial Site/Season	Days before 10mm rain		First sampling time point after 10mm rain		Total rainfall at first time point (mm)	No. of time points after 10mm rain
	Actual	Normalised	Actual	Normalised		
Germany, Spring	4	1.9	7	3.1	25.6	10
Germany, Autumn	2	0.7	3	1.1	25.2	11
UK, Spring	25	10.2	28	12	10.4	8
UK, Autumn	19	3.9	29	5.6	12.2	8
Spain, Spring	41	26.0	58	43	12.9	7
Spain, Autumn	22	16.4	29	20	14.1	8
France, Spring	19	11.3	28	18	29.0	8
France, Autumn	4	1.4	7	2.4	21.0	10

In terms of kinetic modelling and attempting to follow the EFSA 2010 guidance, the Applicant took the following general approach.

The first step (Box 1 of SFO/DFOP flow chart) is to determine if there is any evidence of a lag phase or long-term sorption kinetics behaviour from laboratory degradation studies. The aerobic degradation of XDE-729 Methyl was investigated in four soils as described in Section B.8.1.1(a) and a kinetics evaluation of the data to derive modelling inputs is described at section B.8.1.4(a). The Applicant considered that for all four soils, there was a small tail of XDE-729 methyl residues that was not predicted by the SFO model and could possibly be explained by long-term kinetic sorption behaviour. In three of the soils, the tail of residues was less than 2% AR and in the other soil (Yolo) it was slightly higher (approx 5%). As most of the decline of XDE-729 methyl (95-98%) in the laboratory study was considered to be described well with the SFO model, it was considered valid to run the SFO model for the normalised field dissipation study data after excluding data before 10 mm of rain (flow from Box 3 to Box 4 of SFO/DFOP flow chart). However, because of the evidence of some biphasic decline in all the data sets described above, it was decided to also follow the alternative route and fit the DFOP model (Box 5 of SFO/DFOP flow chart and beyond) so that two sets of kinetics outputs were obtained (*i.e.* SFO and biphasic) which could then be compared in order to come to a final judgement on the most appropriate fit. Depending on the results from DFOP fitting, it was necessary to go to the HS flow chart on some data sets.

The kinetic fitting for each data set was performed in a sequential way starting with parent XDE-729 methyl only, and then adding in each of the metabolites in turn, as described in FOCUS Kinetics guidance.

For the initial fit with parent, SFO was run using the whole data sets. For all data sets, a further SFO fit was run for parent after excluding all time points before 10 mm of rainfall. As shown in the table above, it appears that there were sufficient data points available following exclusion of data before 10mm rainfall to allow viable fitting. Further fitting was also conducted using DFOP and HS on the complete datasets.

After selecting the appropriate model for parent XDE-729 methyl, a second optimisation was run after adding the X11393729 data to the model (SFO only for the

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metabolite) using the previously optimised parameters for parent. Finally, provided that an acceptable fit was obtained, the X11449757 metabolite was added to the kinetics model and optimised.

The optimized rate constants were used to calculate DT_{50} values (from ln2/*k)* for parent and the metabolites. If an acceptable fit could not be obtained for the metabolites, a "top-down" fit was attempted using the metabolite decline data on its own starting at the time of maximum formation (taking into account the requirement for at least 10 mm of rainfall). However, in practice, whilst top-down fits were calculated in many cases, the parameters from sequential modelling were actually selected for modelling for the sake of consistency, rather than adopting a 'mix and match' approach of using parameters from some sequential fits together with some top down parameters.

The acceptability of each kinetics fit was evaluated by visual assessment and statistical analysis as follows:

- Visual assessment: a kinetics model was deemed acceptable if the calculated curve showed a good visual fit to the measured values and the residuals were small and randomly distributed around the zero line

- Chi-square (χ^2) test: the χ^2 analysis was used to calculate the minimum % error required to pass the χ^2 test at the 5% significance level. As an initial guide, if the % error at which the χ^2 test is passed is less than 15%, then this is considered acceptable. Higher % error values were accepted on a case by case basis, particularly for metabolites occurring at low levels, if the visual assessment is acceptable. The Applicant indicated that that in practice achieving a χ^2 error less than 15% was not possible in most cases. The Applicant indicated that considering scatter in the data which can be expected in field studies, χ^2 error values greater than 15% could be accepted on a case by case basis if the visual fits and other statistical parameters were acceptable. The RMS agrees that field study data often show scatter and experience indicates that it is common to see χ^2 errors greater than 15% for both parent and metabolites but where fitting appears to be otherwise reasonable. The RMS considers that the approach taken by the Applicant is pragmatic as it is used on a case-by-case basis.

- Standard error, t-test and confidence intervals: a fit was accepted provided that the standard error was less than the optimised parameter, the t-test probability is less than 0.05 and the lower confidence interval (CI) was not less than zero.

The modelling software tool CAKE was used to optimise the kinetics fits and generate the statistical outputs for the temperature and moisture normalised datasets. The RMS has seen CAKE used in some kinetic assessments and considers its use to be acceptable. However, the RMS has noted from model output that the optimisation method for CAKE has been set as Iteratively Reweighted Least Squares (IRLS). This is a different optimisation method to that apparently recommended by FOCUS Kinetics, this being Non-Linear Least Squares (NLLS, also known as Ordinary Least Squares, OLS). NLLS assumes that different datasets, e.g. parent and metabolite, are subject to the same error variance, however, it has been argued by applicants that this is not the case. Alternative weighting methods such as IRLS have been proposed by

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applicants as way of taking into account different error variance and as a result overcome commonly experienced issues of poor fitting and poor statistical parameters for metabolites where metabolites have been fitted sequentially with parent/precursor. FOCUS Kinetics guidance does not rule out use of different weighting methods, but does not explicitly recommend other methods. The RMS has limited experience with IRLS but has observed that it can lead to improved metabolite fitting. However, the fit of parent/precursor using IRLS often seems to be changed by the addition of metabolite data into a sequential fitting procedure compared to fitting the parent/precursor data only. At times the changes in parent fitting in such sequential procedures can be quite marked; RMS limited experience is that parent degradation rates appear to be increased but to the detriment of the fitting of the parent, however experience is limited and this may not be a common feature to all sequential fits using IRLS. In addition, RMS experience is that IRLS does not affect the fitting of parent only data, only where two or more substances are fitted sequentially; however, this observation is limited to only a small number of data sets. In answer to questions raised on the use of IRLS, the Applicant has provided some additional information on the influence of IRLS as compared to NLLS for the parent and X11393729 fitting. This was in the form of statistics but illustrations of visual fitting for Germany Spring and UK Autumn for X11393729 were also given. Given that this is a generic issue affecting all sites, this is dealt with following the description of kinetic evaluation of all the sites.

The RMS also makes a general point relating to kinetic calculation software. In the case of KinGUI 2, this software appears to default to IRLS weighting, although this can be changed to NLLS easily. It is not known whether this is also the case with CAKE v 1.4 used in this assessment, but seems to be the case for the recently released CAKE v 2. It would therefore be wise for rapporteur evaluators to check the optimisation method of models being used and to make this clear in the evaluation. The RMS is concerned that use of IRLS or other methods of weighting may be used 'by accident' if software models are defaulting to these alternative methods. This is of concern because there is limited experience of the effect of this weighting method on fitting of precursor substances, and because there is currently no official view on the appropriateness of this weighting method.

The RMS previously indicated that KinGUI 1.1 was used for evaluating the unnormalised datasets. To the best understanding of the RMS and from the results presented, it appears that NLLS weighting was used for the calculations on the unnormalised datasets.

Results of the Applicant's calculations are presented below by trials site, first unnormalised data and then normalised data. For the normalised datasets, the RMS has presented most of the fits for information because of the use in the assessment of the relatively new EFSA opinion procedure for DegT50 derivation. This results in a large number of graphs and tables of parameters. Therefore, to put this large amount of information into context, for the purpose of the selection of modelling endpoints for parent XDE-729 methyl, the SFO parameters following exclusion of data points before 10mm rainfall were chosen. For each of the metabolites, the degradation endpoints derived using sequential fitting of the complete data sets have generally been used. Because of the impact of sequential fitting on precursor parameters, this results in

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separate sets of modelling endpoints for parent, X11393729 (formed in sequence from parent) and X11449757 (formed in sequence from parent and X11393729). As a consequence, separate exposure simulations have to be performed to obtain PEC values for parent, X11393729 and X11449757. The Applicant argues that it is acceptable to use the parameters for metabolites obtained from the complete data sets, including rapid degradation phase of the parent, because fast degradation of parent potentially leads to a more conservative assessment of the metabolites. The RMS can accept such an argument.

A summary of the proposed persistence and modelling endpoints is given at the end of this kinetics section.

Germany, Spring

Unnormalised data (Germany, Spring)

Parent

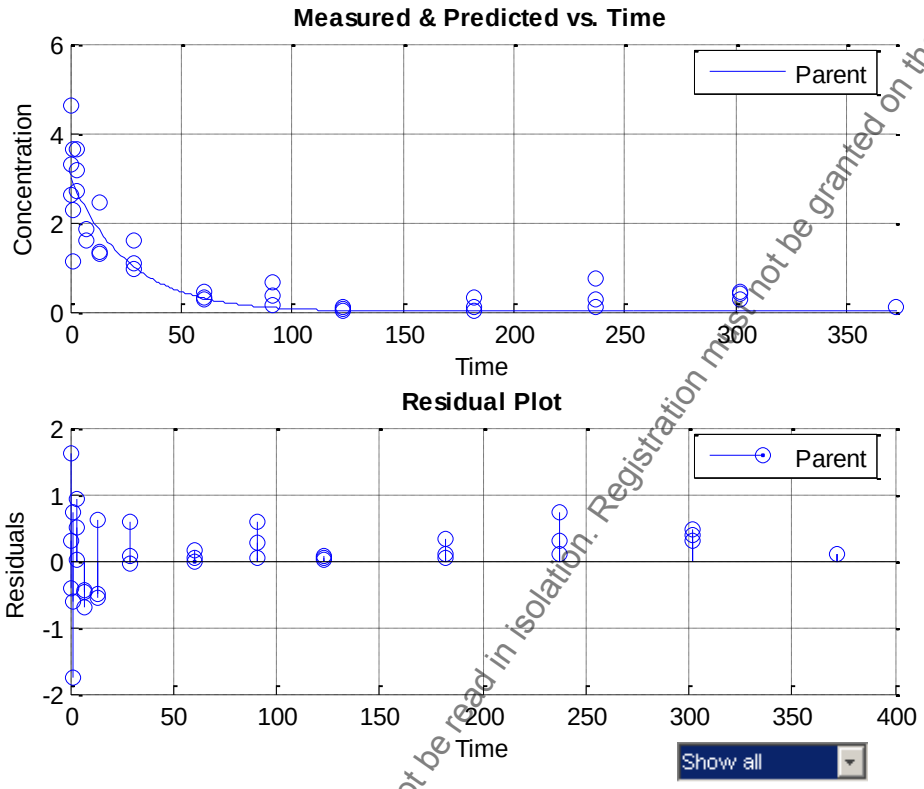
The kinetics fits for the measured data (i.e. not corrected for temperature and moisture) using the SFO and FOMC models for parent XDE-729 methyl only are shown in the following table and figures.

Table B.8.83 Statistics for SFO and FOMC fitting for Germany, Spring field dissipation data, XDE-729 methyl, all data

Model	Parameter	Value	Lower CI	Upper CI	Std Dev	Prob > t	DT_{50} (d)	DT_{90} (d)	% χ^2 error
SFO	M_0 (µg/kg)	3.00	2.60	3.41	0.20	-			
(all data)	k (d^{-1})	0.0381	0.0211	0.0551	0.0084	2.9e-05	18	60	23.6
FOMC	M_0 (µg/kg)	3.23	2.73	3.73	0.25	-			
(all data)	alpha	0.964	0.136	1.791	0.408	0.012	13	119	21.2
	beta	12.02	-7.49	31.53	9.62	0.110			

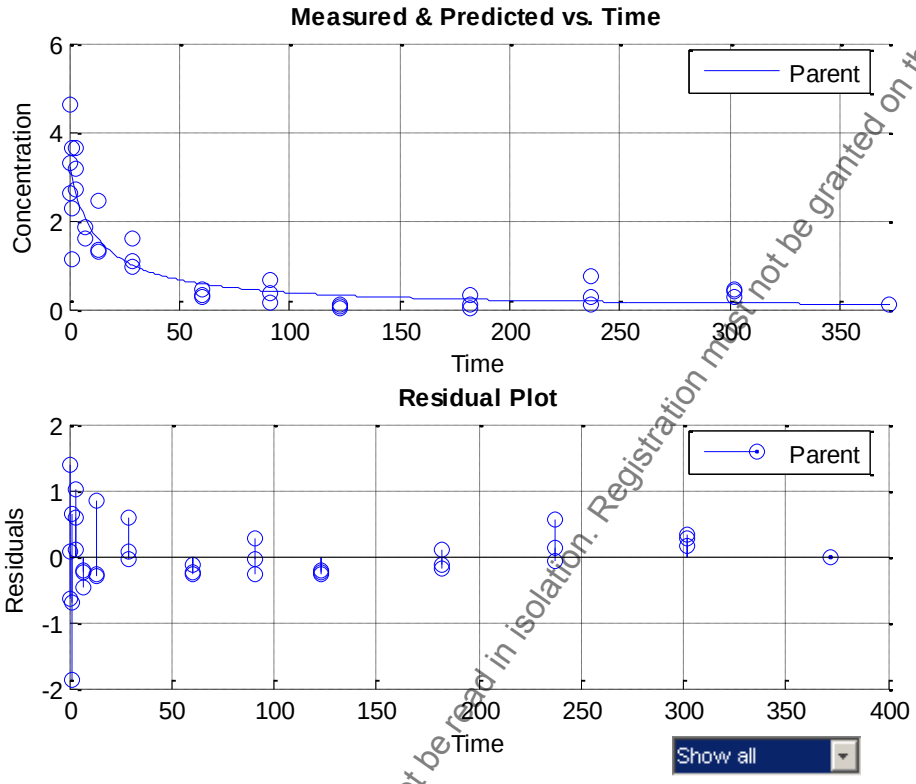
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Figure B.8.48 SFO fitting for Germany, Spring field dissipation data, XDE-729 methyl, all data



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Figure B.8.49 FOMC fitting for Germany, Spring field dissipation data, XDE-729 methyl, all data



The SFO model gave a DT50 of 18 days with a χ^2 error of 23.6% and acceptable t-test and confidence intervals. The FOMC model gave a slightly lower χ^2 error of 21.2% but the β parameter showed unacceptable error and lower CI less than zero. Therefore the Applicant considered that the SFO model gave the best fit.

The Applicant indicated that the residues of XDE-729 methyl had decreased from an initial concentration of 3.50 µg/kg (average of parent ester and X11393729 combined) to less than 10% after 4 months. However, at 8 months and 10 months, slightly higher residues were found corresponding to 11% of the initial residue before declining again at 12 months. The Applicant could find no clear explanation for this apparent slight increase in residues that occurred at 6 to 8 months, which was in the middle of winter, other than experimental variability. The Applicant indicated that this period was in the middle of winter 2010-11 when temperatures in northern Europe were especially low, and it could be expected that there would be very little degradation occurring at this time. The Applicant concluded that approximately 90% of the residue was dissipated over the first 4 months (up to Day 123). Therefore, the SFO model was re-run using data up to Day 123.

From the distribution of residuals for the SFO plot, the Applicant considered that there were two data points that deviated from the predicted curve more than the others. These were points Day 0a and Day 1c. The kinetics fit was re-run after omitting these points and results are shown in the following table.

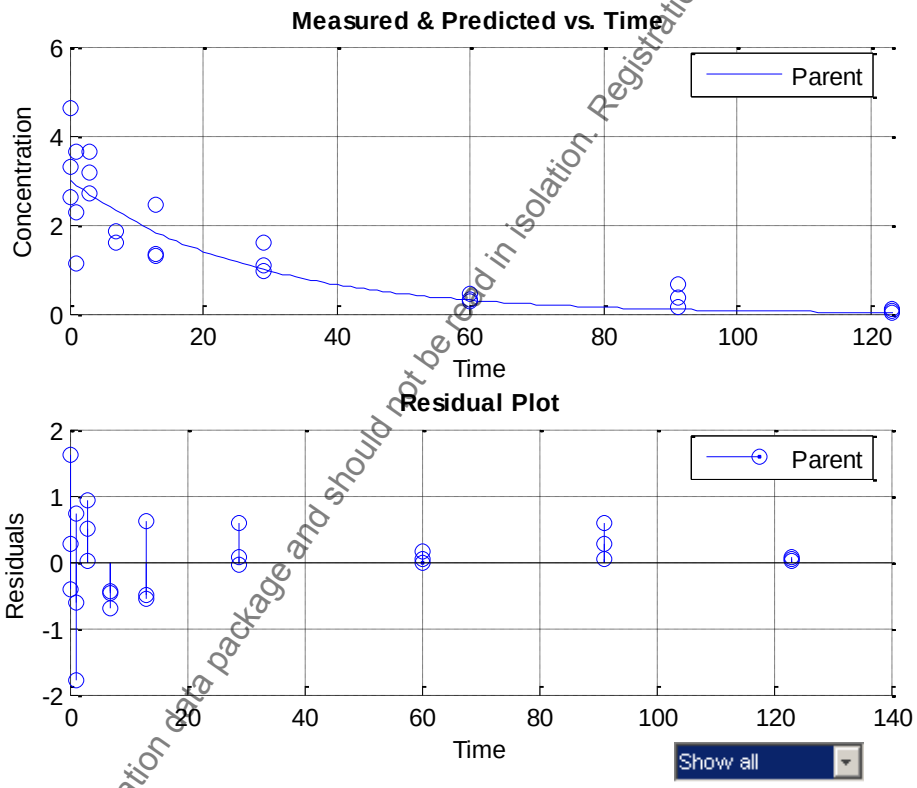
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Table B.8.84 Statistics for SFO fitting for Germany, Spring field dissipation data, XDE-729 methyl, day 0 - 123 data, either including or excluding day 0a and Day 1c data points

Model	Parameter	Value	Lower CI	Upper CI	Std Dev	Prob > t	DT_{50} (d)	DT_{90} (d)	% χ^2 error
SFO (Day 0-123)	M_0 (µg/kg)	3.00	2.53	3.48	0.23	-			
	k (d^{-1})	0.0382	0.0183	0.0581	0.0097	2.8e-04	18	60	18.4
SFO (Day 0-123)[1]	M_0 (µg/kg)	3.00	2.62	3.37	0.18	-			
	k (d^{-1})	0.0370	0.0228	0.0511	0.0068	8.5e-06	19	62	14.7

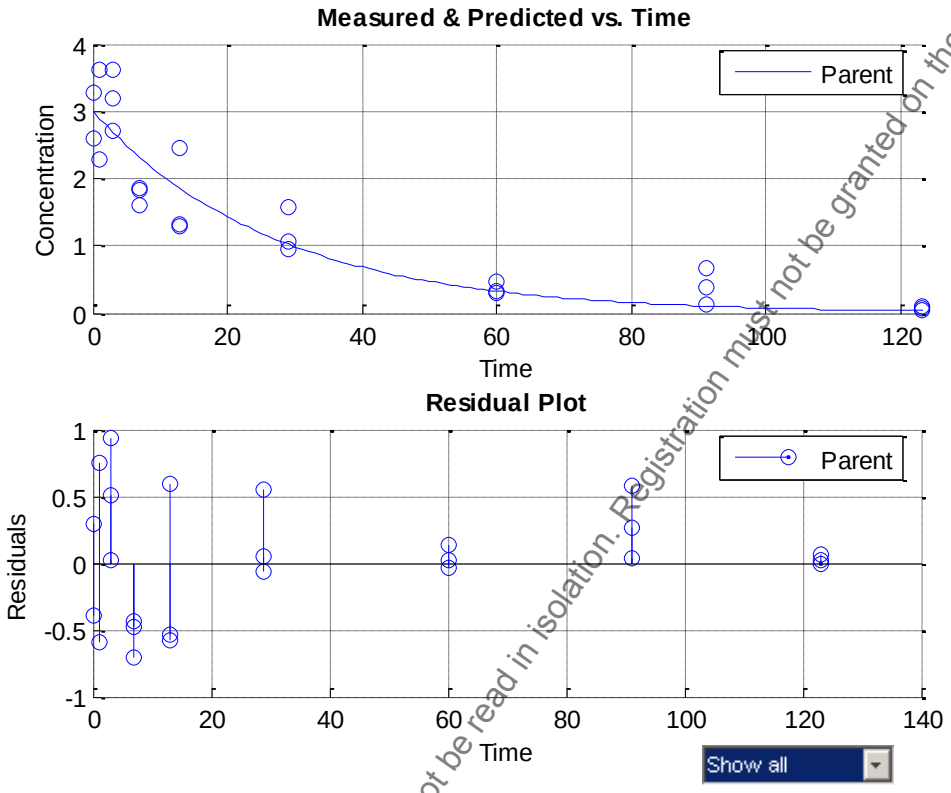
[1] excluding Day 0a and Day 1c

Figure B.8.50 SFO fitting for Germany, Spring field dissipation data, XDE-729 methyl, day 0 - 123 data



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Figure B.8.51 SFO fitting for Germany, Spring field dissipation data, XDE-729 methyl, day 0 - 123 data excluding day 0a and Day 1c data points



Using all data up to Day 123, the χ^2 error is reduced from 24% to 18% and the kinetics parameters are essentially identical to those derived using the whole data set. Removing the Day 0a and Day 1c points as outliers gave a better χ^2 error (< 15%) but did not significantly change the kinetics parameters. Therefore, the SFO parameters derived using all the data up to Day 123 (DT50 and DT90 values 18 days and 60 days, respectively) are proposed by the Applicant for XDE-729 methyl as the best fit for this site. The RMS can accept this proposal.

X11393729

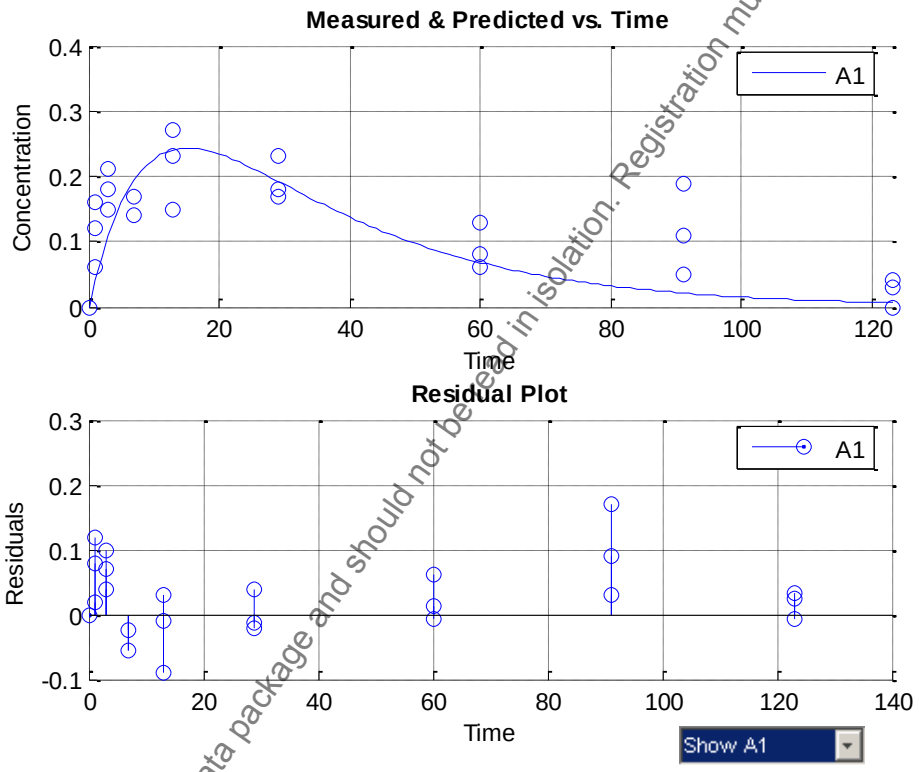
Using the optimised SFO parameters for XDE-729 methyl as initial values, the Applicant added the X11393729 data to the kinetic model as the first metabolite. Only the data up to Day 123 were used since this gave the best chance of obtaining an acceptable fit for the metabolite. The formation fraction was set to an initial value of 0.5 and all parameters for parent and metabolite were optimised. The outputs are shown in the following table and figure (only the plot for X11393729 is shown as the parent plot is very similar to that above).

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Figure B.8.85 SFO fitting for Germany, Spring field dissipation data, XDE-729 methyl+ X11393729, day 0 - 123 data

Model	Parameter	Value	Lower CI	Upper CI	Std Dev	Prob > t	DT_{50} (d)	DT_{90} (d)	% χ^2 error
SFO Parent (Day 0-123)	M_0 (µg/kg)	3.00	2.67	3.33	0.16	-			
	k (d^{-1})	0.0380	0.0243	0.0517	0.0068	5.3e-07	18	61	18.4
SFO Acid (Day 0-123)	Form fraction	0.3998	-0.7955	1.5951	0.5951	-			
	k (d^{-1})	0.1056	-0.3326	0.5439	0.2182	0.3152	6.6	22	35.0

Figure B.8.52 SFO+SFO fitting for Germany, Spring field dissipation data, XDE-729 methyl + X11393729, day 0 - 123 data, X11393729 only shown



The parameters for parent XDE-729 methyl did not change significantly when X11393729 was added to the model. However, the fit for X11393729 gave a high χ^2 error and both the formation fraction and rate constant parameters showed unacceptable error and lower CIs less than zero. Therefore, it was considered by the Applicant to be not possible to obtain acceptable kinetics parameters for X11393729 using this data set.

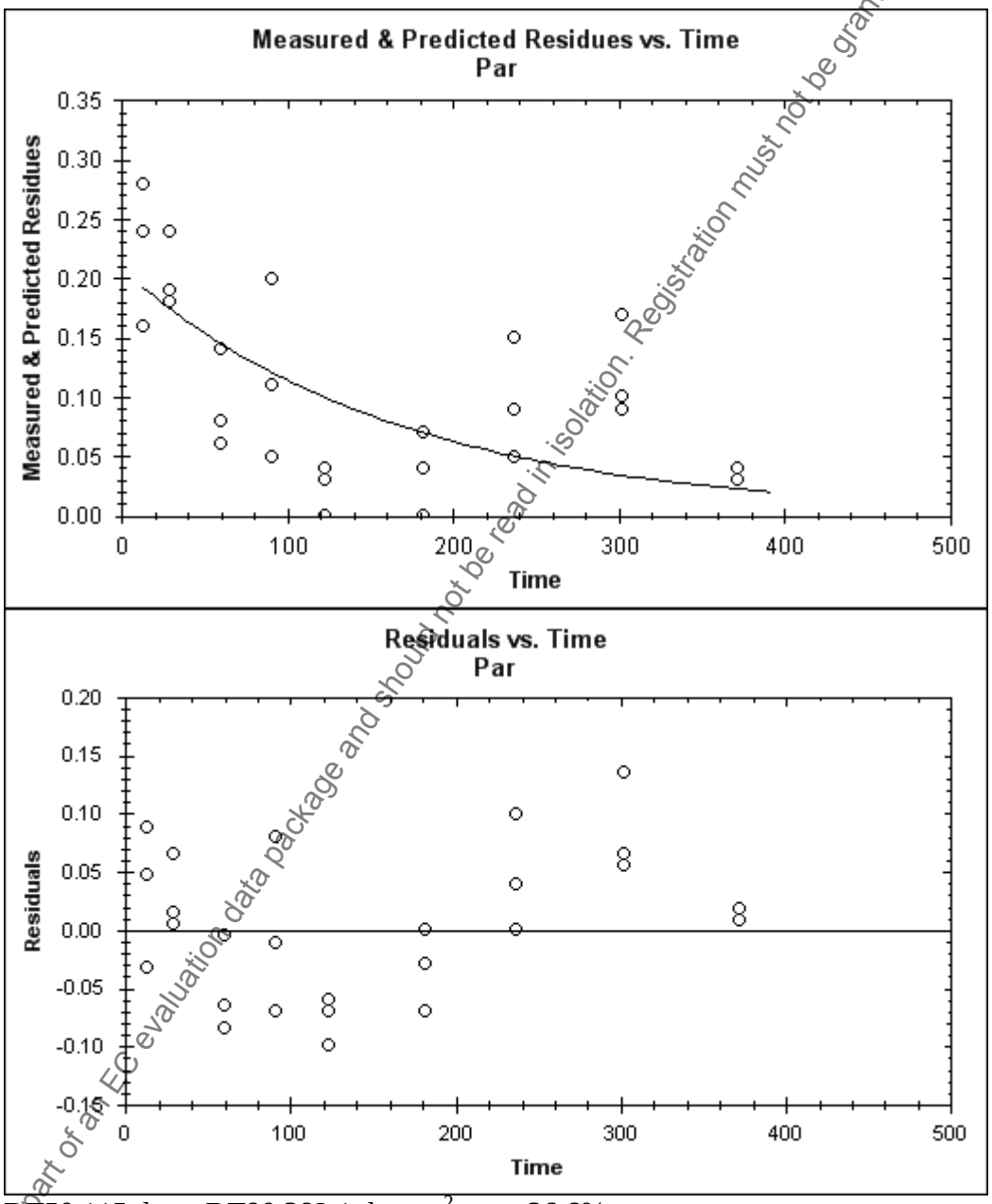
The Applicant considered that there were several reasons why it was not possible to obtain good kinetics data for X11393729 from this data set. Firstly, the maximum amount of X11393729 formed is relatively low compared to the initial concentration of XDE-729 methyl. Using the average values, the maximum level of X11393729 was 0.22 µg/kg compared with an initial concentration of XDE-729 methyl of 3.50 µg/kg. Thus, the maximum level of acid is less than 7% of the initial concentration (molar correction has not been applied since this is negligible). Secondly, the generally high variability between the replicate values and the fluctuation in residue levels towards

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the end of the study results in an even poorer fit for the X11393729 because of the lower residues compared to parent.

The RMS modelled the decline of X11393729 using SFO top down from 13 DAT. KinGUI 2 with NLLS weighting was used. The following fitting was achieved.

Figure 8.53 RMS top-down SFO fit for X11393729, Germany Spring.



DT50 115 days, DT90 382.1 days, χ^2 error 36.6%

The RMS notes that there appear to be at least two distinct peaks of formation and proposes not to use these parameters for risk assessment.

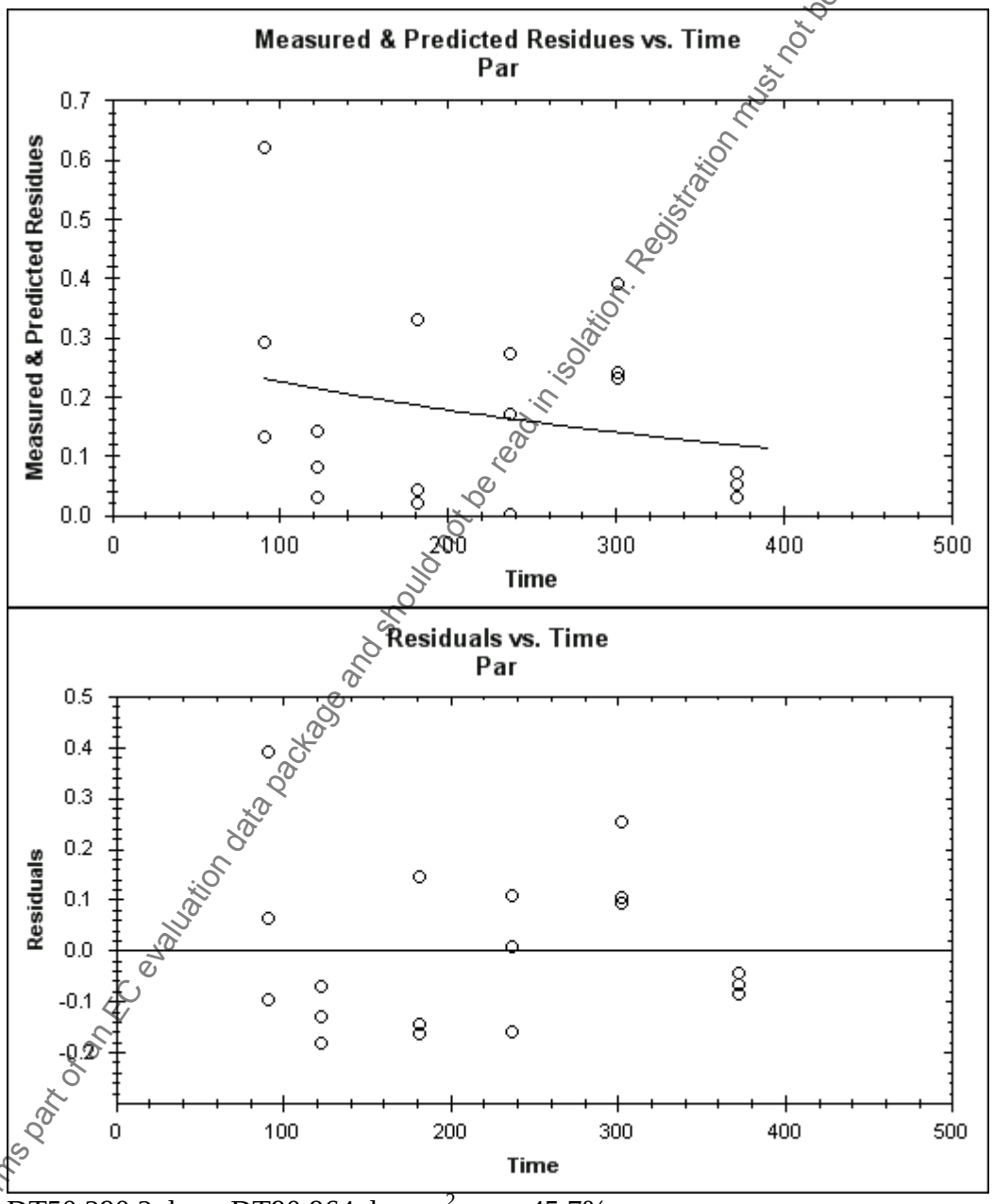
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X11449757

Since it was not possible to obtain an acceptable kinetics fit for X11393729, no attempt was made by the Applicant to fit the X11449757 metabolite.

The RMS modelled the decline of X11449757 using SFO top down from 91 DAT. The following fitting was achieved.

Figure 8.54 RMS top-down SFO fit for X11449757, Germany Spring.



DT50 290.2 days, DT90 964 days, χ^2 error 45.7%

The RMS notes that there appear to be at least two distinct peaks of formation and proposes not to use these parameters for risk assessment.

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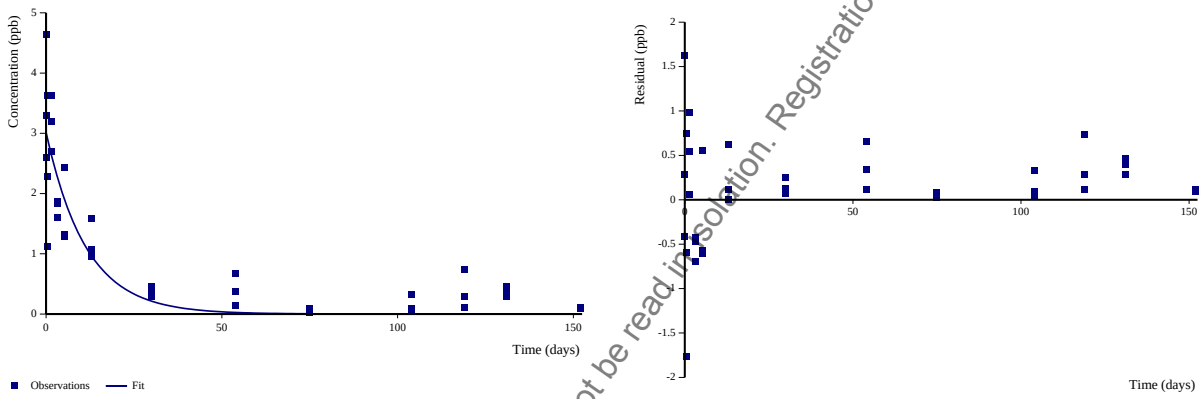
Data normalised to 20 °C and pF 2 (Germany, Spring)

Parent

The results of fitting XDE-729 methyl (all data) to the SFO model are as follows:

Figure B.8.55 Statistics for kinetic fitting of Germany, Spring, Parent only, all data, SFO

Parameter	Value	σ	Prob > t	Lower CI	Upper CI	DT50 (d)	X^2 err (%)
M_0 (µg/kg)	3.017	0.2084	4.04E-17	2.594	3.439	7.9	24.5
k (d^{-1})	0.0882	0.02108	8.47E-05	0.04548	0.131		



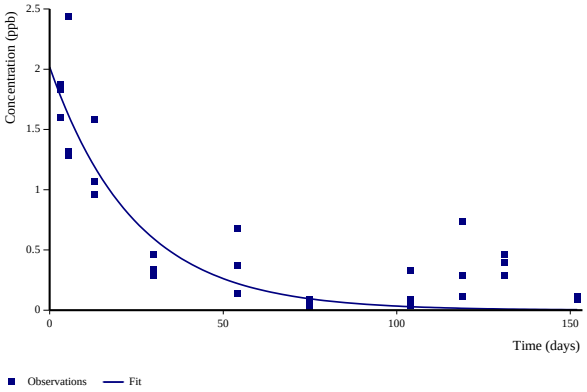
The SFO model gave acceptable t-test and confidence intervals but the χ^2 error was higher than the target value of 15%. Taking into account the considerable scatter in the data, the visual fit is reasonable at early time points but there is a clear pattern of positive residuals from 30 days after treatment (DAT) onwards. During this later phase of the study, there were low and variable levels of XDE-729 methyl detected up to 0.38 µg/kg (average value), which represented approximately 11% of the initial residue of 3.51 µg/kg (average value). Therefore, approximately 89% of the initial residues had dissipated during the earlier part of the study, which gave a good fit to the SFO model.

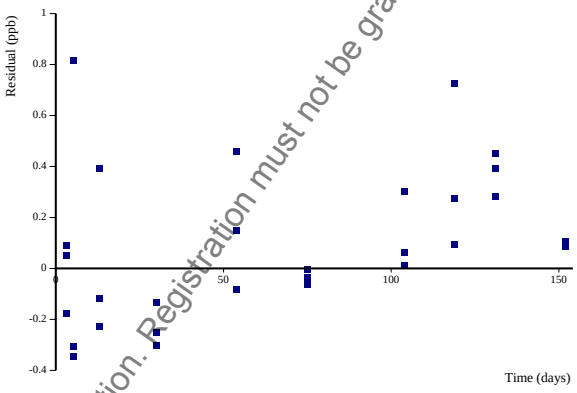
A further SFO fit was conducted after eliminating data points before 10 mm of rainfall. In this study, cumulative rainfall exceeded 10 mm (total = 21.4 mm) at 1.9 DAT (4 DAT in real time). The first soil sampling time point after this was 3.1 DAT (7 DAT in real time), and the total rainfall at this time point was 25.6 mm. During this time, the residues of XDE-729 Methyl (based on average concentrations) had decreased from 3.51 µg/kg to 1.77 µg/kg. Therefore, 50% of the initial concentration of XDE-729 methyl remained in the soil at the starting point of the kinetics fit. The LOQ of 0.05 µg/kg represents 2.8% of this starting value. There were 10 time points after 10 mm of rain, which is sufficient for a kinetics analysis. The results of the SFO fit to the data after 10 mm of rain are as follows:

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Figure B.8.56 Statistics for kinetic fitting of Germany, Spring, Parent only, data after 10 mm rainfall, SFO

Parameter	Value	σ	Prob > t	Lower CI	Upper CI	DT50 (d)	X^2 err (%)
M_0 (µg/kg)	2.018	0.1816	4.49E-12	1.646	2.39	17.0	24.3
k (d^{-1})	0.04082	0.00843	2.15E-05	0.02355	0.058		





A reasonable fit was obtained over the early time points considering the scatter in the data but, as observed for the fit with the whole data set, the model cannot describe the tail of residues at the end of the study. The χ^2 error of 24.3% was similar to that obtained for the whole data set. The DT50 of 17 days is significantly longer than that obtained from the whole data set, which is due to the initial rapid decline being removed from the fit.

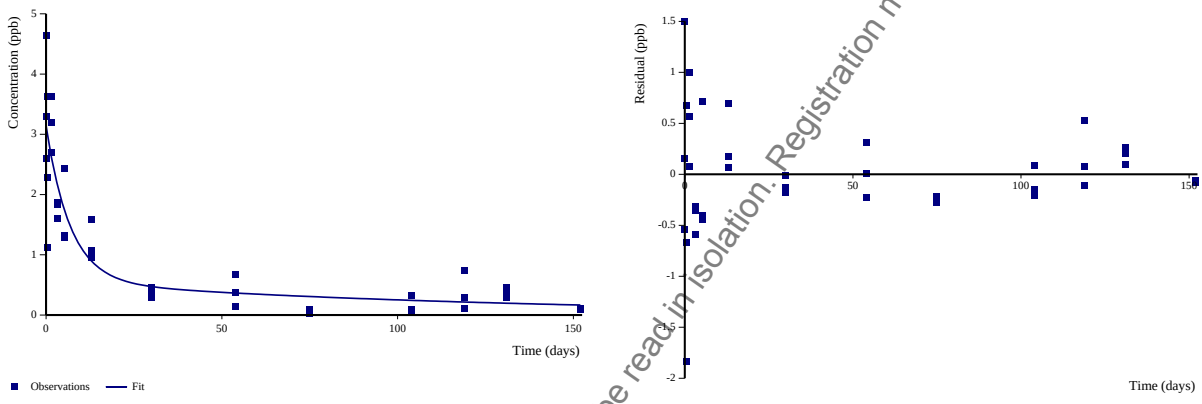
Since the χ^2 error for the SFO fit was higher than desired, the Applicant considered it was not certain that the SFO model gave the most appropriate fit. Therefore, Step 5 of the EFSA assessment scheme was followed by running the DFOP model with all of the data. The results are as follows:

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Figure B.8.57 Statistics for kinetic fitting of Germany, Spring, Parent only, all data, DFOP

Parameter	Value	σ	Prob > t	Lower CI	Upper CI	DT50* (d)	X^2 err (%)
M_0 (µg/kg)	3.141	0.2295	6.48E-16	2.675	3.607	-	22.6
k1 (d^{-1})	0.1461	0.06166	0.01172	0.02094	0.271	4.7	
k2 (d^{-1})	0.008	0.01135	0.2428	-0.01504	0.031	87	
g	0.8219	0.1604	5.52E-06	0.4962	1.148	-	

* DT50 for each rate constant calculated from ln2/k



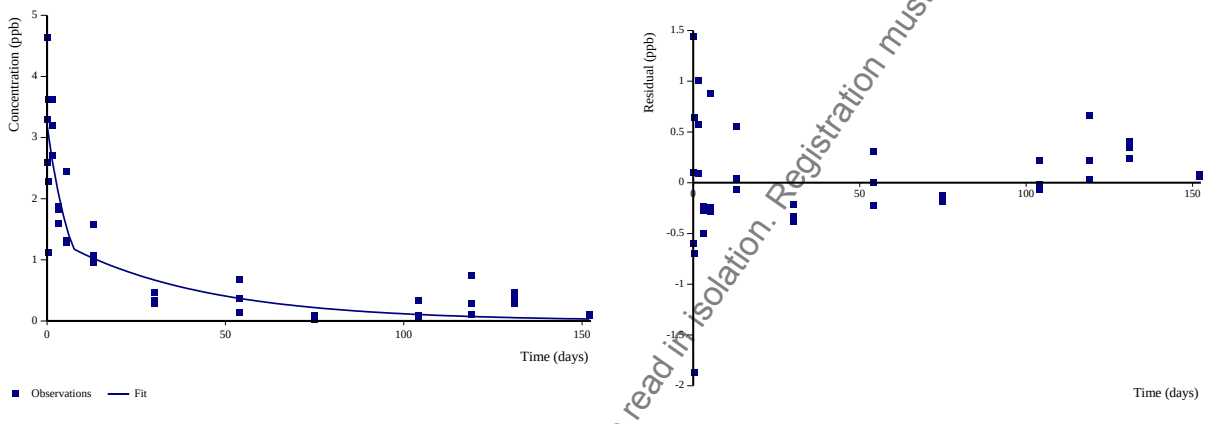
The RMS notes that DFOP gave a better visual fit to the whole dataset compared to SFO, particularly giving a better description of the tail from 30 DAT onwards. The high value of g (0.8219) indicates that the fast decline (k1) dominates and there is a high error on the k2 (slow rate) value with a lower CI less than zero. The EFSA guidance recommends that if g is greater than 0.75 then the DFOP model may be unreliable for deriving bulk matrix degradation rates and the HS model should be run; in addition, failure of t-test and confidence interval for k2 suggest that DFOP is unacceptable. The RMS considers that the poor statistical performance for k2 may be related to the relatively large amount of scatter in the data between replicates and between sample times. The results for the HS model for parent XDE-729 Methyl are as follows:

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Figure B.8.58 Statistics for kinetic fitting of Germany, Spring, Parent only, all data, HS

Parameter	Value	σ	Prob > t	Lower CI	Upper CI	DT50* (d)	X^2 err (%)
M_0 (µg/kg)	3.201	0.2366	9.01E-16	2.721	3.682	-	23.3
k1 (d^{-1})	0.1354	0.03736	0.000455	0.05959	0.211	5.1	
k2 (d^{-1})	0.02492	0.01382	0.04004	-0.00315	0.053	28	
t_b (days)	7.38	3.725	0.02773	-0.1819	14.94	-	

* DT50 for each rate constant calculated from ln2/k



The HS break point at 7.4 DAT is after the 10mm rain time point at 1.9 DAT, which is acceptable according to the HS flowchart. However, the optimised slow phase k2 value of 0.02492 d^{-1} (DT50 = 28 days) gave a lower confidence interval less than zero, therefore the Applicant did not consider the HS parameters to be reliable. The RMS also notes that HS does not give as good a representation of the tail as DFOP and that χ^2 error of the HS is higher than with DFOP.

Overall, the χ^2 error was very similar for all fits but DFOP was rejected because the g value is > 0.75 and the lower CI value is less than zero for the slow phase decline rate constant. Considering the SFO (after 10 mm rain) and the HS models, the visual fits and residuals are very similar (note the different y-axis scales). The Applicant considered that conceptually, the slow phase part of the HS model is similar to an SFO fit using the data after the break point. For this data set, the slow phase of the HS model starts at 7.4 DAT and the first sampling time point after this is at 13 DAT. On the other hand, the SFO fit after 10 mm rain includes the time points at 3.1 and 5.3 DAT. This leads to a steeper decline curve for the SFO model and hence a shorter DT50 compared with the HS slow phase fit. However, as stated above, a total of 25.6 mm of rain had fallen by 3.1 DAT (7 DAT real time), which is more than two times the amount recommended by EFSA to eliminate surface processes. Furthermore, the k2 value derived from the HS model has a lower CI less than zero and was not considered to be reliable by the Applicant. Therefore, the SFO model using data after 10 mm rain was considered by the Applicant to give the most appropriate kinetics fit.

Taking into account the overall arguments presented, the RMS can accept the normalised SFO fit after 10 mm rain, which gives a DT50 value of 17 days.

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Parent and X11393729

In order to derive kinetics parameters for X11393729 from a sequential fit with parent, it is necessary to use appropriate parameters for the parent in order to describe the formation of X11393729 . Since there was generally rapid formation of X11393729 due to the initial rapid decline of parent, the Applicant considered it not valid to use the SFO fit after 10 mm rain for parent since there were significant residues of X11393729 before this time point. The Applicant considered DFOP and HS models to better predict the rapid initial decline of parent and hence would lead to the fastest formation of Acid. However, these fits were rejected due to uncertainty around the slow phase DT50 values; in addition, DFOP failed the flowchart criteria of having g value >0.75. The Applicant considered that for modelling purposes it is preferable to use SFO fits for parent and all metabolites to reflect the kinetics routines used in the models. For this data set, the original SFO fit with all data was considered to give a reasonable fit to parent decline over the initial phase of the study, when most of the Acid is formed. Therefore, for practical purposes, the SFO model for parent was used sequentially with SFO for X11393729, which was added to the kinetics model as the first metabolite (designated as A1).

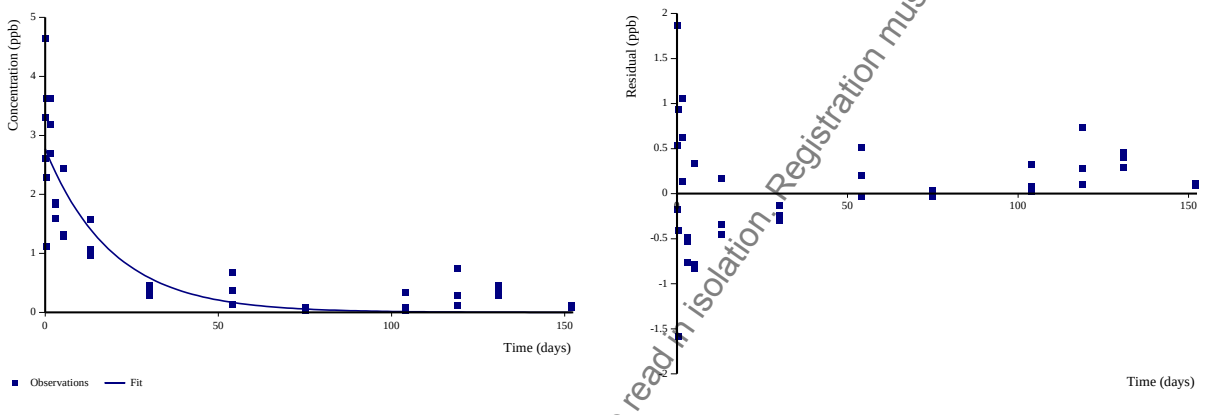
The optimised parameters for parent XDE-729 Methyl and X11393729are as follows:

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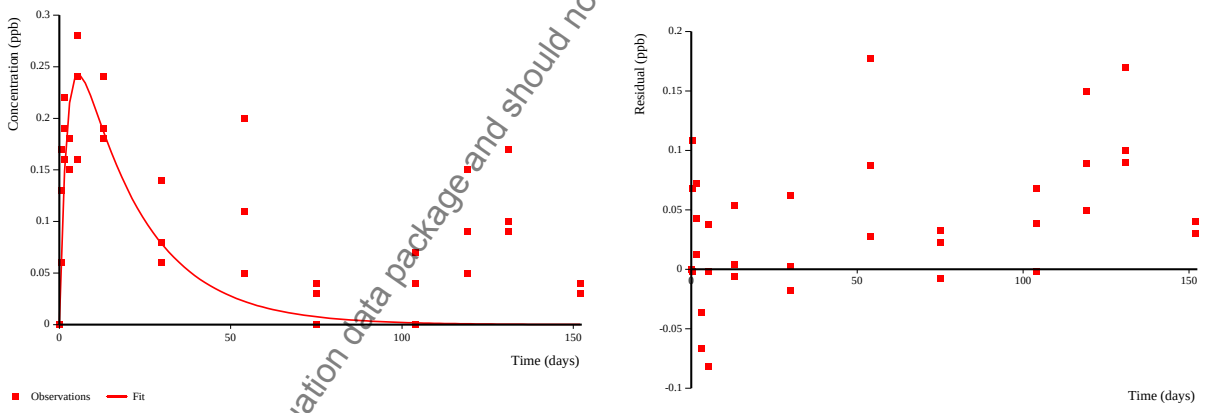
Figure B.8.59 Statistics for kinetic fitting of Germany, Spring, Parent + X11393729, all data, SFO+SFO

Parameter	Value	σ	Prob > t	Lower CI	Upper CI	DT50 (d)	X^2 err (%)
M_0 (µg/kg)	2.771	0.1817	7.637E-25	2.409	3.133	-	
k_Parent (d^{-1})	0.05172	0.01029	1.688E-06	0.03121	0.072	13.4	27.0
f_Par_to_A1	0.9734	0.3501	0.003444	0.2757	1.671	-	
k_A1 (d^{-1})	0.4312	0.1459	0.002095	0.1405	0.722	1.6	42.1

Compartment Parent:



Compartment A1:



After addition of X11393729to the model, the DT50 for parent XDE-729 methyl increased from 7.9 days to 13 days. The model indicated that almost all of the parent is converted to X11393729 (formation fraction = 0.97). Although the t-test and confidence intervals were acceptable, the χ^2 error for X11393729was high (42%). The visual fit showed a reasonable prediction of the formation and initial decline of X11393729 up to approximately 30 DAT but, as observed for parent, the visual fit was poor at later time points due to the "tail" of scattered and variable residues towards the end of the study. Please note the different scales of the parent and metabolite plots which appears to accentuate the extent of the X11393729 residues. The Applicant concluded that this model does not describe the decline of X11393729 very well. The RMS concludes that the SFO+SFO model is simply unable to describe the apparently fluctuating tail of parent residues and consequent apparent pattern of three peaks of

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formation of X11393729. However, the RMS also notes that in this case, the parent fit decreased slightly (χ^2 error of 27 compared to 24.5 for parent only) and DT50 was increased from 7.9 days to 13.4 days. This is because the slope of the parent curve was shallower in the sequential modelling, (predicted initial concentration with parent only fitting was 3.017 µg/kg and reduced to 2.771 µg/kg in the sequential modelling). It may be that the difference between fitting of parent only and fitting with a sequential approach with the metabolite is as a result of using IRLS rather than NLLS.

A second kinetic fit was run using DFOP for parent and SFO for X11393729. Although DFOP was not accepted as the best model for parent, it is possible that it may be suitable to describe the initial conversion of parent to X11393729. The results are as follows:

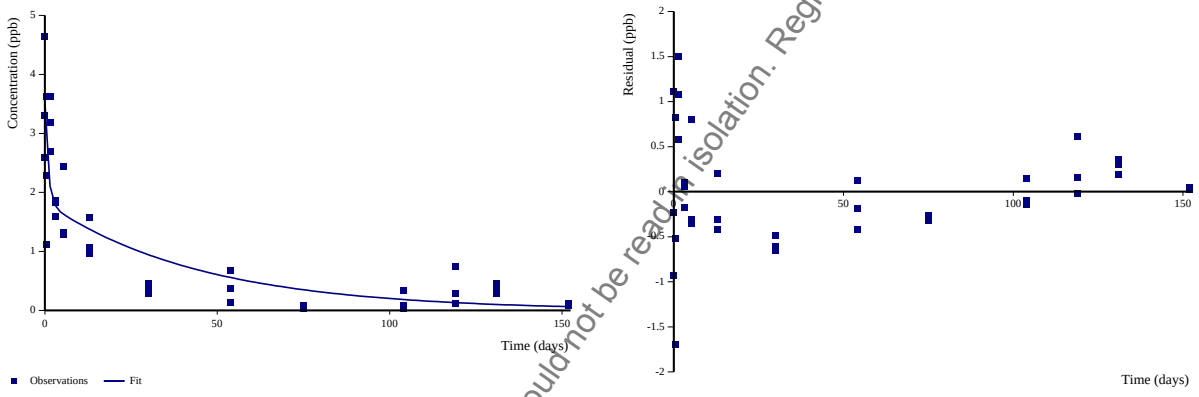
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Figure B.8.60 Statistics for kinetic fitting of Germany, Spring, Parent + X11393729, all data, DFOP+SFO

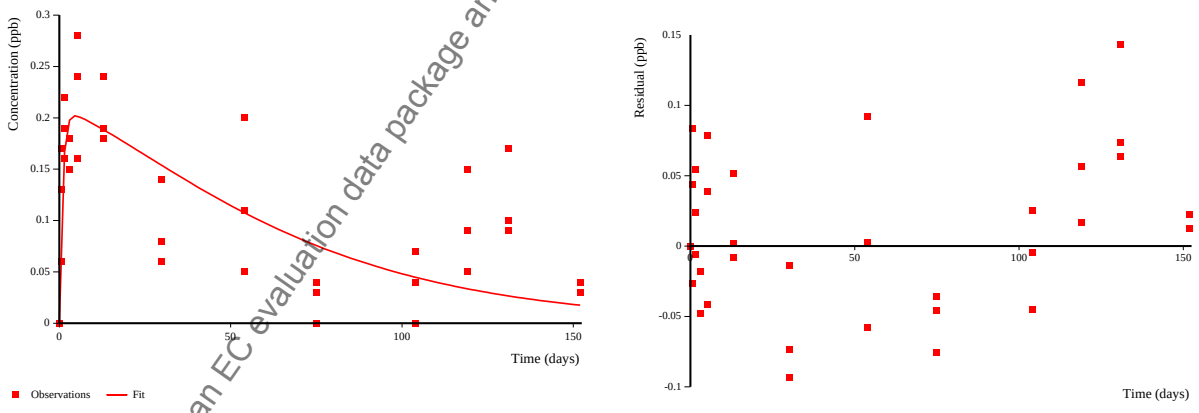
Parameter	Value	σ	Prob > t	Lower CI	Upper CI	DT50* (d)	X^2 err (%)
M_0 (µg/kg)	3.534	0.31	4.32E-18	2.916	4.152	-	28.4
k1 (d^{-1})	1.066	0.4087	0.00553	0.2514	1.881	0.65	
k2 (d^{-1})	0.02206	0.00644	0.00051	0.00923	0.035	31.4	
g	0.4819	0.08707	2.39E-07	0.3083	0.656	-	
f_Par_to_A1	0.1202	0.02853	3.61E-05	0.06329	0.177	-	34.1
k_A1 (d^{-1})	0.0297	0.00729	5.86E-05	0.01517	0.044	23.3	

* DT50 for each rate constant calculated from ln2/k

Compartment Parent:



Compartment A1:



Using DFOP for parent resulted in a lower χ^2 error for the Acid compared with the SFO/SFO fit (34% vs 42%) and the Applicant considered that the visual fit was better at later time points. The RMS cannot concur with the Applicants conclusion here as the fit to the first and highest peak is not particularly good, the fit to the final five sample times is still generally poor and model is simply unable to fit the apparent additional peaks of formation that are occurring later in the study. The formation fraction for X11393729 was 0.12, and the Applicant proposed that this low value may reflect the generally low residues of X11393729 that were detected in this trial. The

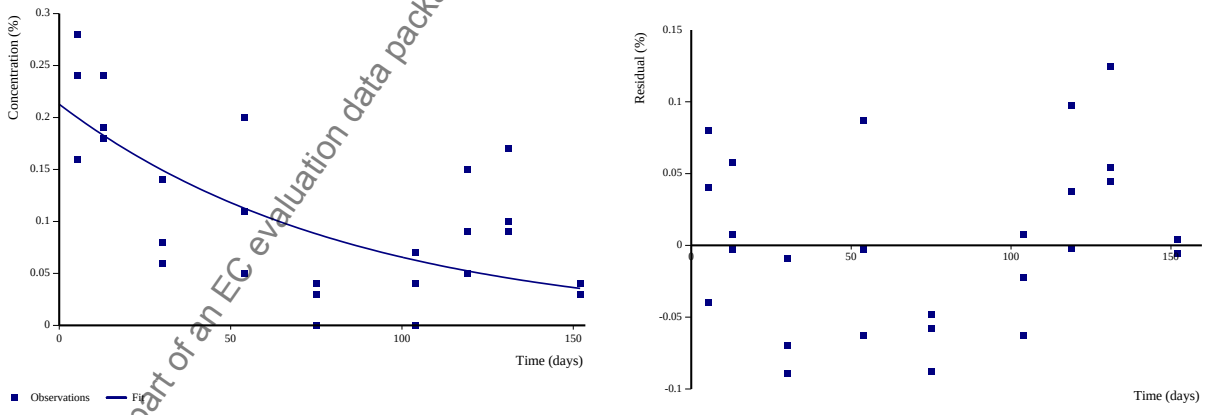
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maximum level of X11393729 detected was 0.23 µg/kg (average value expressed as molar equivalents of parent) and this represents only 6.6% of the average initial concentration of parent of 3.51 µg/kg. The Applicant considered that the formation fraction of 0.12 is likely to be more realistic than the value of 0.97 derived from the SFO/SFO model. The RMS has some difficulty with this fitting, particularly as sequential fitting of X11393729 with the parent makes the parent fit worse (χ^2 error increases from 22.6 for DFOP parent only to 28.4 with DFOP parent + SFO metabolite) and results in faster degradation of parent (both fast and slow phases are faster with the sequential parent and metabolite fit although there is a reduction in g value from 0.82 to 0.48 indicating less substance in the fast phase compartment). The RMS notes that the difference in parent fitting may be related to use of IRLS weighting in the sequential fitting procedure. Thus the RMS considers that parameters from this sequential fitting are not acceptable unless the parent exposure modelling is clearly differentiated from modelling for the metabolites where parent in modelling for metabolite concentrations has less conservative kinetic parameters with the presumption that this may drive a more conservative metabolite assessment.

Because of the high χ^2 error value from this DFOP/SFO fit, a further kinetics fit was performed on X11393729 using a top-down SFO model. The top-down fit was performed starting at 5.3 DAT (13 DAT real time), which is the time of maximum formation of X11393729. This gave 9 time points on the decline curve. The results are as follows:

Figure B.8.61 Statistics for kinetic fitting of Germany, Spring, X11393729, top down from peak (occurred after 10mm rainfall), SFO

Parameter	Value	σ	Prob > t	Lower CI	Upper CI	DT50 (d)	X^2 err (%)
k (d^{-1})	0.01176	0.00287	0.00019	0.00585	0.018	58.9	32.4



The fit gave a χ^2 error of 32%, which is only slightly improved on that obtained for the DFOP/SFO sequential fit with parent. The t-test and confidence intervals were acceptable. The visual fit for top-down SFO was similar to that obtained for DFOP/SFO although the distribution of residuals around the zero line was slightly better at later time points. Despite high variability in the replicates at most time points,

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the visual fit was considered reasonable by the Applicant considering that X11393729 was detected at a maximum of less than 7% of the initial parent concentration.

Statistically, the top-down fit for X11393729 gave the best fit. However, the DFOP/SFO sequential fit with parent was similar and also gives a calculated formation fraction. Therefore, the Applicant considered two options may be considered for model inputs for X11393729 at this site. The first option would be to use the k1 degradation rate for parent from the DFOP model together with a formation fraction of 0.12 and DT50 of 23 days for X11393729. The second option would be to use a top down DT50 of 59 days for X11393729 with the applied dose rate adjusted for the maximum amount observed (6.6%). In the final analysis, the Applicant decided to use the values from the sequential fitting as this is consistent with their overall approach to selection of input parameters for exposure modelling of the metabolites.

Parent, X11393729 and X11449757

The X11449757 data were added to the model and a sequential fit was performed for Parent, X11393729 and X11449757 using DFOP for the parent (which had previously given a better fit for X11393729). X11393729 is designated ‘A1’; X11449757 is designated ‘A2’. The results are as follows:

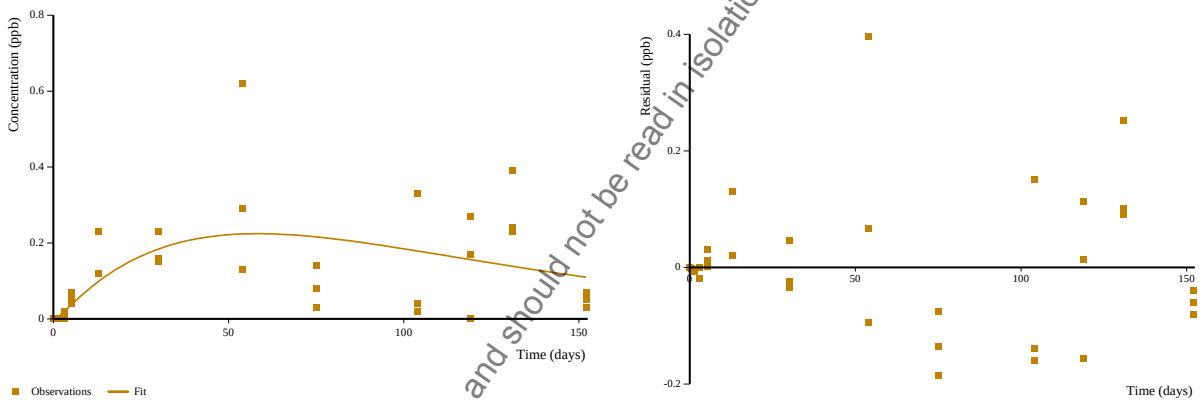
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Figure B.8.62 Statistics for kinetic fitting of Germany, Spring, Parent + X11393729 + X11449757, all data, DFOP+SFO+SFO

Parameter	Value	σ	Prob > t	Lower CI	Upper CI	DT50* (d)	X^2 err (%)
M_0 (µg/kg)	3.391	0.2889	2.28E-21	2.819	3.964	-	26.6
k1 (d^{-1})	0.8173	0.3219	0.006262	0.1793	1.455	0.85	
k2 (d^{-1})	0.02385	0.00703	0.000481	0.00992	0.038	29.1	
g	0.4463	0.09838	7.40E-06	0.2513	0.641	-	
f_Par_to_A1	0.1509	0.04027	0.000143	0.07112	0.231	-	36.5
k_A1 (d^{-1})	0.04293	0.0122	0.000317	0.01875	0.067	16.2	
f_A1_to_A2	1	0.4266	0.01045	0.1544	1.846	-	55.7
k_A2 (d^{-1})	0.01512	0.00662	0.01214	0.00200	0.028	45.8	

* DT50 for each rate constant calculated from ln2/k

Compartment A2:



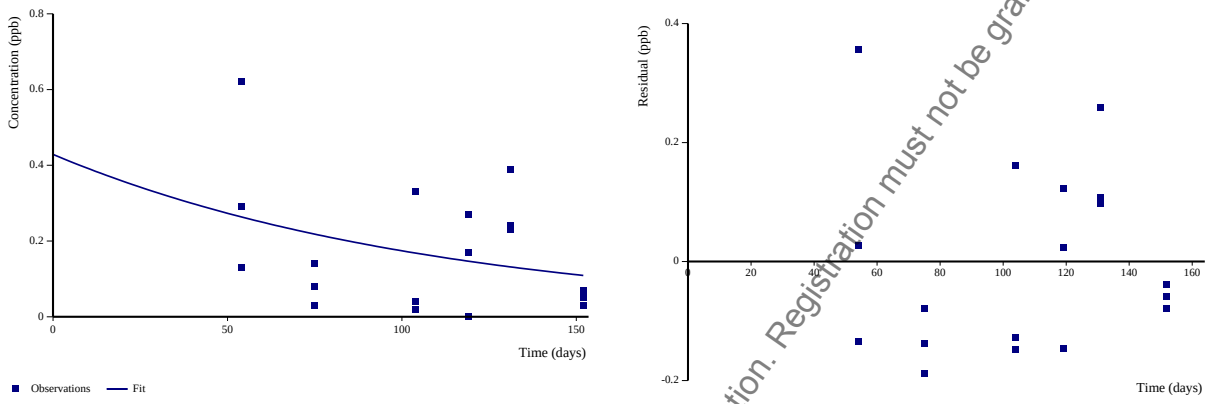
Only the X11449757 visual fit is shown here (quality of fit for parent and X11393729 were slightly changed by inclusion of X11449757 but not by a large amount). The t-test and confidence intervals were acceptable but χ^2 error was very high (55.7) The RMS considers that it is likely that the scattered nature of the later sample points is a consequence of the results for parent and X11393729 at this site.

A top-down fit was applied to X11449757 starting from the time of maximum formation at 54 DAT (91 DAT real time). The results are as follows:

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Figure B.8.63 Statistics for kinetic fitting of Germany, Spring, X11449757, top down from peak (occurred after 10mm rainfall), SFO

Parameter	Value	σ	Prob > t	Lower CI	Upper CI	DT50 (d)	X^2 err (%)
k (d^{-1})	0.00900	0.00657	0.09483	-0.00493	0.023	77	43.4



The kinetic fit was considered to be poor with a high χ^2 error and lower confidence interval less than zero, which is not unexpected given the high scatter in the data. The Applicant concluded that it was not possible to derive any useful kinetic data for X11449757 from this data set. The RMS agrees with this conclusion.

Germany, Autumn

Unnormalised data (Germany, Autumn)

Parent

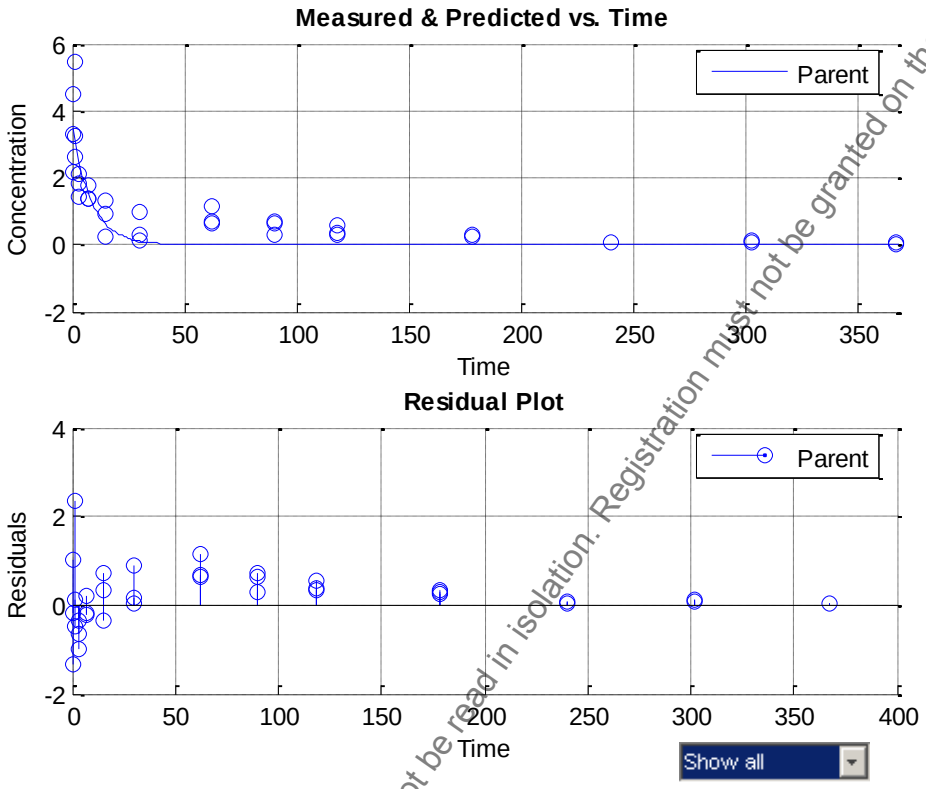
The kinetics fits for the measured data (i.e. not corrected for temperature and moisture) using the SFO and FOMC models for parent XDE-729 Methyl only are shown in the following table.

Table B.8.86 Statistics for SFO and FOMC fitting for Germany, Autumn field dissipation data, XDE-729 methyl, all data

Model	Parameter	Value	Lower CI	Upper CI	Std Dev	Prob > t	DT_{50} (d)	DT_{90} (d)	% χ^2 error
SFO	M_0 (µg/kg)	3.49	2.91	4.07	0.29	-			
(all data)	k (d^{-1})	0.1152	0.0602	0.1701	0.0271	7.0e-05	6.0	20	32.1
FOMC	M_0 (µg/kg)	3.67	3.02	4.32	0.32	-			
(all data)	alpha	0.6886	0.2380	1.1392	0.2222	0.0019	5.0	78	24.4
	beta	2.8696	-1.4970	7.2362	2.1530	0.0955			

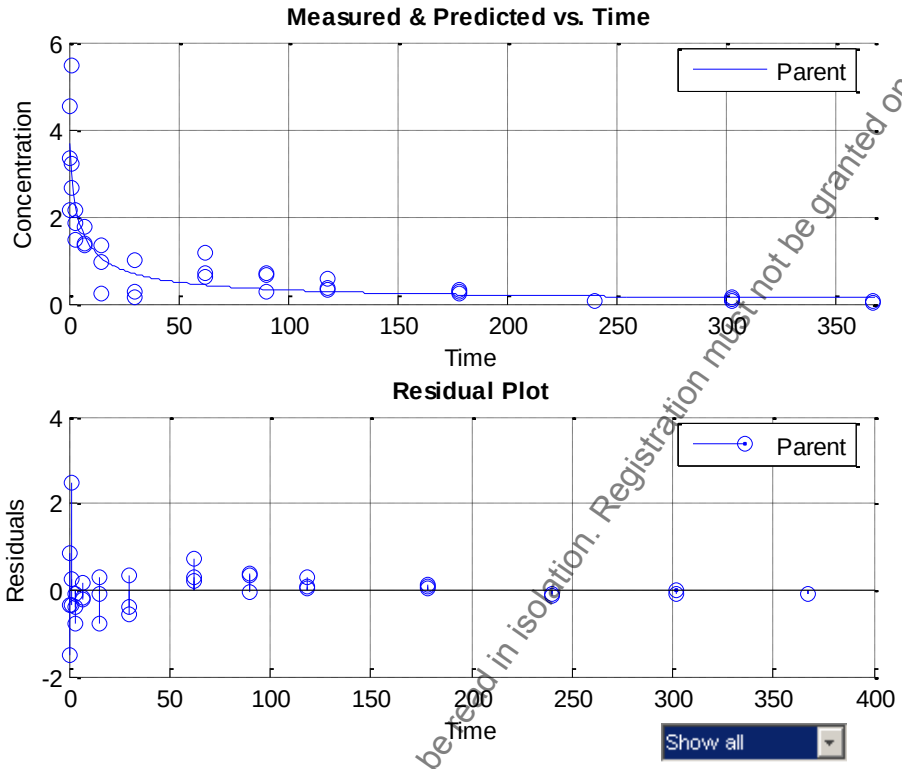
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Figure B.8.64 SFO fitting for Germany, Autumn field dissipation data, XDE-729 methyl, all data



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Figure B.8.65 FOMC fitting for Germany, Autumn field dissipation data, XDE-729 methyl, all data



The SFO model gave a DT50 of 6.0 days with a χ^2 error of 32% and acceptable t-test. The FOMC model gave a lower χ^2 error of 24% but the Applicant considered that the β parameter showed unacceptable error and lower CI less than zero. The RMS agrees that the lower CI is of concern, but notes that the t-test is not strictly relevant for FOMC parameters (as noted by FOCUS Kinetics guidance). The Applicant considered that the SFO model was the best fit, although the χ^2 error is high. This high error is due mainly to the high variability in the data at early time points. However, in spite of the poor result of the lower CI for the FOMC fit, the RMS considers that FOMC is the better model for describing the decline, being much better able to describe the obvious tail of residues. The RMS thus proposes best fit parameters from this trial site as FOMC DT50 of 5 days and DT90 of 78 days.

X11393729

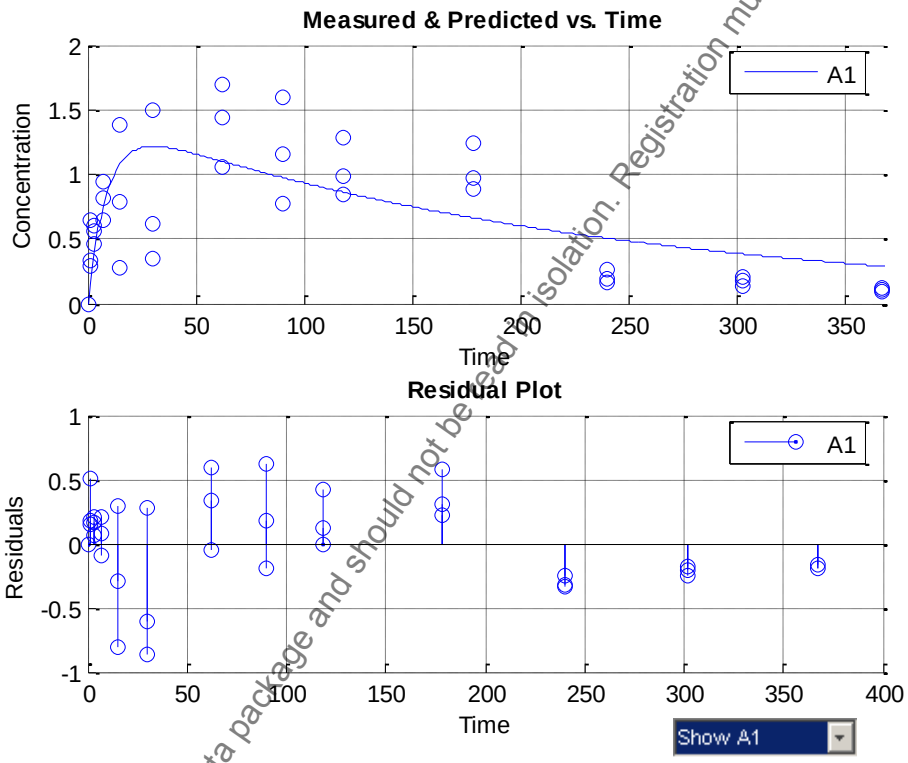
Using the optimised SFO parameters for parent XDE-729 methyl as initial values, X11393729 was added to the kinetics model with the formation fraction set to an initial value of 0.5. The optimised parameters for parent and metabolite are shown in the following table and figure. Only the fit for X11393729 is shown as the fitting for parent was not significantly affected.

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Table B.8.87 Statistics for SFO+SFO fitting for Germany, Autumn field dissipation data, XDE-729 methyl+ X11393729, all data

Model	Parameter	Value	Lower CI	Upper CI	Std Dev	Prob > t	DT_{50} (d)	DT_{90} (d)	% χ^2 error
SFO Parent	M_0 (µg/kg)	3.46	3.02	3.91	0.22	-			
	k (d^{-1})	0.1108	0.0712	0.1505	0.0199	2.0e-07	6.3	21	32.1
SFO Acid	Form fraction	0.4015	0.2561	0.5469	0.0730	-			
	k (d^{-1})	0.0044	0.0012	0.0076	0.0016	0.0040	158	524	31.8

Figure B.8.66 SFO+SFO fitting for Germany, Spring field dissipation data, XDE-729 methyl + X11393729, all data, X11393729 only shown

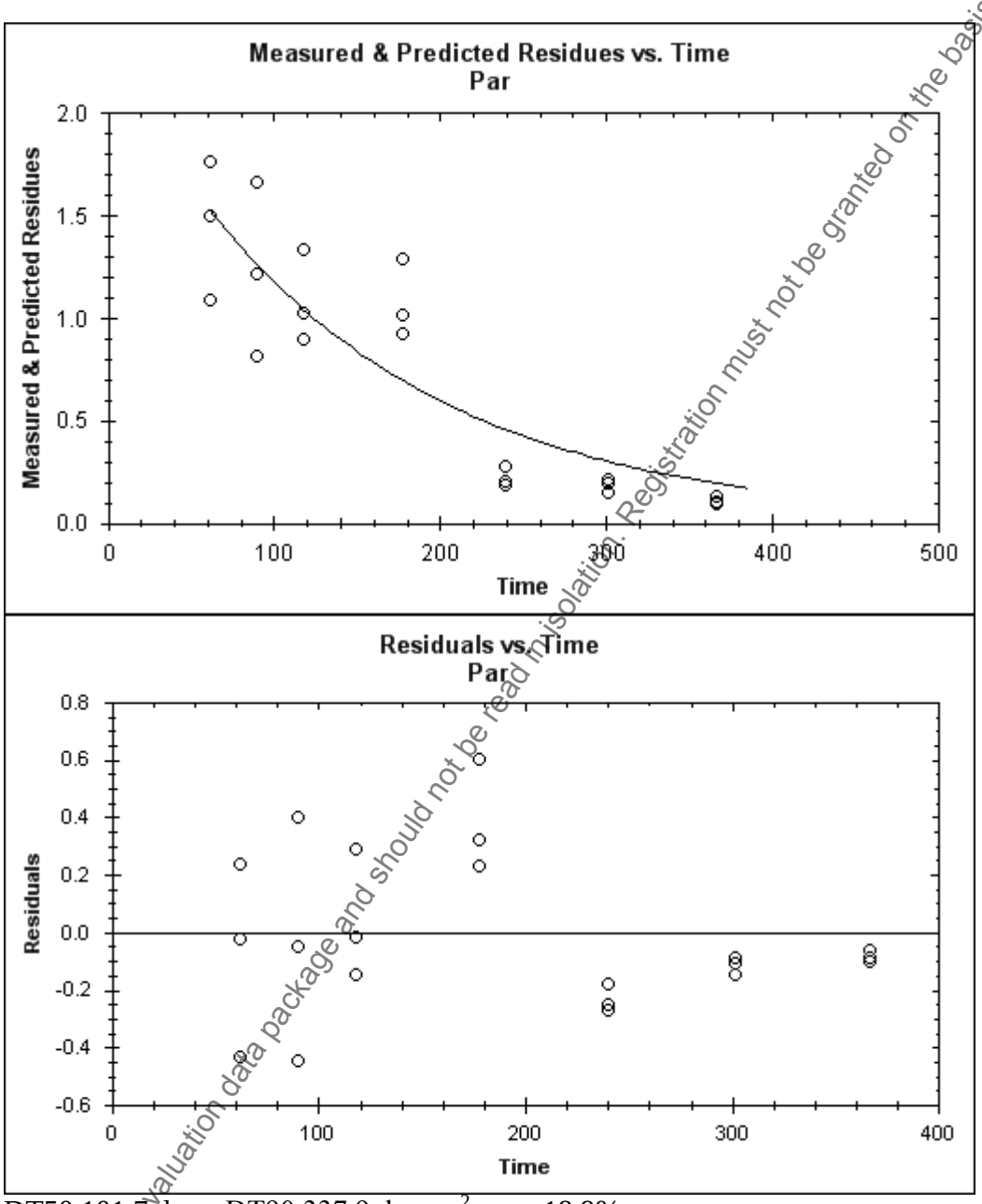


The parameters for parent were similar to those obtained with parent alone. Although the χ^2 error was significantly greater than 15% for both parent and metabolite, considering the high variability in the triplicate values at some time points, the visual fit is considered to give a reasonable estimation of the degradation rate for both ester and acid. Therefore, the Applicant proposed a best-fit degradation DT50 for X11393729 at this site of 158 days with a formation fraction of 0.402.

The RMS calculated a separate SFO top down DT50.

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Figure 8.67 RMS top-down SFO fit for X11393729, Germany Autumn, data from 62 DAT.



DT50 101.7 days, DT90 337.9 days, χ^2 error 18.9%

The RMS considers that the SFO top down DT50 is appropriate for use in simple calculations such as PECsoil calculation and proposes the DT50 value of 101.7 days for this trials site.

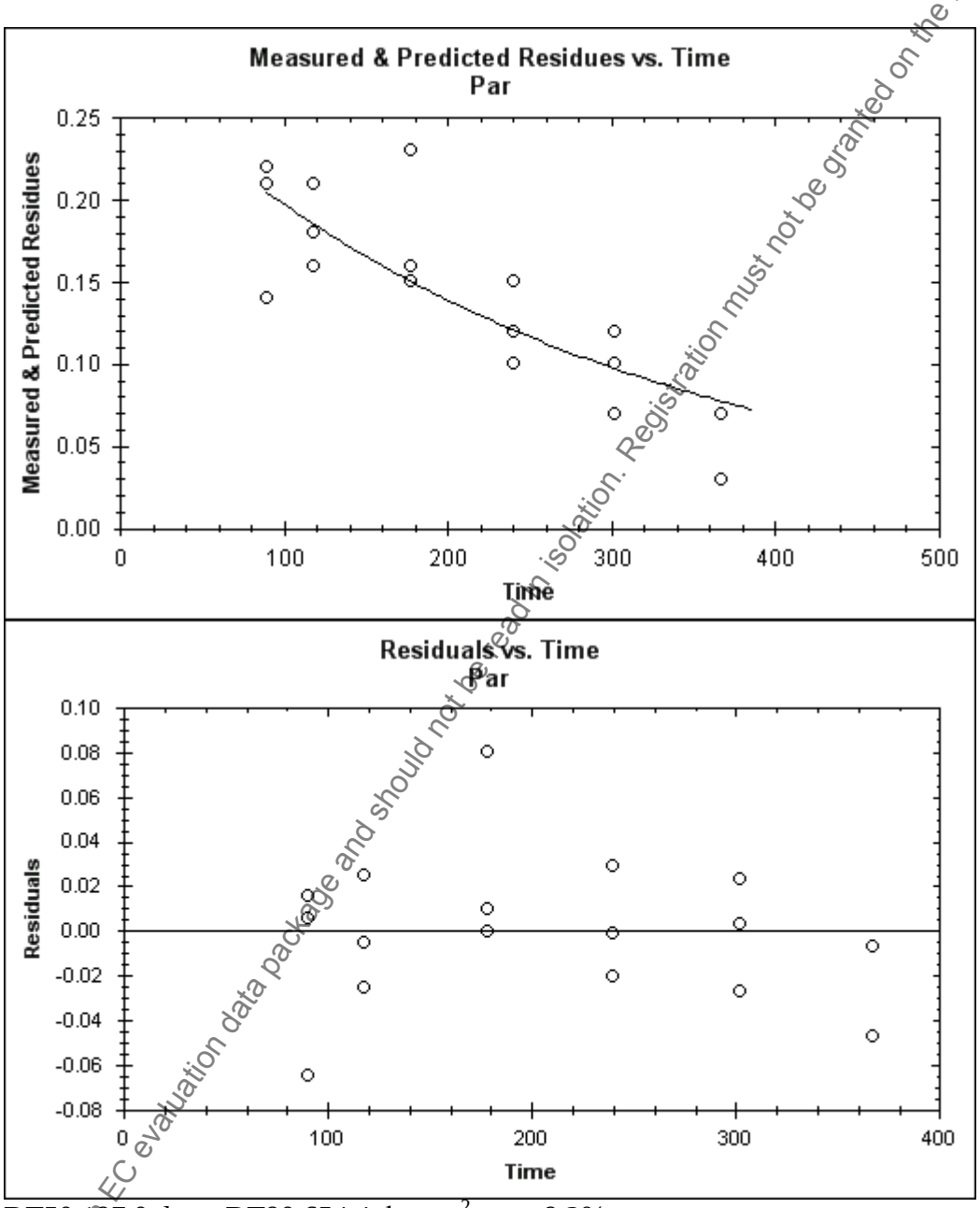
X11449757

X11449757 was detected at very low levels in this data set (maximum average residue 0.18 µg/kg which equates to approximately 5% of the initial residue). Therefore, no attempt was made by the Applicant to fit X11449757 to the kinetics model with the ester and acid.

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The RMS calculated a separate SFO top down DT50.

Figure 8.68 RMS top-down SFO fit for X11449757, Germany Autumn, data from 90 DAT.



DT50 197.0 days, DT90 654.4 days, χ^2 error 9.2%

The RMS considers that the SFO top down DT50 is appropriate for use in simple calculations such as PECsoil calculation and proposes the DT50 value of 197.0 days for this trials site.

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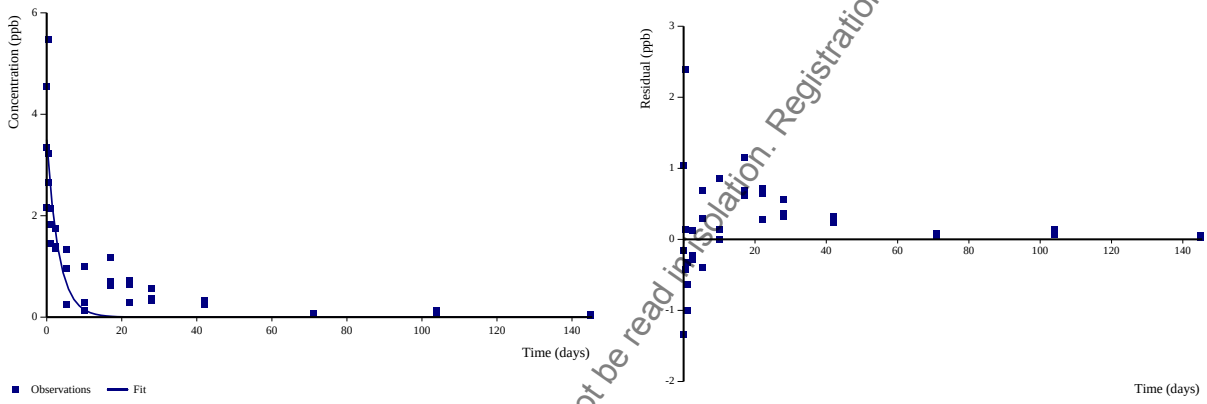
Data normalised to 20 °C and pF 2 (Germany, Autumn)

Parent

The results of fitting XDE-729 methyl (all data) to the SFO model are as follows:

Figure B.8.69 Statistics for kinetic fitting of Germany, Autumn, Parent only, all data, SFO

Parameter	Value	σ	Prob > t	Lower CI	Upper CI	DT50 (d)	X^2 err (%)
M_0 (µg/kg)	3.496	0.2887	9.705E-15	2.911	4.081	2.2	31.9
k (d^{-1})	0.3176	0.0742	6.326E-05	0.1673	0.468		



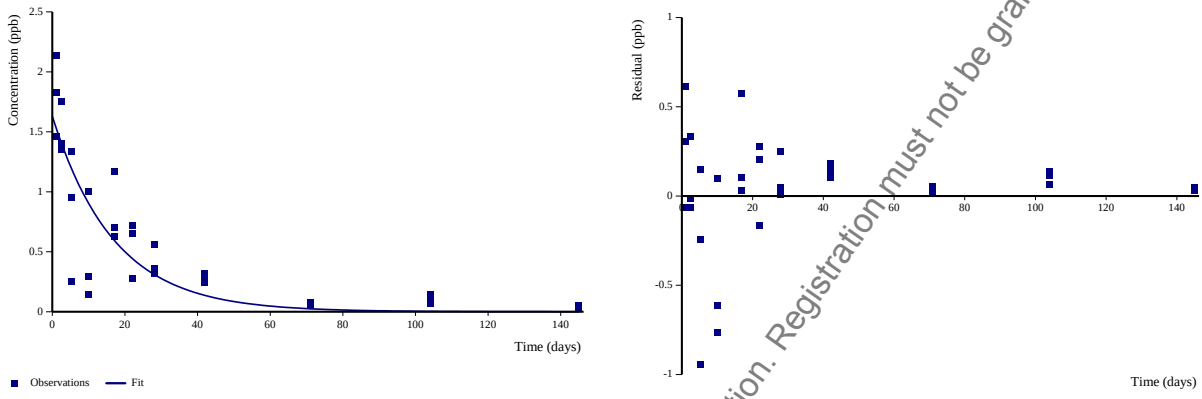
The SFO model gives a high χ^2 error and the visual fit clearly shows that there is a biphasic pattern with initial rapid decline followed by slower decline.

A further SFO fit was conducted after eliminating data points before 10 mm rainfall. The cumulative rainfall exceeded 10 mm (total = 20.2 mm) at 0.7 DAT (2 DAT real time). The first sampling time point after this was 1.1 DAT (3 DAT real time), and the total rainfall at this time point was 25.2 mm. Therefore, the kinetics model was run taking 1.1 DAT as the first time point. During this time, the residues of XDE-729 methyl, based on average concentrations, had decreased from 3.35 µg/kg to 1.81 µg/kg. Therefore, 54% of the initial concentration of XDE-729 methyl remained in the soil at the starting point of the kinetics fit. The LOQ of 0.05 µg/kg represents 2.8% of this starting value. This gave 11 time points on the decline curve. The results of the SFO fit are as follows:

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Figure B.8.70 Statistics for kinetic fitting of Germany, Autumn, Parent only, data after 10 mm rainfall, SFO

Parameter	Value	σ	Prob > t	Lower CI	Upper CI	DT50 (d)	X^2err (%)
M_0 (µg/kg)	1.629	0.1476	1.44E-12	1.328	1.93	11.7	27.3
k (d^{-1})	0.05904	0.01153	7.61E-06	0.03552	0.083		



A reasonable visual fit was obtained despite wide scatter in the replicates and between some sampling times at early time points. There is a small tail of residues at later time points which do not fit to the model but this is much less than for the spring trial in Germany. The DT50 of 11.7 days is significantly longer than that obtained from the whole data set due to some of the initial rapid decline being removed from the fit. The χ^2 error of 27.3% is lower than that obtained with the whole data set but is still higher than the target value of 15%.

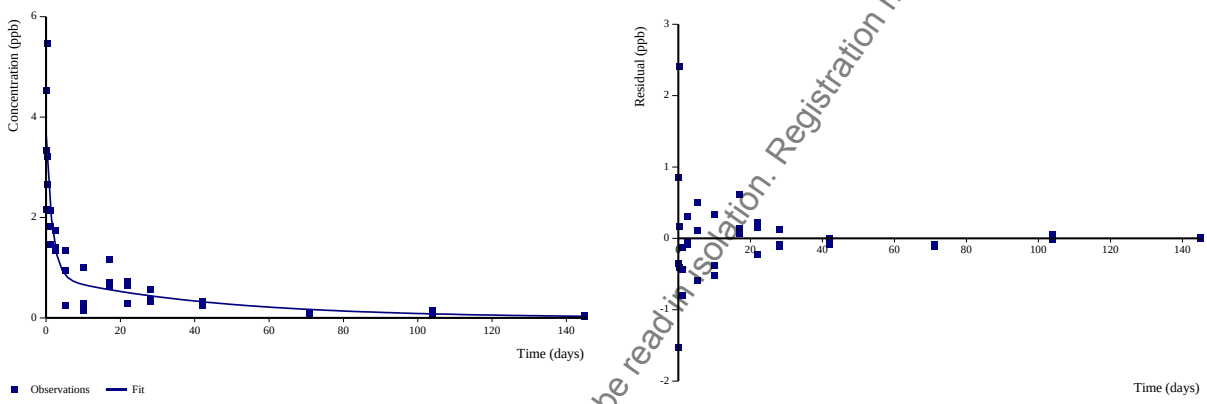
Since the χ^2 error is higher than desired, it is not certain that the SFO model gives the most appropriate fit. Therefore, Step 5 of the EFSA assessment scheme was followed by running the DFOP model with all of the data. The results are as follows:

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Figure B.8.71 Statistics for kinetic fitting of Germany, Autumn, Parent only, all data, DFOP

Parameter	Value	σ	Prob > t	Lower CI	Upper CI	DT50* (d)	X^2 err (%)
M_0 (µg/kg)	3.691	0.2937	7.82E-15	3.095	4.287	-	22.2
k1 (d^{-1})	0.6125	0.2222	0.004614	0.1613	1.064	1.1	
k2 (d^{-1})	0.02238	0.01981	0.1331	-0.01783	0.063	30.9	
g	0.777	0.1004	2.19E-09	0.5731	0.981	-	

* DT50 for each rate constant calculated from ln2/k



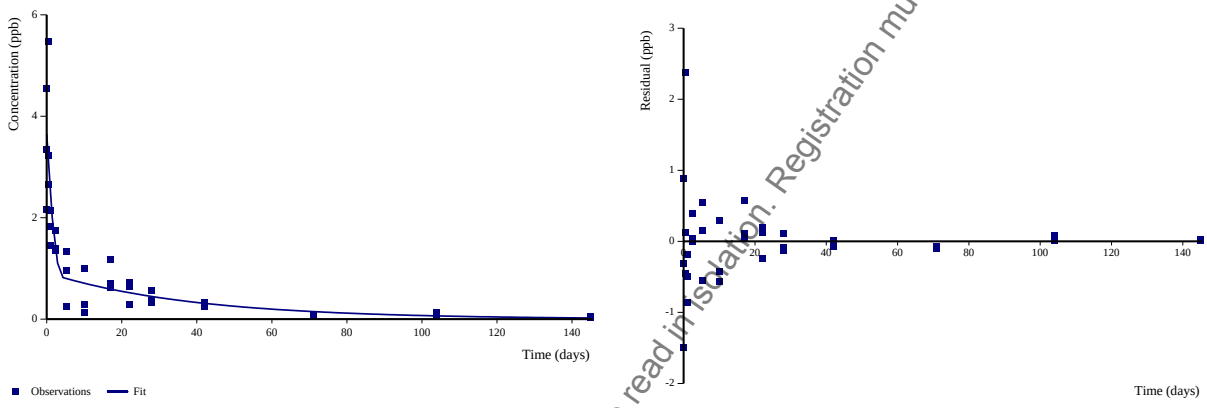
The high value of g (0.777) indicates that the fast decline dominates and there is a high error on the k2 value, with a lower CI less than zero. Because g is greater than 0.75 then the HS model was run. The results for the HS model for parent XDE-729 Methyl are as follows:

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Figure B.8.72 Statistics for kinetic fitting of Germany, Autumn, Parent only, all data, HS

Parameter	Value	σ	Prob > t	Lower CI	Upper CI	DT50* (d)	X^2 err (%)
M_0 (µg/kg)	3.653	0.2788	2.341E-15	3.087	4.219	-	22.1
k1 (d^{-1})	0.4121	0.09699	7.563E-05	0.2152	0.609	1.7	
k2 (d^{-1})	0.0256	0.01937	0.09741	-0.01372	0.065	27.1	
t_b (days)	3.585	1.161	0.001967	1.228	5.941	-	

* DT50 for each rate constant calculated from ln2/k



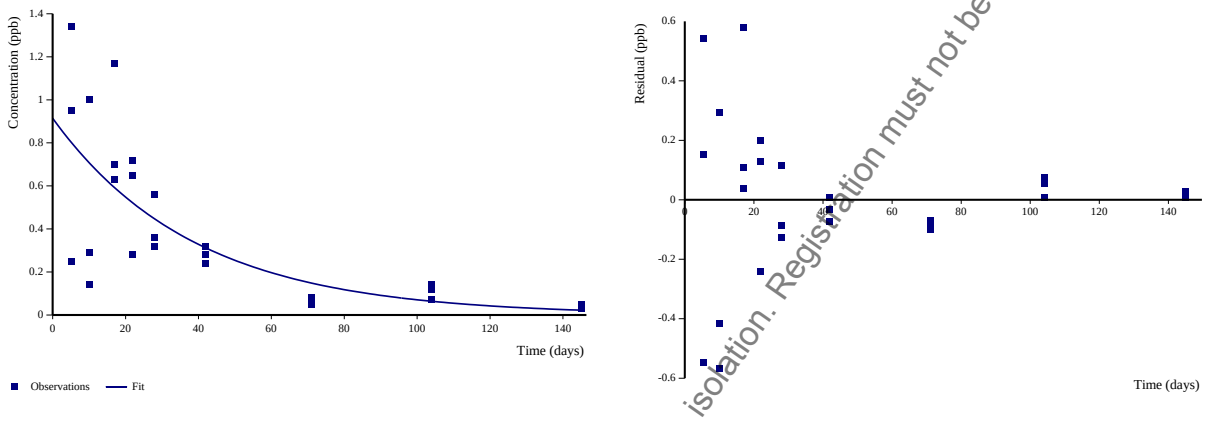
The break point of 3.6 DAT is after the 10 mm rain time point of 1.1 DAT. At the 3.4 DAT (10 DAT real time) sample time, which is just before the breakpoint, the rainfall was 47.6 mm, almost five times higher than the recommended 10 mm. The optimised k2 value of 0.0256 d^{-1} gives a slow phase DT50 of 27 days but the lower confidence interval was less than zero and t-test was > 0.05, therefore the value was considered by the Applicant as not reliable.

Since the HS model is essentially two SFO models applied to different parts of the curve, the Applicant performed a further SFO fit on the data after the breakpoint derived in the previous HS fit. The aim was to obtain acceptable statistical parameters. The first time point after 3.6 DAT is 5.3 DAT and the average residue of XDE-729 Methyl at this time was 0.85 µg/kg which is equivalent to 25% of the initial residue of 3.35 µg/kg. The LOQ of 0.05 µg/kg represents 5.9% of this starting value. Since 75% of the initial residue is excluded from this fit, it can be considered as a conservative approach to deriving a bulk matrix DT50 value. At this time point, 59 mm of rain had fallen so the Applicant considered it unlikely that any surface dissipation processes would be occurring after this time. The results of this SFO fit are as follows:

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Figure B.8.73 Statistics for kinetic fitting of Germany, Autumn, Parent only, data from 5.3 DAT, SFO

Parameter	Value	σ	Prob > t	Lower CI	Upper CI	DT50 (d)	X^2 err (%)
M_0 (µg/kg)	0.9142	0.1564	2.14E-06	0.592	1.236	27.1	23.6
k (d^{-1})	0.0256	0.00876	0.00365	0.00755	0.044		



The χ^2 error was lower than for the previous SFO fits and the residuals were more evenly distributed around the x axis. Also, the DT50 was identical to that obtained from the slow phase of the HS model. Therefore, since all statistical parameters were within acceptable ranges, the DT50 value of 27 days was proposed as acceptable by the Applicant. Taking all the assessments above into account, the RMS can accept the SFO DT50 value of 27 days from this trial.

Parent + X11393729

As described for the Germany/Spring data set, in order to describe the formation of X11393729 under realistic worst case conditions, the sequential fit was initial performed using SFO for parent together with SFO for X11393729.

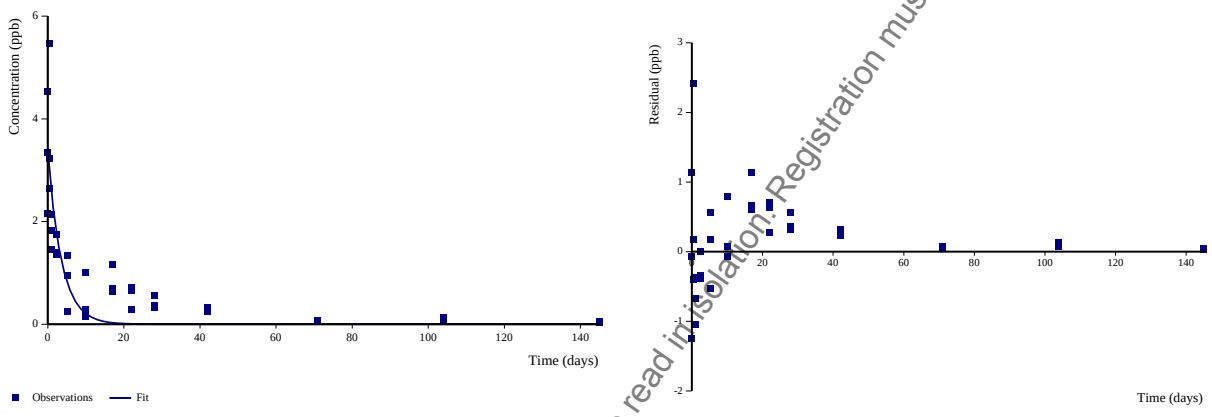
The optimised parameters for parent and X11393729 (designated A1) are as follows:

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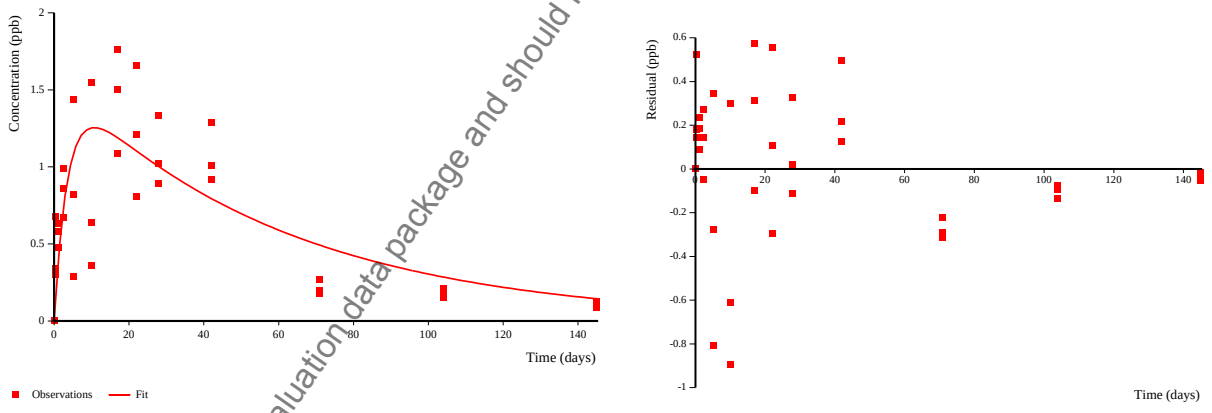
Figure B.8.74 Statistics for kinetic fitting of Germany, Autumn, Parent + X11393729, all data, SFO+SFO

Parameter	Value	σ	Prob > t	Lower CI	Upper CI	DT50 (d)	X^2 err (%)
M_0 (µg/kg)	3.409	0.2662	9.41E-21	2.878	3.939	-	
k_Parent (d^{-1})	0.2799	0.05386	8.64E-07	0.1726	0.387	2.5	32.1
f_Par_to_A1	0.4396	0.06445	1.06E-09	0.3112	0.568	-	
k_A1 (d^{-1})	0.01655	0.00425	0.00011	0.00808	0.025	41.9	24.8

Compartment Parent:



Compartment A1:



After addition of the X11393729 metabolite to the model, the fitting and consequent DT50 for parent was similar to that obtained for parent alone (2.5 days and 2.2 days, respectively). The χ^2 error for the X11393729 was 25%, the t-test and confidence intervals were acceptable and the visual fit is reasonable. The RMS notes that given the scatter in replicate data, the model is able to reasonably simulate peak formation of X11393729.

As described for the Germany/Spring dataset, a second kinetic fit was run by the Applicant using DFOP for parent and SFO for X11393729 , to check if this model is suitable to describe the initial conversion of Parent to X11393729 . The results are as follows:

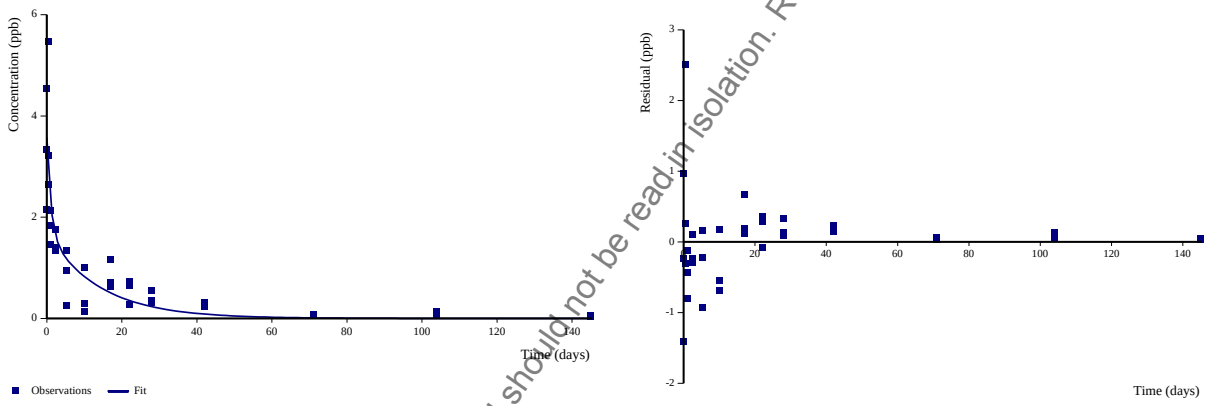
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Figure B.8.75 Statistics for kinetic fitting of Germany, Autumn, Parent + X11393729, all data, DFOP+SFO

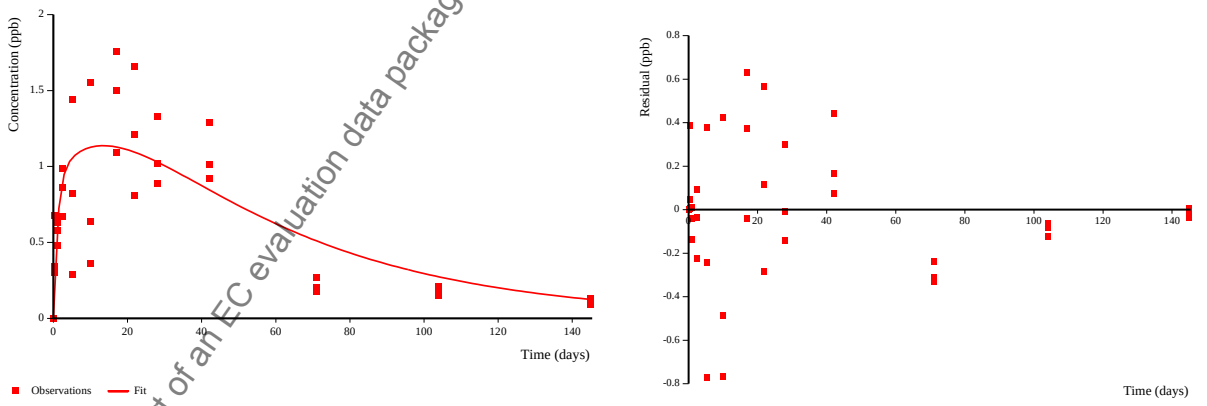
Parameter	Value	σ	Prob > t	Lower CI	Upper CI	DT50* (d)	X^2 err (%)
M_0 (µg/kg)	3.572	0.2868	6.18E-20	3.001	4.144	-	26.8
k1 (d^{-1})	0.8991	0.4697	0.02977	-0.03714	1.835	0.8	
k2 (d^{-1})	0.07074	0.03119	0.01316	0.00857	0.133	9.8	
g	0.5284	0.1481	0.00032	0.2332	0.824	-	
f_Par_to_A1	0.4772	0.07918	3.25E-08	0.3193	0.635	-	23.0
k_A1 (d^{-1})	0.01922	0.00463	4.44E-05	0.00999	0.028	36.1	

* DT50 for each rate constant calculated from ln2/k

Compartment Parent:



Compartment A1:



Using DFOP for parent resulted in a better statistical and visual fit for the parent compared to SFO, although the lower CI for the k1 parameter was less than zero. The RMS also notes that sequential fitting with X11393729 adversely affects the parent fitting as χ^2 error is increased. The biphasic nature of the fit to parent data is less pronounced with a lower proportion in the fast phase compartment. overall degradation appears to be increased with a poorer fit of parent to the later time points. For X11393729, the fits were very similar using both the SFO/SFO and DFOP/SFO

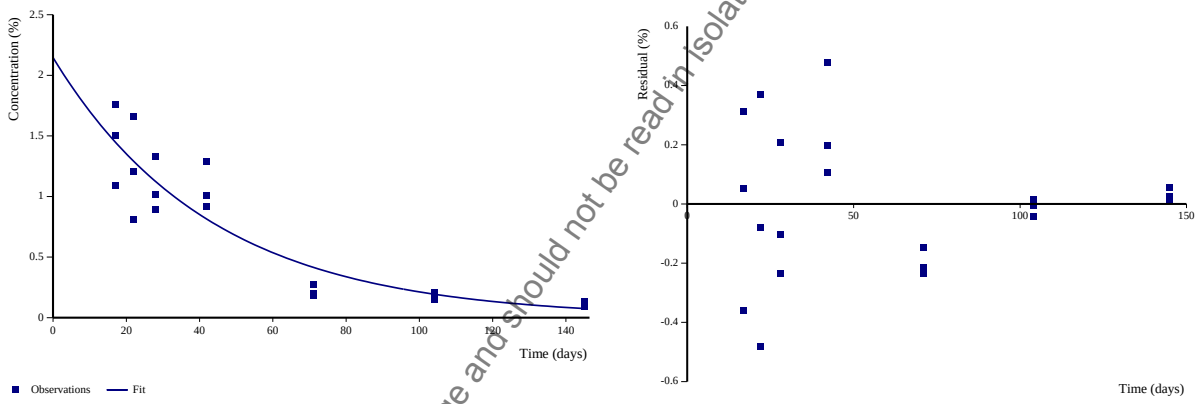
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sequential models, with χ^2 error values of 25% and 23%, respectively, and similar visual fits. The RMS notes that the DFOP/SFO fit gives a slightly lower peak concentration than the SFO/SFO fit. The DT50 values (42 days and 36 days, SFO/SFO and DFOP/SFO respectively) and formation fractions (0.44 and 0.48, SFO/SFO and DFOP/SFO respectively) were also similar.

Finally, since all sequential fits did not meet all acceptance criteria, a top-down SFO fit was performed on the X11393729, starting at 17 DAT (62 DAT real time), the time of maximum formation of X11393729 . This gave 7 time points on the decline curve. An SFO fit was applied to the data and results are shown in the following table:

Figure B.8.76 Statistics for kinetic fitting of Germany, Autumn, X11393729, top down from peak (occurred after 10mm rainfall), SFO

Parameter	Value	σ	Prob > t	Lower CI	Upper CI	DT50 (d)	X^2 err (%)
k (d^{-1})	0.02312	0.00436	2.06E-05	0.01398	0.032	30.0	13.3



The top-down SFO fit gave a much lower χ^2 error (13%) than any of the sequential fits with parent and the residuals are evenly distributed (albeit with high scatter in the data)

The Applicant concluded that the top-down fit with X11393729 gave a better fit, both statistically and visually, than either of the sequential fits with parent. The top-down DegT50 of 30 days was considered by the Applicant as a conservative estimate for X11393729 as it does not take into account formation kinetics. Alternatively, the Applicant proposed the SFO/SFO sequential fit with parent as a valid approach for deriving model inputs for the X11393729. The degradation of parent is over-predicted in this sequential model but considered this is a worst-case situation with respect to formation of the X11393729. The RMS notes that peak concentrations of X11393729 were probably under predicted but the speed of decline from peak was under-estimated. The visual and statistical fit for the X11393729 were considered to be good by the Applicant and the sequential fitting was also considered to have the advantage of yielding a formation fraction for the X11393729, which is not possible with the top-down model. Therefore, a DegT50 of 2.5 days for parent together with a formation fraction of 0.44 and a DegT50 of 42 days for X11393729 is proposed as inputs for modelling the X11393729 metabolite. The RMS notes that if performing exposure

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modelling for parent sequentially with metabolites, this could lead to under prediction of environmental concentrations of parent, but could give precautionary concentrations of X11393729.

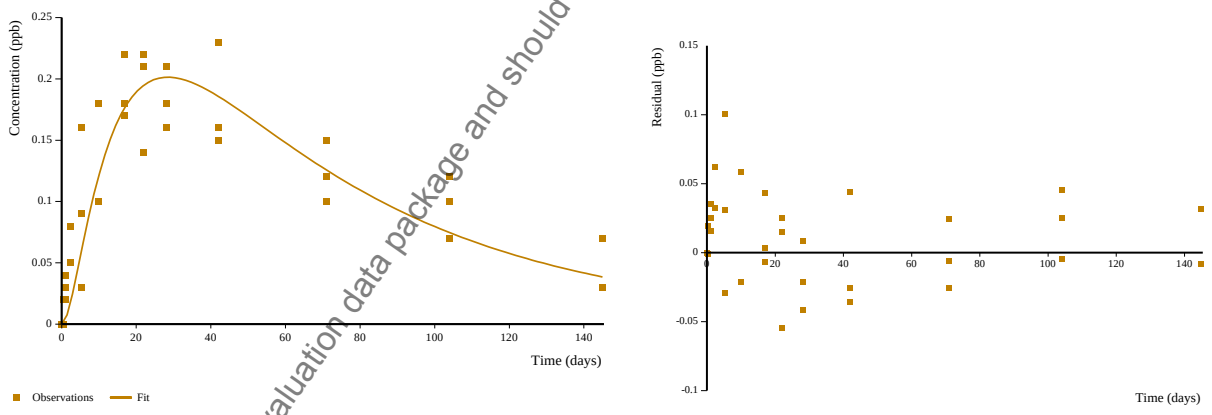
Parent + X11393729 + X11449757

The X11449757 data were added to the model and a sequential fit was performed for parent, X11393729 and X11449757 using SFO for the parent. The results are as follows:

Figure B.8.77 Statistics for kinetic fitting of Germany, Autumn, Parent + X11393729 + X11449757, all data, SFO+SFO+SFO

Parameter	Value	σ	Prob > t	Lower CI	Upper CI	DT50 (d)	X^2 err (%)
M_0 (µg/kg)	3.608	0.2792	3.67E-24	3.054	4.161		32.2
k_Parent (d^{-1})	0.3727	0.06582	5.95E-08	0.2422	0.503	1.9	
f_Par_to_A1	0.4085	0.05118	7.20E-13	0.307	0.51		25.7
k_A1 (d^{-1})	0.01619	0.00296	1.40E-07	0.01033	0.022	42.8	
f_A1_to_A2	1	0.3306	0.001545	0.3449	1.655		16.3
k_A2 (d^{-1})	0.07812	0.01954	5.77E-05	0.0394	0.117	8.9	

Compartment A2:



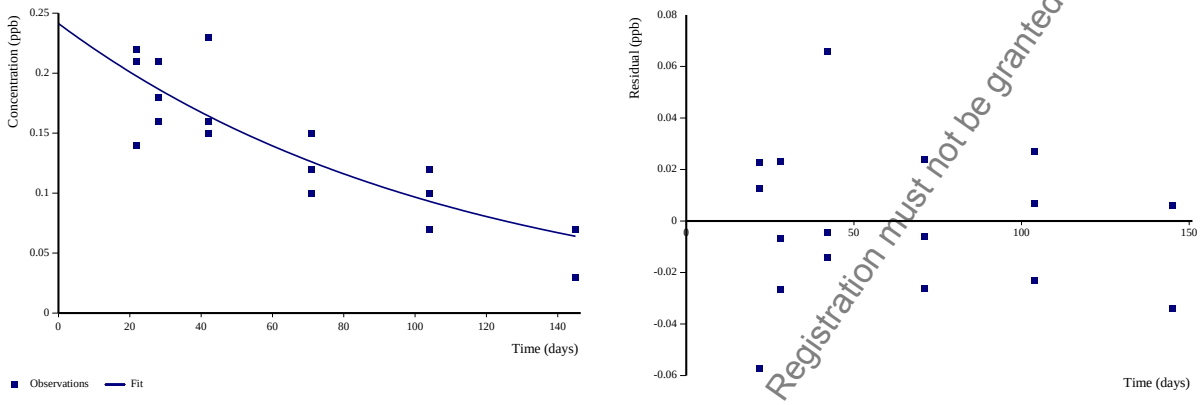
Only the X11449757 visual fit is shown here. The parameters for parent and X11393729 were very similar after addition of X11449757. The visual fit for X11449757 was good and the statistical parameters were acceptable. Therefore, the calculated DT50 of 8.9 days together with a formation fraction of 1 could be proposed.

To complete the kinetics analysis, a top-down fit was applied to X11449757starting from the time of maximum formation at 22 DAT (90 DAT real time). This gave 6 time points on the decline curve. The results are as follows:

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Figure B.8.78 Statistics for kinetic fitting of Germany, Autumn, X11449757, top down from peak (occurred after 10mm rainfall), SFO

Parameter	Value	σ	Prob > t	Lower CI	Upper CI	DT50 (d)	X^2 err (%)
k (d^{-1})	0.00915	0.00159	1.46E-05	0.00579	0.013	75.7	4.6



The kinetics fit was visually good with a low χ^2 error.

The best fit DT50 for X11449757was 76 days using the top-down SFO model, which can be considered as a conservative value. Alternatively, the sequential fit with the SFO model gave an acceptable fit for this metabolite and a DegT50 of 8.9 days and a formation fraction of 1 (from X11393729) together with the optimised parameters for parent and X11393729 described above can be proposed as realistic inputs for modelling X11449757. The RMS can agree to use of the parameters from the sequential fitting as this is consistent with the overall approach used by the Applicant for parameters fro exposure modelling.

UK, Spring

Unnormalised data (UK, Spring)

Parent

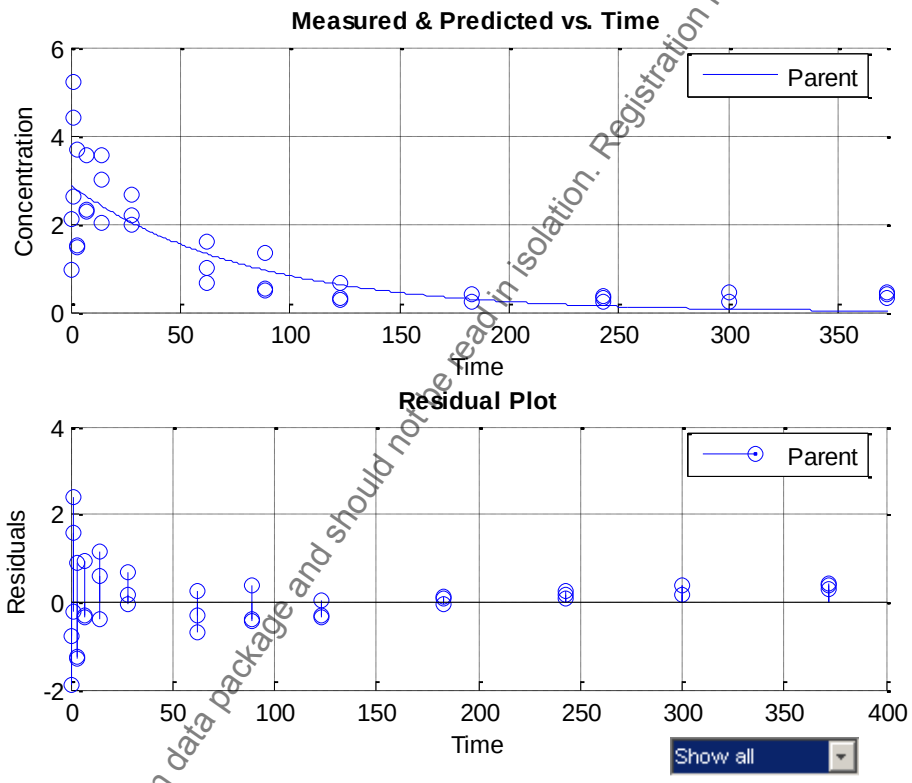
The kinetics fits for the measured data (i.e. not corrected for temperature and moisture) using the SFO and FOMC models for parent XDE-729 methyl only are shown in the following table.

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Table B.8.88 Statistics for SFO and FOMC fitting for UK, Spring field dissipation data, XDE-729 methyl, all data

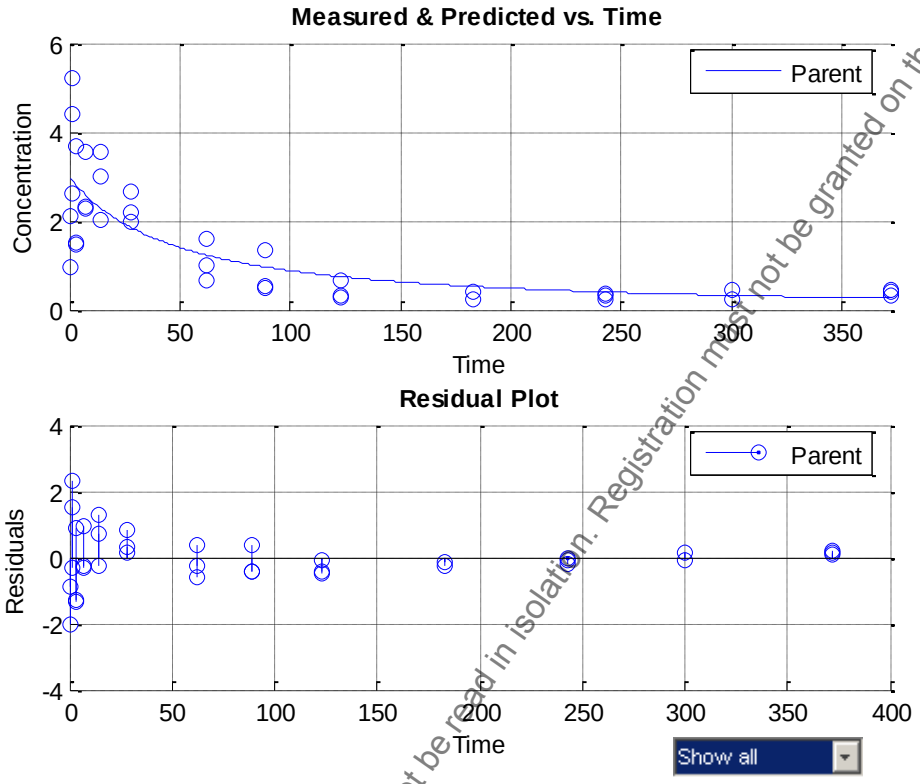
Model	Parameter	Value	Lower CI	Upper CI	Std Dev	Prob > t	DT_{50} (d)	DT_{90} (d)	% χ^2 error
SFO (all data)	M_0 (µg/kg) k (d^{-1})	2.87 0.0125	2.42 0.0063	3.32 0.0186	0.22 0.0030	- 1.0e-04	56	185	29.4
FOMC (all data)	M_0 (µg/kg) alpha beta	2.98 1.2336 59.17	2.41 -1.0684 -120.7	3.55 3.5355 239.0	0.28 1.1350 88.69	- 0.1422 0.2545	45	323	31.2

Figure B.8.79 SFO fitting for UK, Spring field dissipation data, XDE-729 methyl, all data



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Figure B.8.80 FOMC fitting for UK, Spring field dissipation data, XDE-729 methyl, all data



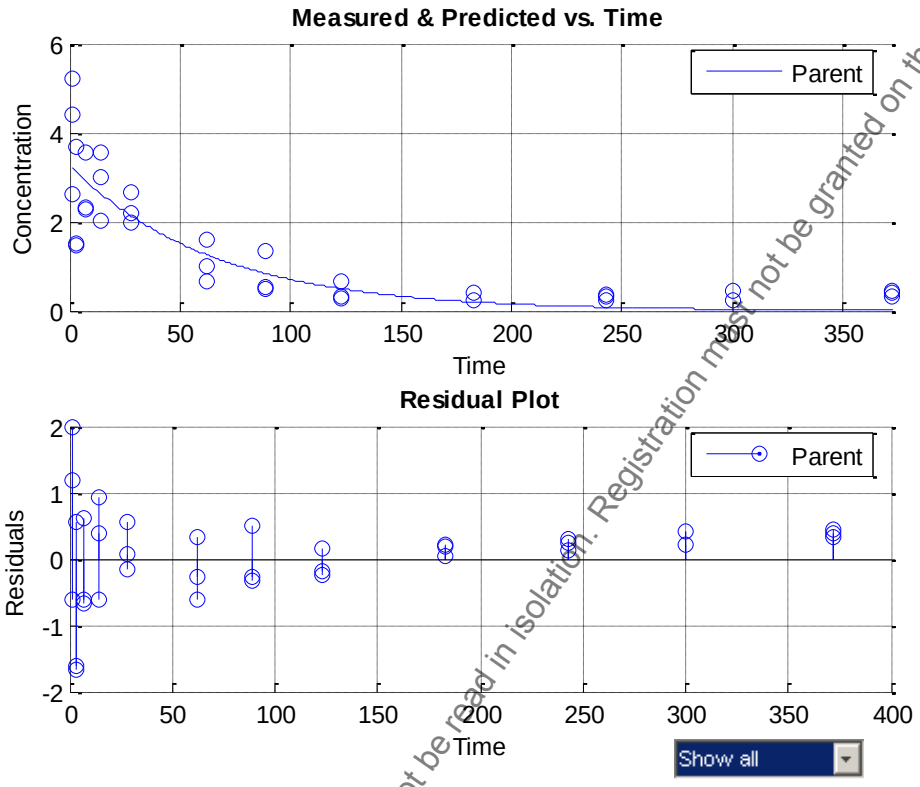
The SFO model gave a DT50 of 56days with a χ^2 error of 29% and acceptable t-test. The FOMC model gave a slightly higher χ^2 error and both the α and the β parameters showed unacceptable errors and lower CI less than zero. The SFO model was considered by the Applicant to give the best fit but visual examination showed wide scatter of data particularly at the early time points. Also, at Day 0, the measured residues are considerably lower than the predicted value (31% of theoretical), and were significantly lower than any of the other seven data sets. Low Day 0 residues are a common observation with field dissipation studies and this is acknowledged in FOCUS Kinetics guidance. In an attempt to improve the statistics, the kinetics fitting was repeated by the Applicant after omitting the Day 0 data. The results are shown in the following table.

Table B.8.89 Statistics for SFO and FOMC fitting for UK, Spring field dissipation data, XDE-729 methyl, omitting day 0 data

Model	Parameter	Value	Lower CI	Upper CI	Std Dev	Prob > t	DT_{50} (d)	DT_{90} (d)	% χ^2 error
SFO (exc D0)	M_0 (µg/kg)	3.21	2.75	3.68	0.23	-			
	k (d^{-1})	0.0154	0.0089	0.0219	0.0032	1.5e-05	45	150	22.7
FOMC (exc D0)	M_0 (µg/kg)	3.39	2.79	4.00	0.30	-			
	alpha	1.1411	-0.3484	2.6306	0.7321	0.0643	32	250	23.0
	beta	38.35	-50.93	127.62	43.88	0.1942			

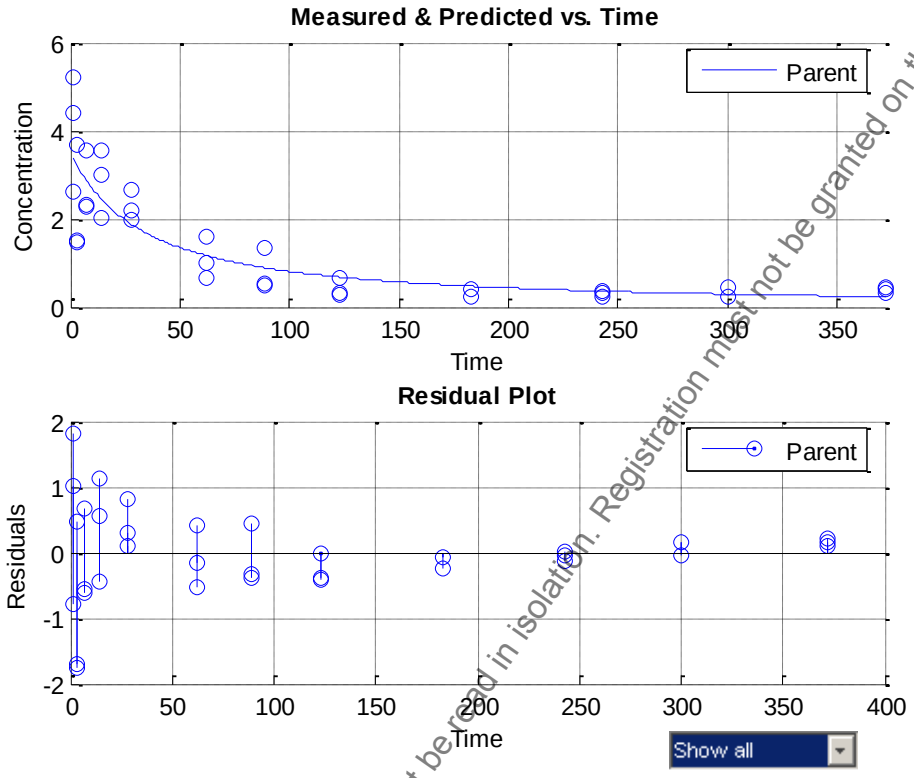
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Figure B.8.81 SFO fitting for UK, Spring field dissipation data, XDE-729 methyl, omitting day 0 data



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Figure B.8.82 FOMC fitting for UK, Spring field dissipation data, XDE-729 methyl, omitting day 0 data



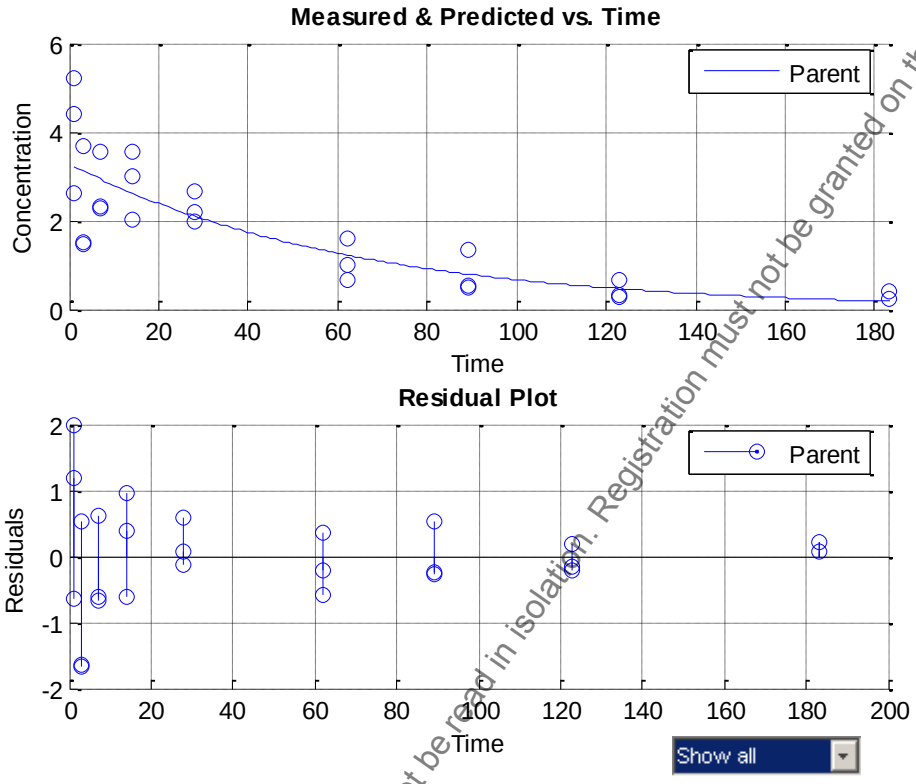
Omitting the Day 0 data improved the fit but the Applicant considered FOMC still gave unacceptable statistical outputs (lower CI less than zero, high t-test). The Applicant considered a similar pattern was seen in the UK trial as was seen in Germany with a tail of residues extending beyond 4 months at approximately 10% of the initial residue (based on the predicted Day 0 value of 3.21 µg/kg). Therefore, a further SFO fit was conducted using data from Day 1 to Day 183. Results are shown in the following table.

Table B.8.90 Statistics for SFO and FOMC fitting for UK, Spring field dissipation data, XDE-729 methyl, 1-183 DAT data

Model	Parameter	Value	Lower CI	Upper CI	Std Dev	Prob > t	DT_{50} (d)	DT_{90} (d)	% χ^2 error
SFO (D1-D183))	M_0 (µg/kg)	3.23	2.69	3.77	0.26	-			
	k (d^{-1})	0.0160	0.0081	0.0238	0.0038	1.5e-04	43	144	19.0

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Figure B.8.83 SFO fitting for UK, Spring field dissipation data, XDE-729 methyl, 1-183 DAT data



Using the shortened data set, the χ^2 error is reduced from 23% to 19% and the kinetics parameters are very similar to those derived using the whole data set. Therefore, the Applicant proposed the best-fit DT50 and DT90 values for XDE-729 methyl at this trials site as 43 days and 144 days, respectively. The RMS can accept these values.

X11393729

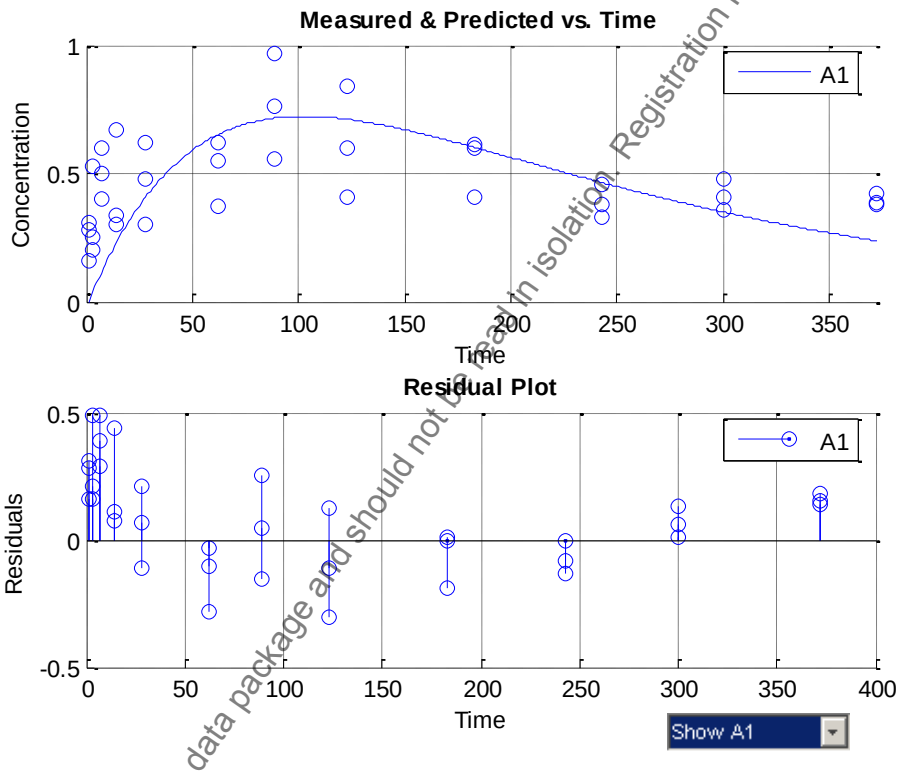
Using the optimised SFO parameters for parent XDE-729 methyl as initial values, X11393729 was added to the kinetics model as the first metabolite. Note that the Day 0 data were omitted but all later time points were included so that the residues of X11393729 formed at later time points were included in the fit. The formation fraction was set to an initial value of 0.5 and all parameters for parent and metabolite were optimised. The outputs are shown in the following table and figure; only X11393729 fitting is shown as parent fitting was virtually unchanged.

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Table B.8.91 Statistics for SFO+SFO fitting for UK, Spring field dissipation data, XDE-729 methyl+ X11393729, omitting day 0 data

Model	Parameter	Value	Lower CI	Upper CI	Std Dev	Prob > t	DT_{50} (d)	DT_{90} (d)	% χ^2 error
SFO Parent (exc D0)	M_0 (µg/kg)	3.22	2.88	3.56	0.17	-			
	k (d^{-1})	0.0156	0.0108	0.0203	0.0024	5.6e-09	45	148	22.7
SFO Acid (exc D0)	Form fraction	0.4023	0.1191	0.6854	0.1419	-			
	k (d^{-1})	0.0057	-7.9e-04	0.0123	0.0033	0.0420	121	402	32.0

Figure B.8.84 SFO+SFO fitting for UK, Spring field dissipation data, XDE-729 methyl+ X11393729, all data

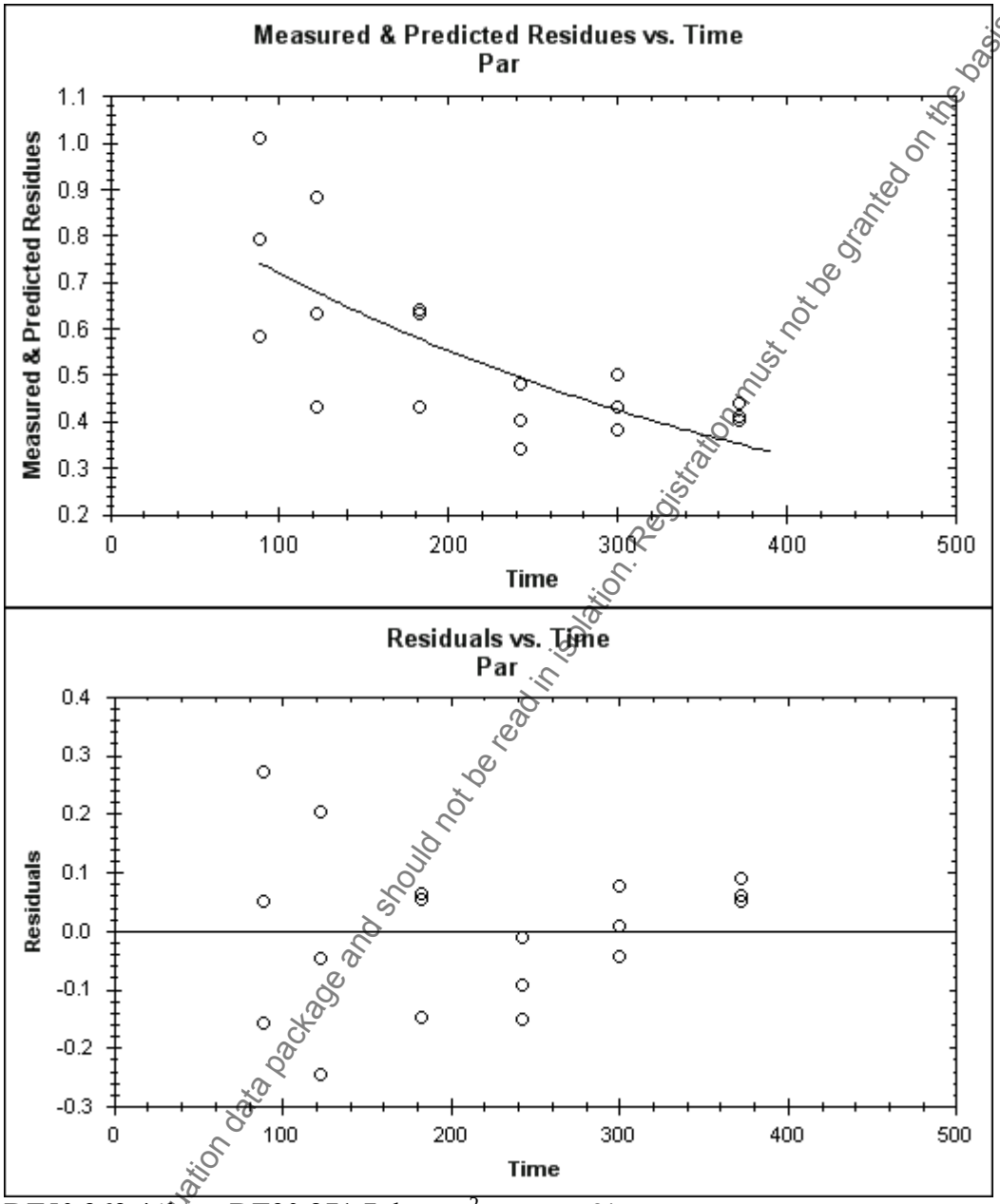


The parameters for parent XDE-729 methyl were only slightly changed after addition of X11393729 to the model. However, the parameters for X11393729 were considered by the Applicant to show high error and lower CI less than zero. The Applicant therefore considered it not possible to obtain acceptable kinetics parameters for X11393729 from this data set.

The RMS calculated a separate SFO top down DT50.

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Figure 8.85 RMS top-down SFO fit for X11393729, UK Spring, data from 89 DAT.



DT50 262.4 days, DT90 871.7 days, χ^2 error 7.5%

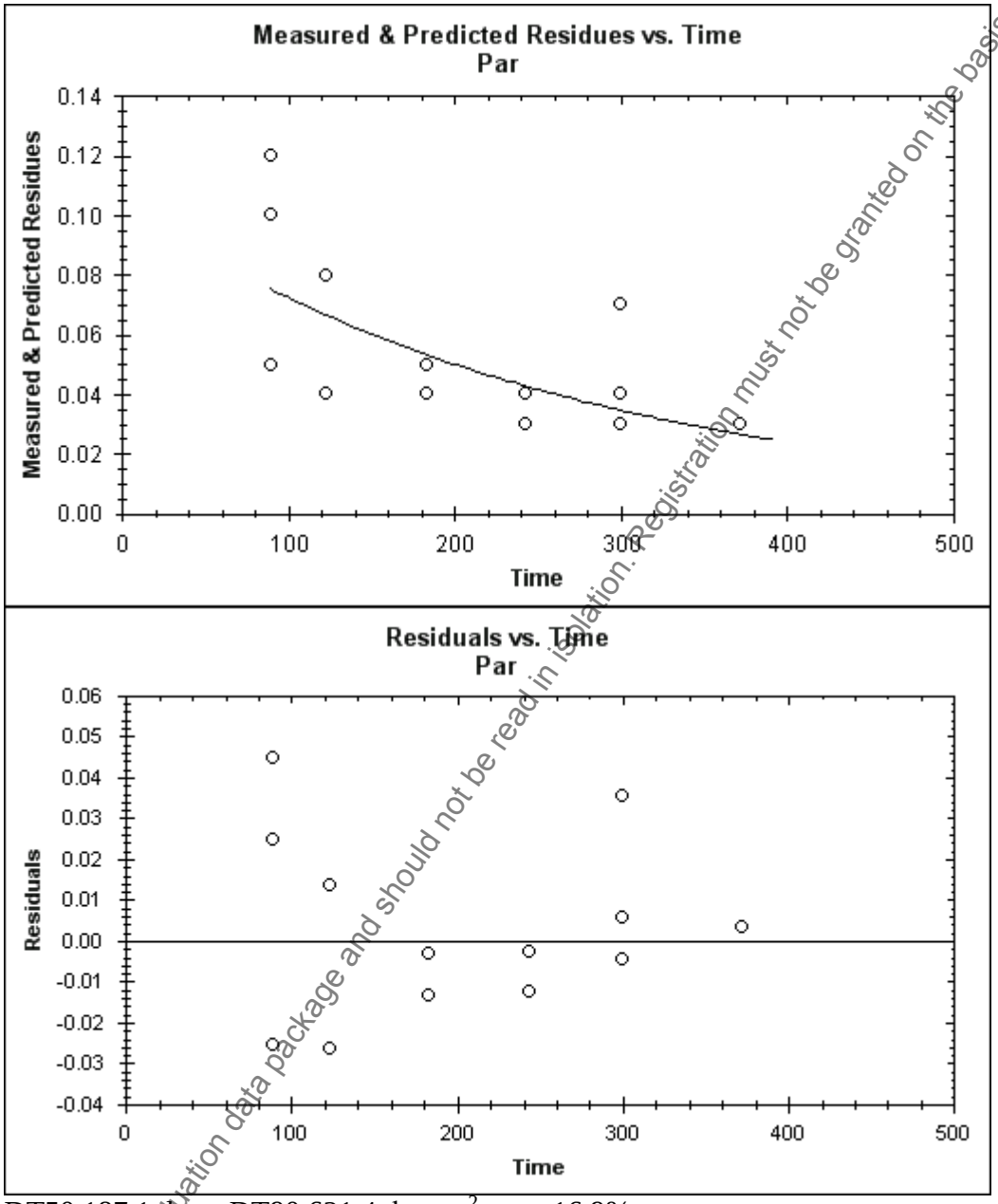
The RMS considers that the SFO top down DT50 is appropriate for use in simple calculations such as PECsoil calculation and proposes the DT50 value of 262.4 days for this trials site.

X11449757

The RMS did not attempt any fitting for X11449757. The RMS calculated a separate SFO top down DT50.

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Figure 8.86 RMS top-down SFO fit for X11449757, UK Spring, data from 89 DAT.



DT50 187.1 days, DT90 621.4 days, χ^2 error 16.9%

The RMS considers that the SFO top down DT50 is appropriate for use in simple calculations such as PECsoil calculation and proposes the DT50 value of 187.1 days for this trials site.

Data normalised to 20 °C and pF 2 (UK, Spring)

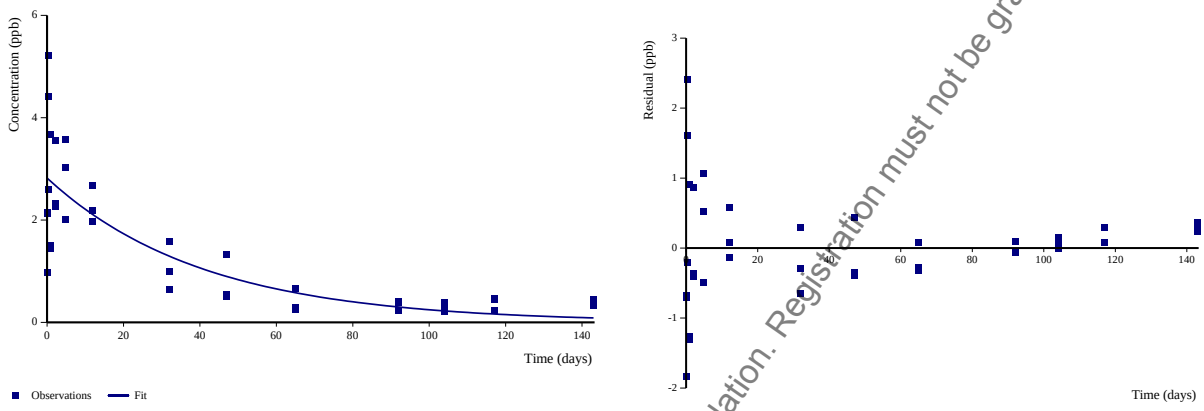
Parent

The results of fitting XDE-729 methyl (all data) to the SFO model are as follows:

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Figure B.8.87 Statistics for kinetic fitting of UK, Spring, parent only, all data, SFO

Parameter	Value	σ	Prob > t	Lower CI	Upper CI	DT50 (d)	X^2 err (%)
M_0 (µg/kg)	2.82	0.2059	2.32E-16	2.403	3.237	28.5	27.9
k (d^{-1})	0.02436	0.00559	5.02E-05	0.01304	0.036		



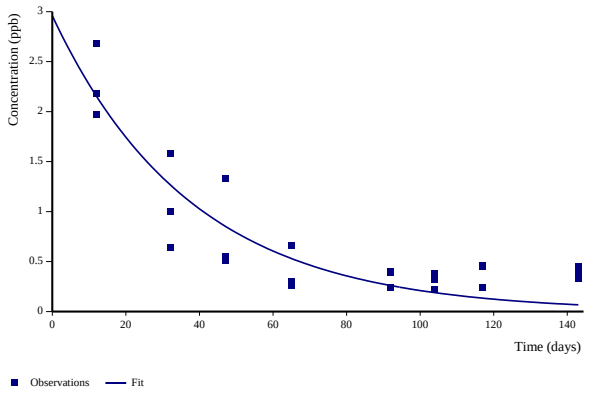
The SFO model gives a χ^2 error greater than 15% but the visual fit was reasonable. The RMS notes that there is a considerable scatter in replicate values at the earliest time points that probably contributes to the high χ^2 error.

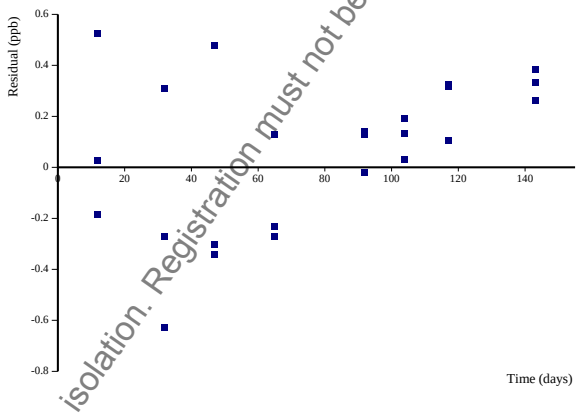
A further SFO fit was conducted after eliminating data points before 10 mm rainfall. The cumulative rainfall exceeded 10 mm (total = 10.4 mm) at 10.2 DAT (25 DAT real time). The first sampling time point after this was 12 DAT (28 DAT real time), and the total rainfall at this time point was 10.4 mm. Therefore, the kinetics fitting was run taking 12 DAT as the first time point. This gave 8 time points on the decline curve. The Applicant considered that there was no obvious decline in residues of XDE-729 methyl during the initial 28 day (real time) period of the trial and there was high variability in the data at these early time points both within an individual time point and between time points. In fact the average residue of XDE-729 Methyl at 28 DAT (2.28 µg/kg) was higher than the 0 DAT value of 1.75 µg/kg. The results of the SFO fit to these data are as follows:

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Figure B.8.88 Statistics for kinetic fitting of UK, Spring, parent only, data after 10mm rainfall, SFO

Parameter	Value	σ	Prob > t	Lower CI	Upper CI	DT50 (d)	X^2err (%)
M_0 (µg/kg)	2.958	0.3175	2.15E-09	2.3	3.617	26.2	19.3
k (d^{-1})	0.02644	0.003642	1.43E-07	0.01889	0.034		





Using the data after 10 mm rain gave an improved fit with a similar DT50 to that derived from the whole data set. The χ^2 error was just above 15% and the visual fits showed a tail of low residues towards the end of the study that could not be predicted by the model, similar to that observed with other data sets. The average residues for individual sample points at the last four sample times in this trial ranged from 0.31 µg/kg to 0.39 µg/kg, which represents 14-17% of the "initial" residue at 12 DAT (the first time point after 10 mm rain).

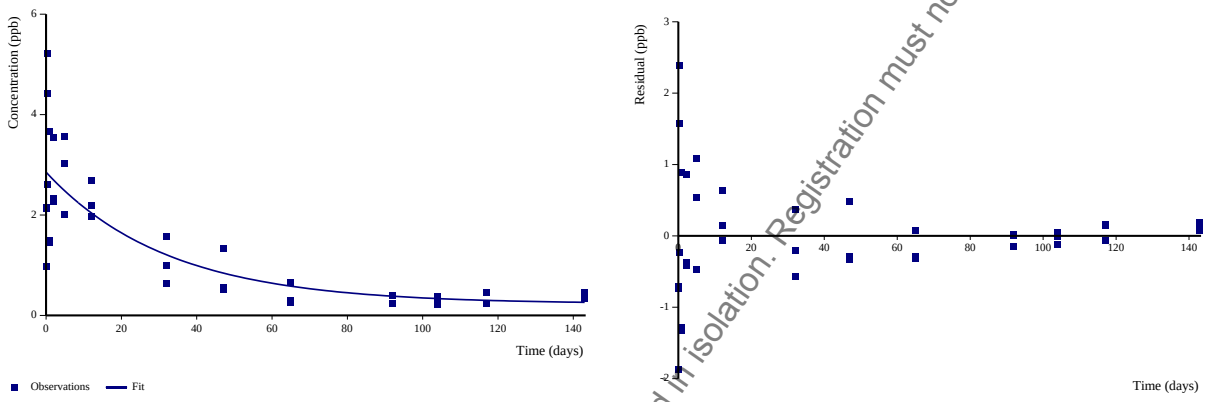
Since there was some evidence of biphasic behaviour, Step 5 of the EFSA assessment scheme was followed by running the DFOP model with all the data. The results are as follows:

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Figure B.8.89 Statistics for kinetic fitting of UK, Spring, parent only, all data, DFOP

Parameter	Value	σ	Prob > t	Lower CI	Upper CI	DT50* (d)	X^2 err (%)
M_0 (µg/kg)	2.853	0.232	1.47E-14	2.382	3.324	-	29.7
k1 (d^{-1})	0.03086	0.03642	0.2013	-0.04308	0.105	22.5	
k2 (d^{-1})	7.2E-06	0.07676	0.500	-0.1558	0.156	>1000	
g	0.9196	0.8448	0.1419	-0.7955	2.635	-	

* DT50 for each rate constant calculated from ln2/k



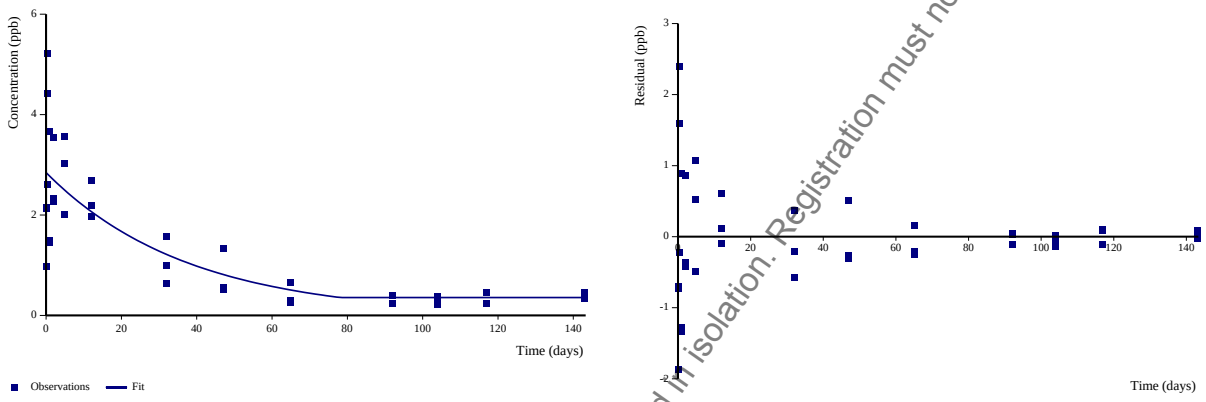
The visual fit is good but the high value of g (0.9196) indicates that the fast decline dominates and there is a high error on both the k1 and k2 value, lower confidence intervals for k1, k2 and g are all less than 0 and there is a high χ^2 error. Therefore, this fit was rejected and the HS model was run. The results are as follows:

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Figure B.8.90 Statistics for kinetic fitting of UK, Spring, parent only, all data, HS

Parameter	Value	σ	Prob > t	Lower CI	Upper CI	DT50* (d)	X^2 err (%)
M_0 (µg/kg)	2.845	0.2144	1.62E-15	2.409	3.28	-	29.4
k1 (d^{-1})	0.02659	0.00716	0.000356	0.01205	0.041	26.1	
k2 (d^{-1})	4.4E-13	0.03328	0.500	-0.06757	0.068	NC	
t_b (days)	78.1	54.46	0.0802	-32.46	188.7	-	

* DT50 for each rate constant calculated from ln2/k NC = not calculated



The RMS notes that the breakpoint occurs just before the tail of residues and the calculated DT50 of the k2 rate constant is 1.6 x 10^{12} days, i.e. essentially no degradation. The χ^2 error was similar to the DFOP model fit and there was high error on the k2 parameter with lower confidence interval including zero. Furthermore the breakpoint was very long (78 days) at which point the residues are very low, so only a small amount of the initial residue is described by the slow phase degradation. The Applicant therefore rejected the HS fit.

Both the DFOP and HS models gave high χ^2 error values, poor t-test and lower CIs less than zero for the slow phase decline rate constant. The Applicant concluded that the best fit was obtained with the SFO model on the data after 10 mm rain, which gave a significantly lower χ^2 error, and the DegT50 value of 26 days was accepted by the Applicant for XDE-729 methyl for this data set. The RMS notes that this study had very variable residues and little apparent real decline in residues before the exclusion of data before 10mm rainfall. This is perhaps surprising. In addition, there is a tail in the observed residues at the last four sampling points. Clearly this is a difficult dataset for relatively simple kinetic models to fit. The RMS notes that the SFO decline curve fitted to data after excluding points prior to 10mm rainfall cannot predict this tail. However, the RMS notes that this tail, whilst representing up to 17% of the measured residue post-10mm rainfall, represents up to 9.5% of the highest average measured residue. With this in mind, the RMS considers that it is reasonable to use the proposed DT50 of 26 days from this site as it is likely to represent the majority of degradation in the bulk soil matrix.

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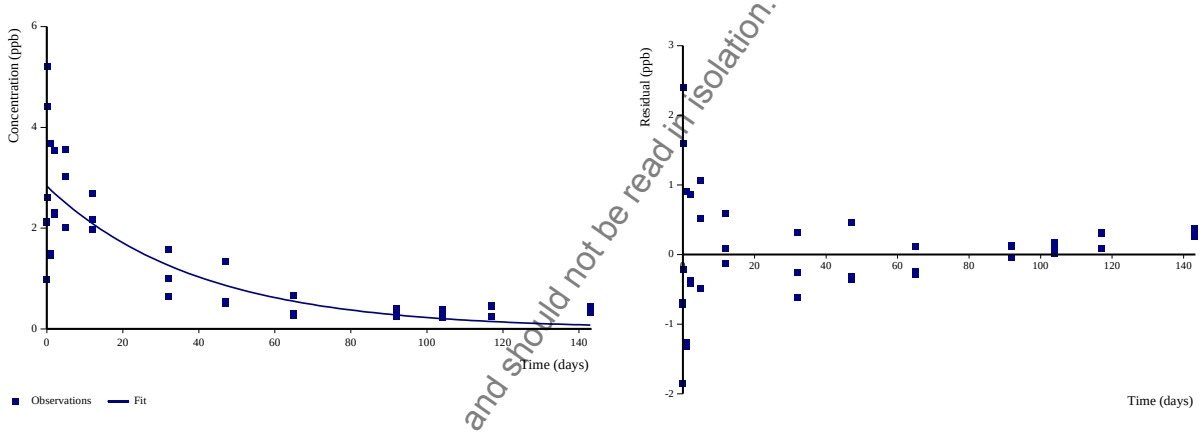
Parent + X11393729

The applicant considered that the SFO model gave a reasonable fit for parent with all data and therefore a sequential fit was run using SFO for both parent and X11393729; X11393729 is designated A1. The results are as follows:

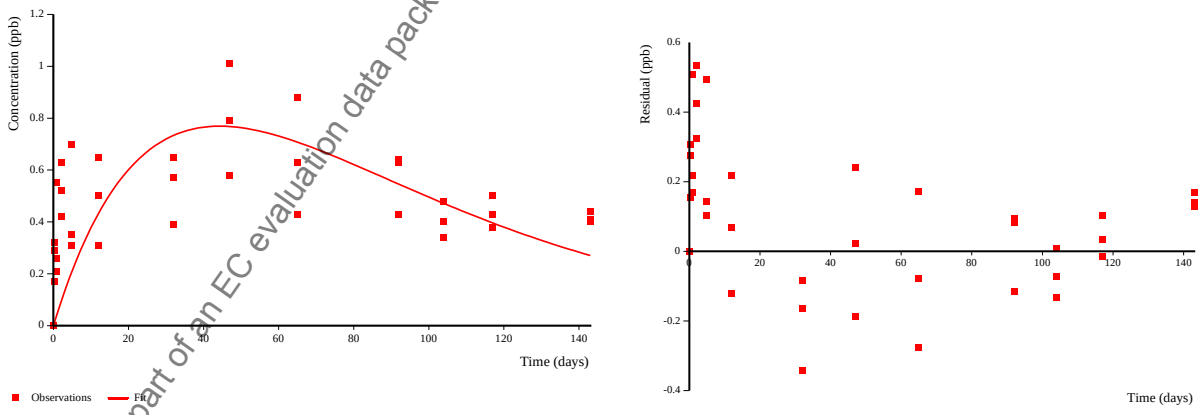
Figure B.8.91 Statistics for kinetic fitting of UK, Spring, parent + X11393729, all data, SFO+SFO

Parameter	Value	σ	Prob > t	Lower CI	Upper CI	DT50 (d)	X^2 err (%)
M_0 (µg/kg)	2.833	0.2069	2.82E-22	2.421	3.246	-	
k_Parent (d^{-1})	0.02528	0.00585	2.35E-05	0.01364	0.037	27.4	27.9
f_Par_to_A1	0.66	0.1994	0.000722	0.2626	1.057	-	
k_A1 (d^{-1})	0.02005	0.00634	0.001142	0.00741	0.033	34.6	33.0

Compartment Parent:



Compartment A1:



After addition of X11393729 to the model, the DT50 for parent was similar to that obtained for parent alone (27 days and 29 days, respectively). The χ^2 error for X11393729 was high (33%), but the t-test and confidence intervals were acceptable. The Applicant considered that the visual fit showed that the model predicted the maximum amount of X11393729 formed and the decline reasonably well, although it

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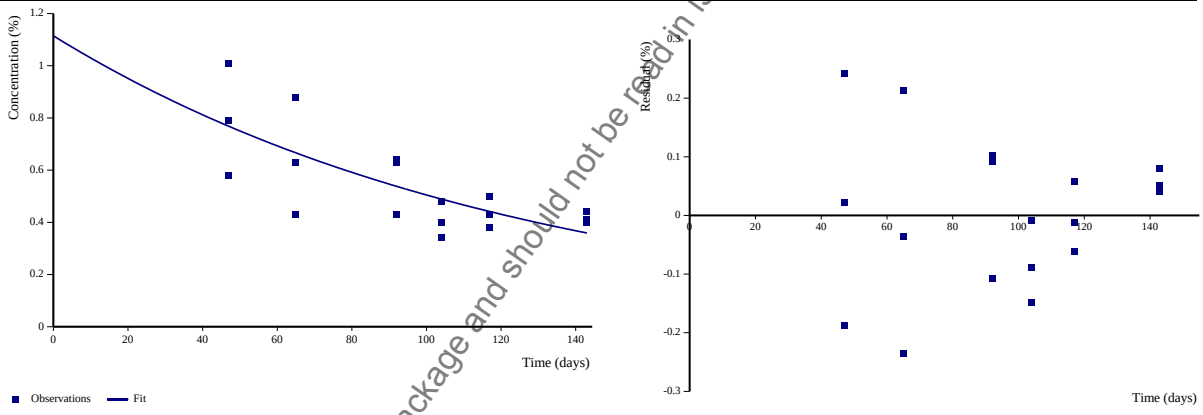
did not predict the rapid increase at early time points. The RMS can concur with this assessment.

A kinetic fit using a DFOP/SFO sequential model for parent and X11393729 was attempted by the Applicant but failed to complete successfully. As the DFOP model for parent on its own gave, in the opinion of the Applicant, a poor fit, no more attempts were made to fit a biphasic model to parent. The RMS interprets 'poor fit' as relatively high χ^2 error, poor t-test and lower confidence interval for k2 rate constant less than zero.

In an attempt to improve the fit for X11393729, a top-down SFO fit was performed on the X11393729, starting at 47 DAT (89 DAT real time), the time of maximum formation. This gave 6 time points on the decline curve. The results are as follows:

Figure B.8.92 Statistics for kinetic fitting of UK, Spring, X11393729, top down from peak (occurred after 10mm rainfall), SFO

Parameter	Value	σ	Prob > t	Lower CI	Upper CI	DT50 (d)	X^2 err (%)
k (d^{-1})	0.00792	0.00184	0.000273	0.00402	0.012	87.5	6.5



The "top down" SFO fit for the X11393729 gave a low χ^2 error (6.5%) and acceptable t-test and confidence intervals. The visual fit was good despite some wide scatter in the data.

The top-down DegT50 of 88 days is proposed by the Applicant as a conservative estimate for X11393729. The RMS can agree with this, whilst noting that no formation fraction is available to use along side this top-down DT50. Alternatively, the Applicant proposed the results of the SFO/SFO sequential fit with parent could be used to derive model inputs since this gives a formation fraction for X11393729 and is the preferred kinetic for running model simulations. The parameters for parent were very similar for all the model fits, including the sequential fit with X11393729. The visual fit for the X11393729 is good and therefore, a DegT50 of 27 days for parent together with a formation fraction of 0.66 and a DegT50 of 35 days for X11393729 is proposed as inputs for modelling X11393729. As above, the RMS can agree with this proposal.

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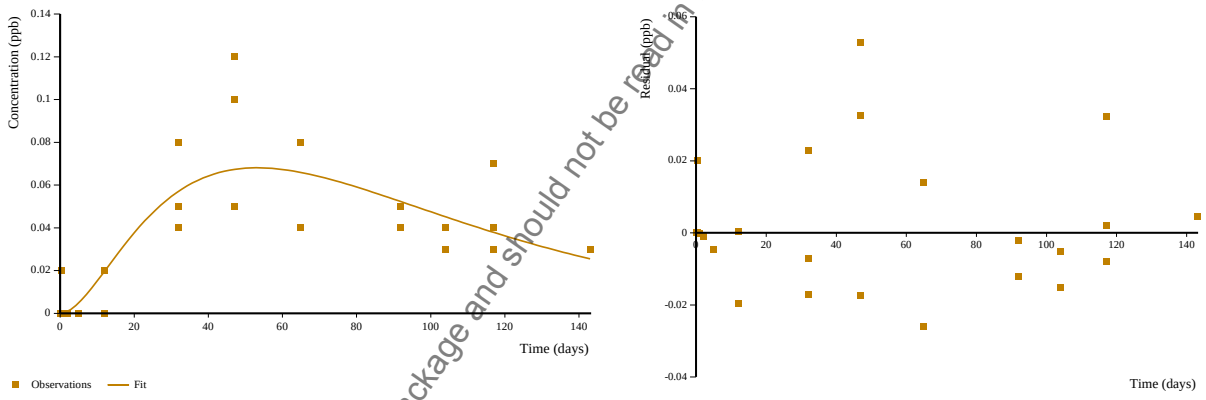
Parent + X11393729 + X11449757

The X11449757 data were added to the model and a sequential fit was performed for Parent, X11393729 and X11449757 using SFO for the parent; X11449757 is designated A2. The results are as follows:

Figure B.8.93 Statistics for kinetic fitting of UK, Spring, Parent + X11393729 + X11449757, all data, SFO+SFO+SFO

Parameter	Value	σ	Prob > t	Lower CI	Upper CI	DT50 (d)	X^2 err (%)
M_0 (µg/kg)	2.831	0.2067	6.76E-26	2.422	3.241		27.9
k_Parent (d^{-1})	0.02509	0.00579	1.64E-05	0.01361	0.037	27.6	
f_Par_to_A1	0.7122	0.2141	0.000598	0.2878	1.136		33.2
k_A1 (d^{-1})	0.02242	0.00660	0.000477	0.00933	0.036	30.9	
f_A1_to_A2	0.4403	0.3146	0.08223	-0.1831	1.064		26.1
k_A2 (d^{-1})	0.1104	0.06153	0.03772	-0.01151	0.232	6.3	

Compartment A2:



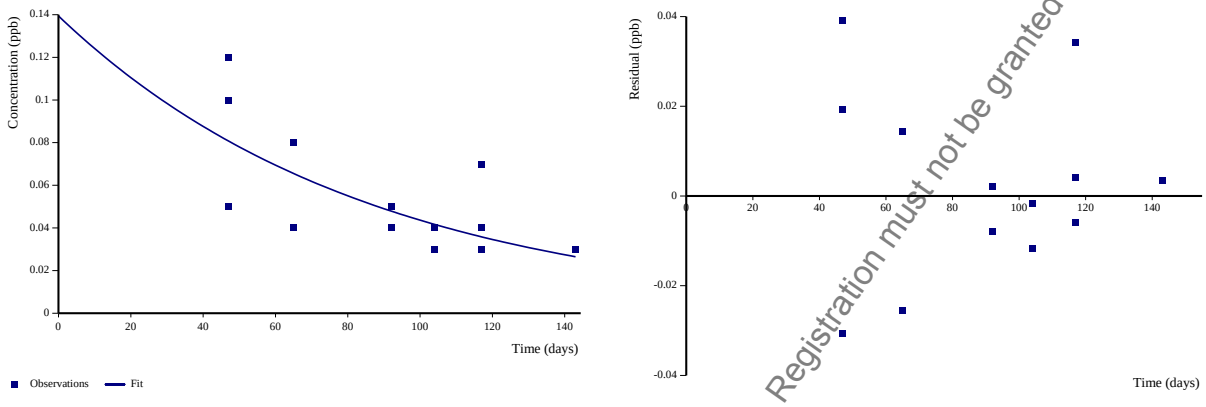
Only the X11449757 visual fit is shown here. The visual fit showed high scatter and the lower CI was less than zero for the X11449757 rate constant, therefore this fit is not reliable. Fits for parent and X11393729 were similar to the previous parent + X11393729 fitting.

A top-down fit was performed for X11449757 starting with the time of maximum formation at 47 DAT (89 DAT real time). This resulted in 6 time points on the decline curve. The results are as follows:

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Figure B.8.94 Statistics for kinetic fitting of UK, Spring, X11449757, top down from peak (occurred after 10mm rainfall), SFO

Parameter	Value	σ	Prob > t	Lower CI	Upper CI	DT50 (d)	X^2 err (%)
k (d^{-1})	0.01161	0.00306	0.000796	0.00512	0.018	59.7	13.1



The "top down" SFO fit for the X11449757 metabolite gave a χ^2 error of 13% and acceptable t-test. Note that the X11449757 metabolite was detected at very low levels in this study with a maximum residue of 0.09 µg/kg, which is less than 5% of the initial residue.

The top-down DegT50 of **60 days** is proposed by the Applicant as a conservative estimate for X11449757. The RMS can agree with this.

UK, Autumn

Unnormalised data (UK, Autumn)

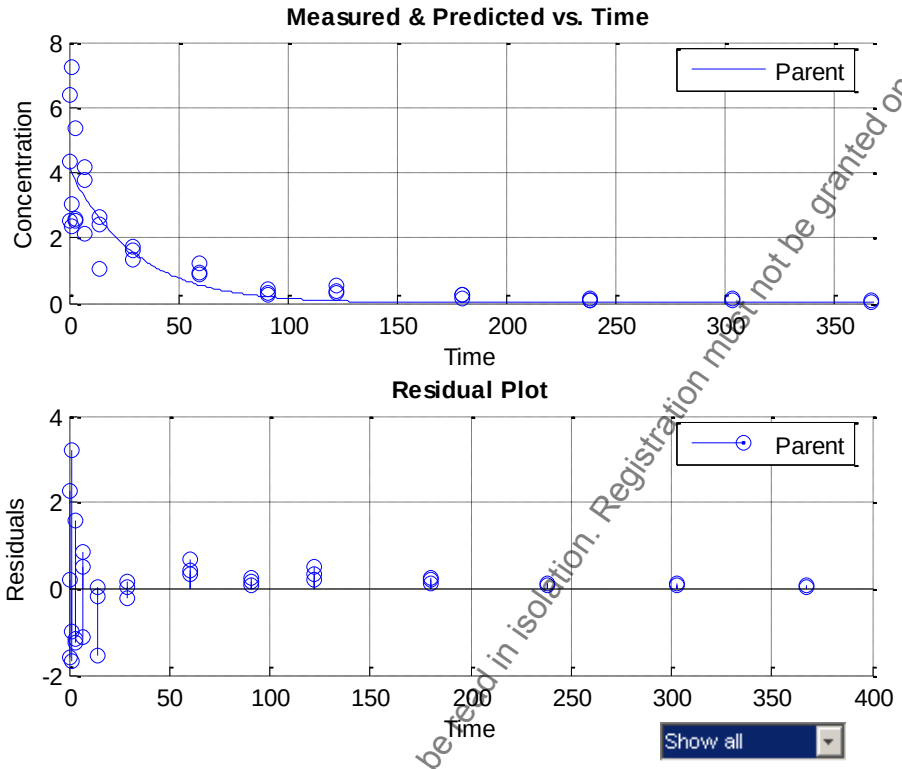
The kinetics fits for the measured data (i.e. not corrected for temperature and moisture) using the SFO and FOMC models for parent XDE-729 methyl only are shown in the following table and figures.

Table B.8.92 Statistics for SFO and FOMC fitting for UK, Autumn field dissipation data, XDE-729 methyl, all data

Model	Parameter	Value	Lower CI	Upper CI	Std Dev	Prob > t	DT_{50} (d)	DT_{90} (d)	% χ^2 error
SFO	M_0 (µg/kg)	4.15	3.49	4.81	0.33				
(all data)	k (d^{-1})	0.0337	0.0161	0.0514	0.0087	2.1e-04	21	68	13.3
FOMC	M_0 (µg/kg)	4.39	3.59	5.19	0.40				
(all data)	alpha	1.3116	-0.5352	3.1584	0.9106	0.0792	15	106	8.2
	beta	22.10	-28.56	72.76	24.98	0.1911			

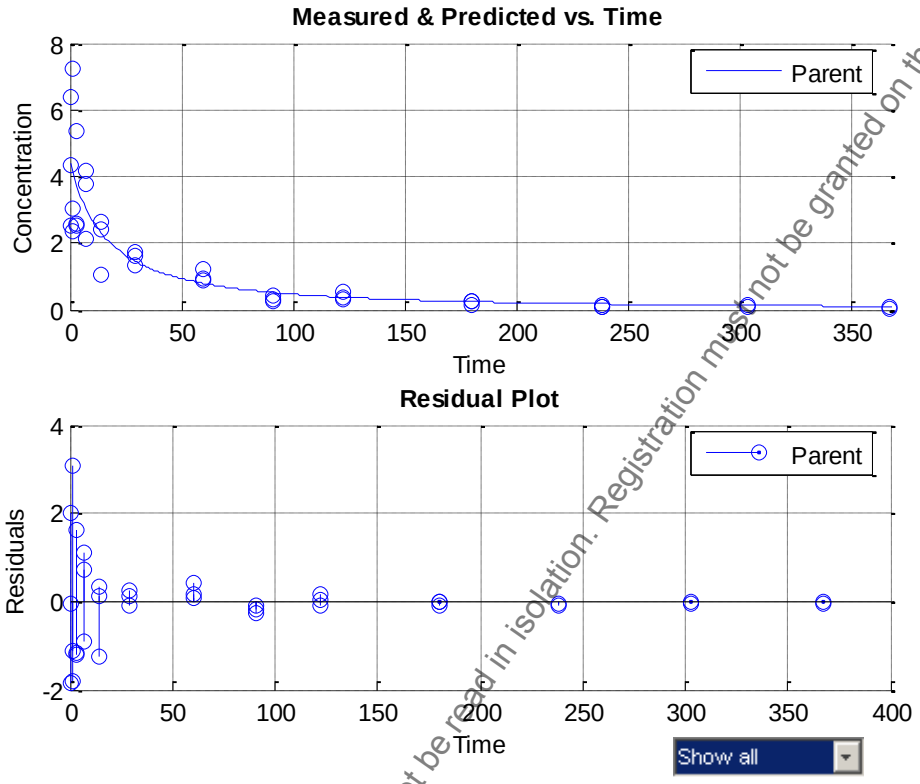
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Figure B.8.95 SFO fitting for UK, Autumn field dissipation data, XDE-729 methyl, all data



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Figure B.8.96 FOMC fitting for UK, Autumn field dissipation data, XDE-729 methyl, all data



The SFO model gave a DT50 of 21 days with a χ^2 error of 13% and acceptable t-test. The FOMC model gave a lower χ^2 error but both the α and β parameters showed high error and lower CIs less than zero. Therefore, the Applicant proposed to accept the SFO model as the best-fit. However, the RMS considers in this case that whilst the lower CI arte not ideal, FOMC is the better model to describe the data and can accept the FOMC parameters for the purpose of persistence information. Therefore the RMS proposes best fit FOMC parameters DT50 15 days, DT90 106 days for parent at this trials site.

X11393729

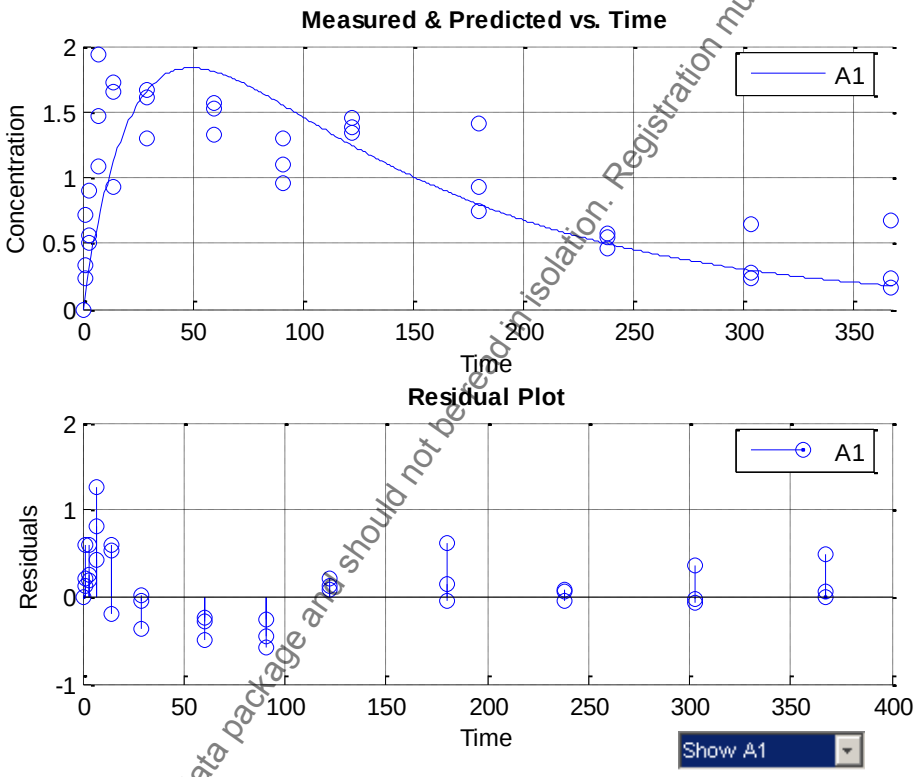
Using the optimised SFO parameters for parent XDE-729 methyl as initial values, X11393729 was added to the kinetics model by the Applicant with the formation fraction set to an initial value of 0.5. The optimised parameters for parent and metabolite are shown in the following table and figure. Only the X11393729 fit is shown as the parent fitting was not affected greatly.

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Table B.8.93 Statistics for SFO+SFO fitting for UK, Autumn field dissipation data, XDE-729 methyl+ X11393729, all data

Model	Parameter	Value	Lower CI	Upper CI	Std Dev	Prob > t	DT_{50} (d)	DT_{90} (d)	% χ^2 error
SFO Parent	M_0 (µg/kg)	4.28	3.77	4.80	0.26	-			
	k (d^{-1})	0.0411	0.0257	0.0565	0.0077	5.4e-07	17	86	14.1
SFO Acid	Form fraction	0.6374	0.3574	0.9174	0.1405	-			
	k (d^{-1})	0.0081	0.0028	0.0134	0.0027	0.0017	86	285	30.8

Figure B.8.97 SFO+SFO fitting for UK, Autumn field dissipation data, XDE-729 methyl+ X11393729, all data

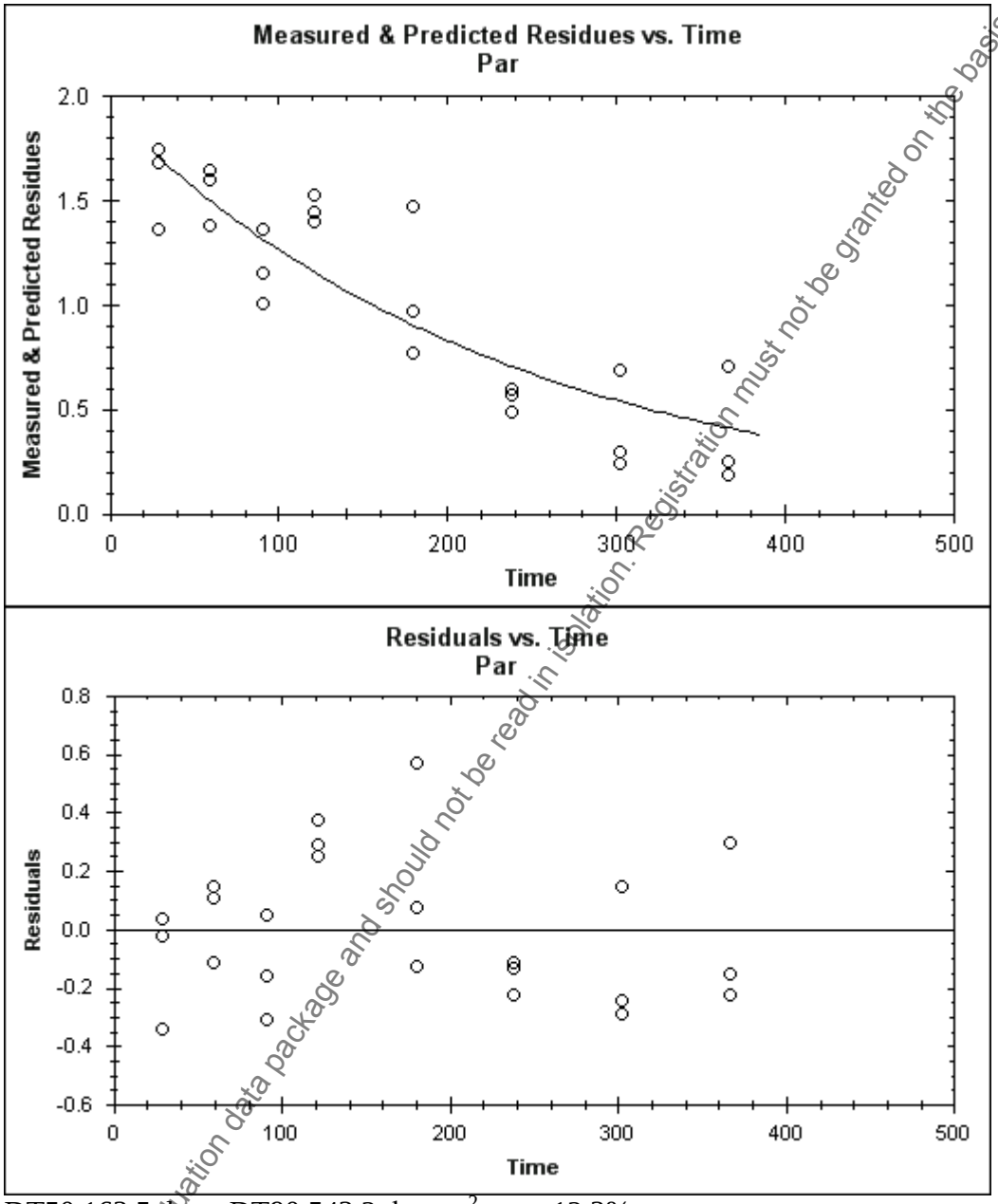


The DT50 for parent ester decreased slightly from 21 to 17 days after addition of X11393729 to the model with a slight worsening of the χ^2 error, but the χ^2 error was still less than 15%. The χ^2 error for X11393729 was considered by the Applicant to be high (31%) but all other statistical parameters were acceptable and the visual fit was considered by the Applicant to be reasonable, despite high variability in the triplicate samples at some time points. Therefore, the fit was accepted by the Applicant and proposed the DT50 for X11393729 at this trials site of 86 days with a formation fraction of 0.637.

The RMS calculated a separate SFO top down DT50.

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Figure 8.98 RMS top-down SFO fit for X11393729, UK Autumn, data from 29 DAT.



DT50 163.5 days, DT90 543.2 days, χ^2 error 12.3%

The RMS considers that the SFO top down DT50 is appropriate for use as a persistence endpoint in simple calculations such as PECsoil calculation and proposes the DT50 value of 163.5 days for this trials site.

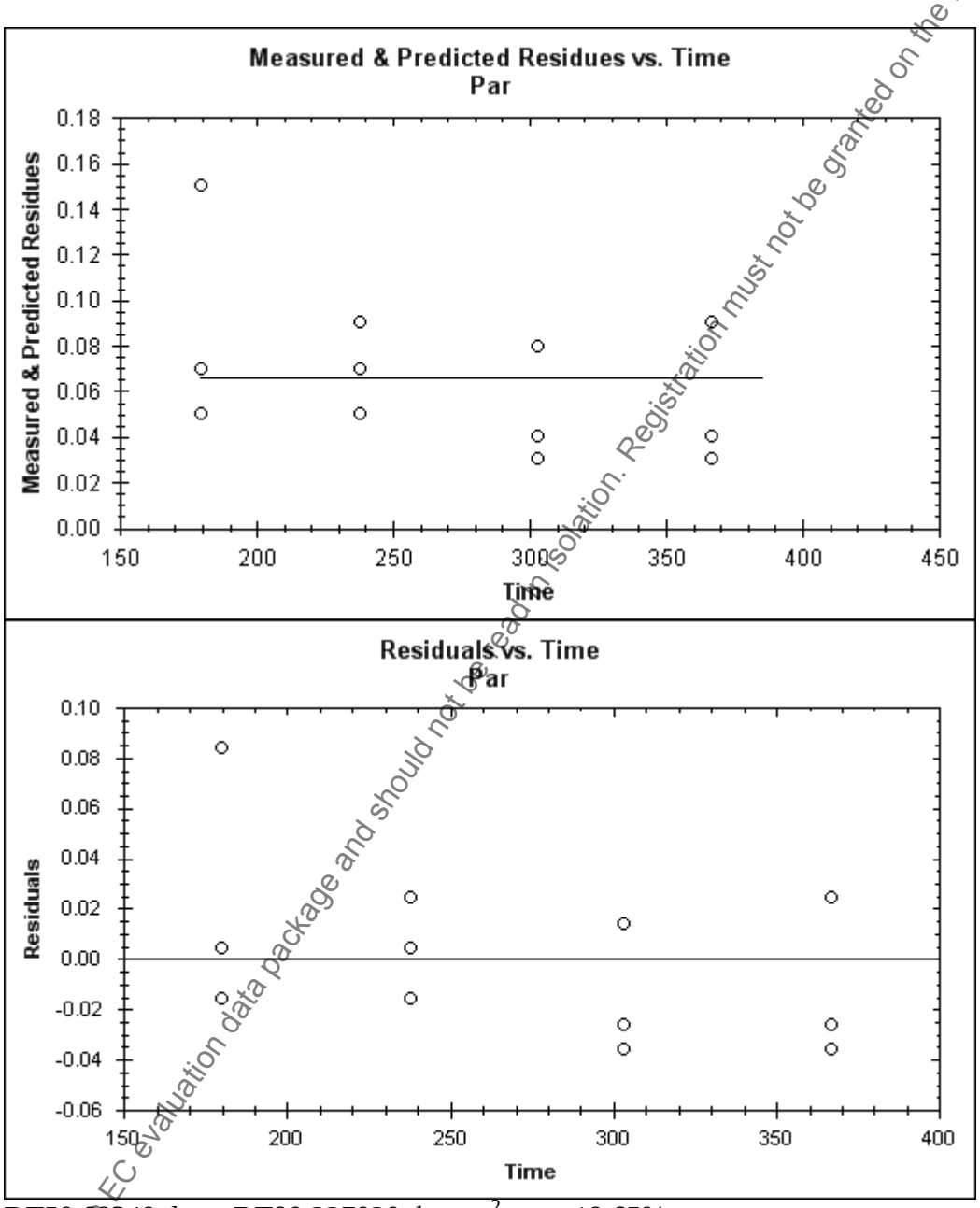
X11449757

Since X11449757 was detected at very low levels in this data set (maximum average value was 0.08 µg/kg), the Applicant considered there was no obvious pattern of formation and decline. Therefore, the Applicant made no attempt to fit X11449757 to the kinetic model.

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The RMS calculated a separate SFO top down DT50.

Figure 8.99 RMS top-down SFO fit for X11449757, UK Autumn, data from 180 DAT.



DT50 68340 days, DT90 227020 days, χ^2 error 19.65%

The RMS noted that the t-test for the rate constant from this fitting failed (value 0.5). The residues were only slightly above the LOQ and there were only four sample times available. This suggests slow but protracted formation at this site. The RMS proposes that the results from this site should not be used for risk assessment purposes as the decline rate only indicative of relative persistence at this site.

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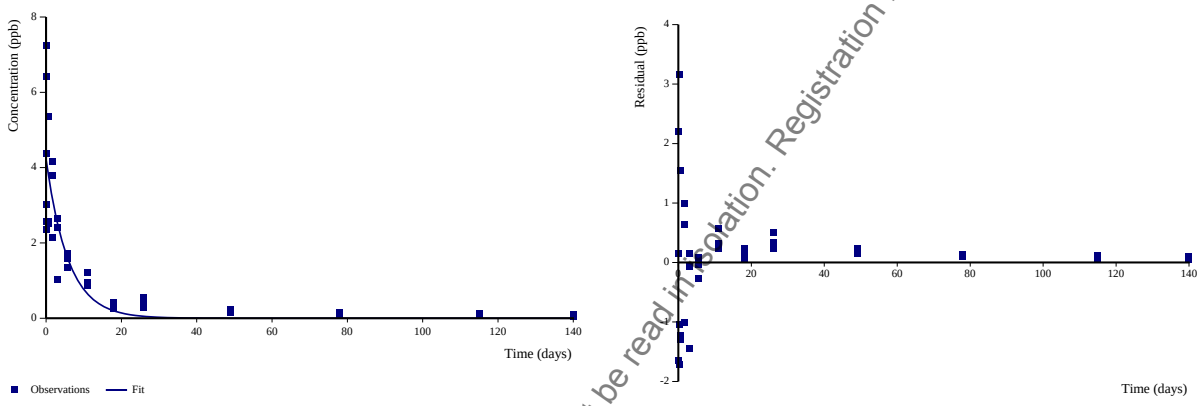
Data normalised to 20 °C and pF 2 (UK, Autumn)

Parent

The results of fitting XDE-729 methyl (all data) to the SFO model are as follows:

Figure B.8.100 Statistics for kinetic fitting of UK, Autumn, parent only, all data, SFO

Parameter	Value	σ	Prob > t	Lower CI	Upper CI	DT50 (d)	X^2 err (%)
M_0 (µg/kg)	4.213	0.3295	1.90E-15	3.545	4.88	4.1	12.2
k (d^{-1})	0.1705	0.04154	0.000107	0.0863	0.255		



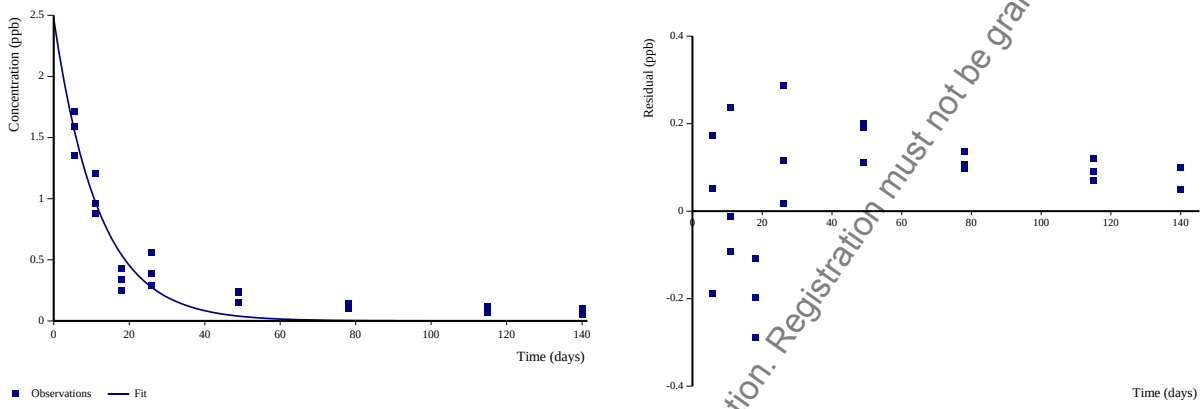
The SFO model gave a low χ^2 error and the visual fit is good. There is a tail of low residues that declines slowly from 0.41 µg/kg to 0.07 µg/kg at the end of the study but, based on the initial residue of 4.45 µg/kg, this represents only 9% to less than 2% of the applied material.

A further SFO fit was conducted after eliminating data points before 10 mm rainfall. Cumulative rainfall exceeded 10 mm (total = 10.8 mm) at 3.9 DAT (19 DAT real time). The first soil sampling time after this was 5.6 DAT (29 DAT real time), and the total rainfall at this time point was 12.2 mm. This gave 8 time points on the decline curve. The results of the SFO fit to these data are as follows:

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Figure B.8.101 Statistics for kinetic fitting of UK, Autumn, parent only, data after 10 mm rainfall, SFO

Parameter	Value	σ	Prob > t	Lower CI	Upper CI	DT50 (d)	X^2err (%)
M_0 (µg/kg)	2.47	0.2417	4.07E-10	1.969	2.971	8.2	20.1
k (d^{-1})	0.08467	0.01023	1.66E-08	0.06346	0.106		



The residuals are evenly distributed around the line over the first few time points. Thereafter, there is a slight under-prediction of the residues due to the tail of residues at later times. The χ^2 error was greater than 15% but all other statistical parameters were acceptable.

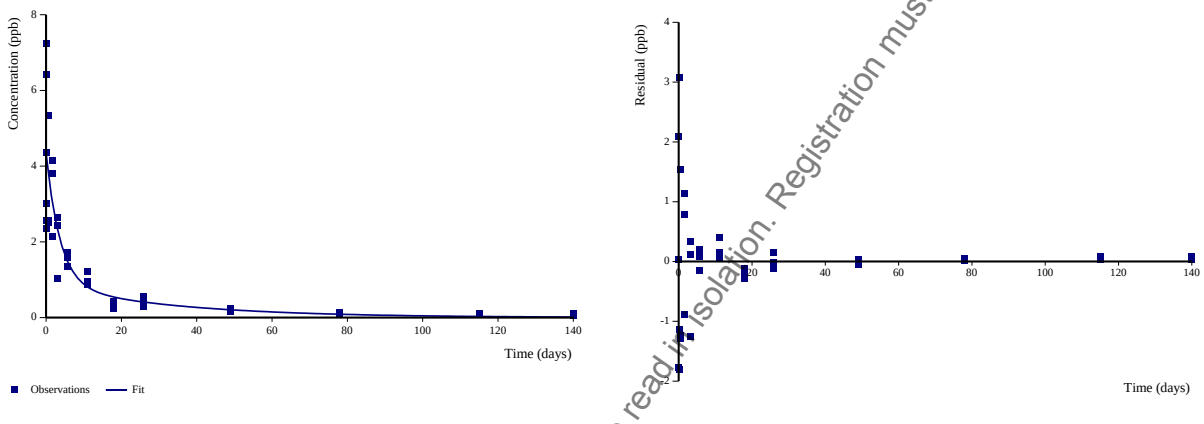
In line with EFSA guidance, the DFOP model was run with all the data. The results for the DFOP model for Parent are as follows:

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Figure B.8.102 Statistics for kinetic fitting of UK, Autumn, parent only, all data, DFOP

Parameter	Value	σ	Prob > t	Lower CI	Upper CI	DT50* (d)	X^2 err (%)
M_0 (µg/kg)	4.338	0.3708	5.98E-14	3.586	5.091	-	9.4
k1 (d^{-1})	0.2702	0.1682	0.05858	-0.07125	0.612	2.6	
k2 (d^{-1})	0.02953	0.06185	0.318	-0.09604	0.155	23.5	
g	0.7982	0.3196	0.00869	0.1493	1.447	-	

* DT50 for each rate constant calculated from ln2/k



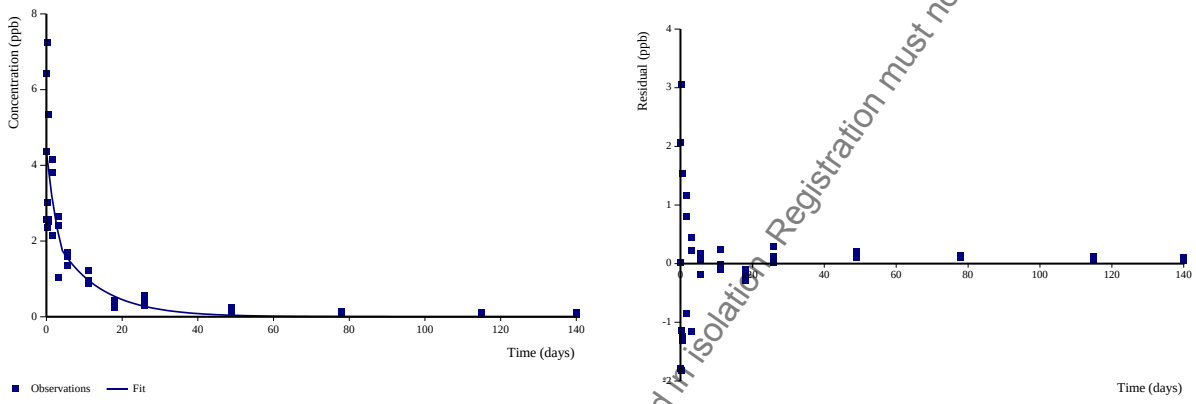
The χ^2 error is low but there was high error on both the k1 and k2 parameters, lower confidence intervals were less than zero and g was greater than 0.75. The RMS notes however that the DFOP fit is generally very good. In view of the statistical issues and failure of the 'g' value in relation to the EFSA criteria, the HS model was run for parent. The results are as follows:

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Figure B.8.103 Statistics for kinetic fitting of UK, Autumn, parent only, all data, HS

Parameter	Value	σ	Prob > t	Lower CI	Upper CI	DT50* (d)	X^2 err (%)
M_0 (µg/kg)	4.355	0.3719	5.857E-14	3.6	5.11	-	9.4
k1 (d^{-1})	0.2204	0.07762	0.003742	0.0628	0.378	3.1	
k2 (d^{-1})	0.08469	0.06274	0.09288	-0.04269	0.212	8.2	
t_b (days)	4.178	3.554	0.1239	-3.038	11.39	-	

* DT50 for each rate constant calculated from ln2/k



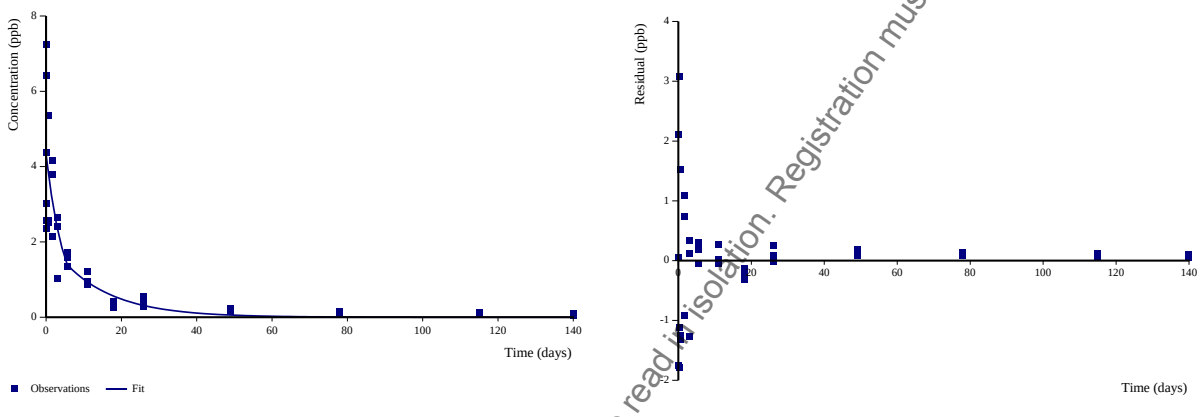
The χ^2 error was low but there is high error on the k2 parameter. The visual fit was good but the break point of 4.2 days occurred before 10 mm rainfall (5.6 days). Therefore, the HS was run again after fixing the breakpoint to 5.6 days. The results are as follows:

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Figure B.8.104 Statistics for kinetic fitting of UK, Autumn, parent only, all data, HS, breakpoint fixed at 5.6 days

Parameter	Value	σ	Prob > t	Lower CI	Upper CI	DT50* (d)	X^2err (%)
M_0 (µg/kg)	4.315	0.3462	6.35E-15	3.613	5.017	-	9.5
k1 (d^{-1})	0.2021	0.05306	0.000262	0.09451	0.31	3.4	
k2 (d^{-1})	0.07363	0.05508	0.09482	-0.03807	0.185	9.4	
t_b (days)	5.6 (fixed)	-	-	-	-	-	

* DT50 for each rate constant calculated from ln2/k



Fixing the breakpoint made only a small change to the optimised parameters. However, the k2 parameter still gave a lower CI less than zero, and therefore is unreliable. The k2 value of 0.07363 d^{-1} equates to a DegT50 of 9.4 days. The Applicant pointed out that this is very close to the SFO value (after 10 mm rain) of 8.2 days and since the Applicant considered that the SFO after 10 mm rainfall gave acceptable statistics it was proposed to accept the SFO after 10mm rainfall value of 8.2 days. Given the relatively close values of HS slow phase DT50 and the SFO DT50 after 10mm rainfall, the RMS can accept the choice of 8.2 days.

Parent + X11393729

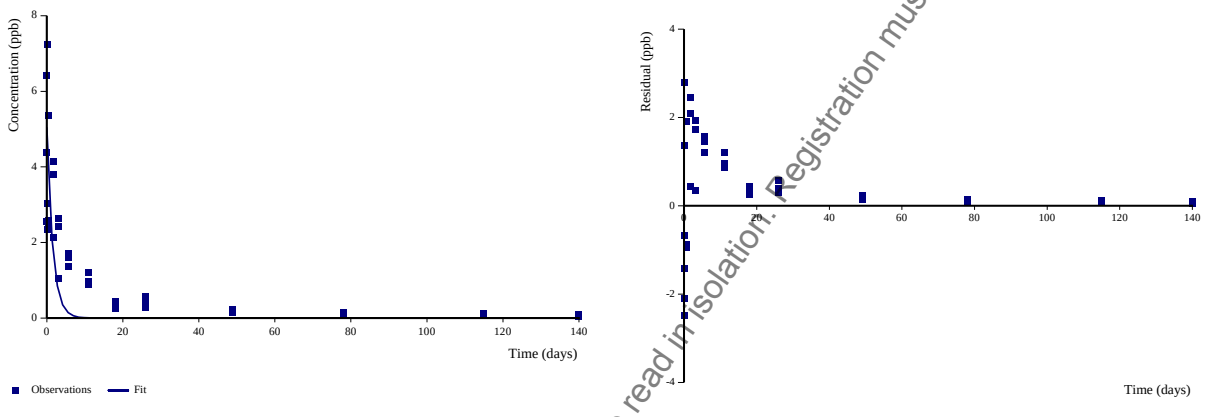
Since the SFO model with all the data gave a reasonable fit for parent, the Applicant ran a sequential fit using SFO for both parent and X11393729 (X11393729 is designated A1). The results are as follows:

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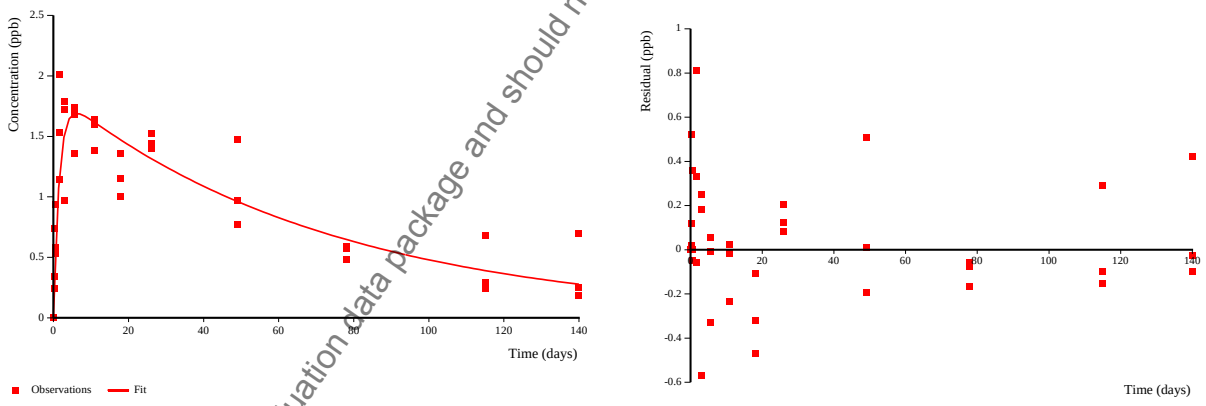
Figure B.8.105 Statistics for kinetic fitting of UK, Autumn, parent + X11393729, all data, SFO+SFO

Parameter	Value	σ	Prob > t	Lower CI	Upper CI	DT50 (d)	χ^2 err (%)
M_0 (µg/kg)	5.047	0.4865	2.217E-16	4.078	6.016	-	
k_Parent (d^{-1})	0.6366	0.1092	6.863E-08	0.4189	0.854	1.1	39.6
f_Par_to_A1	0.3643	0.04477	3.57E-12	0.2751	0.454		
k_A1 (d^{-1})	0.01366	0.00210	4.09E-09	0.00948	0.018	50.7	13.5

Compartment Parent:



Compartment A1:



After addition of X11393729 to the model, the DT50 for parent was shorter than that obtained for Parent alone (1.1 days vs 4.1 days). The χ^2 error for the parent was significantly increased (from 12% to 40%), but other statistical parameters were acceptable. The χ^2 error and other statistical parameters for X11393729 were acceptable, and the visual fit was good.

Since the fit for Parent was not so good after adding X11393729 to the SFO/SFO model, a further sequential kinetics fit was run using DFOP for parent. The results are as follows:

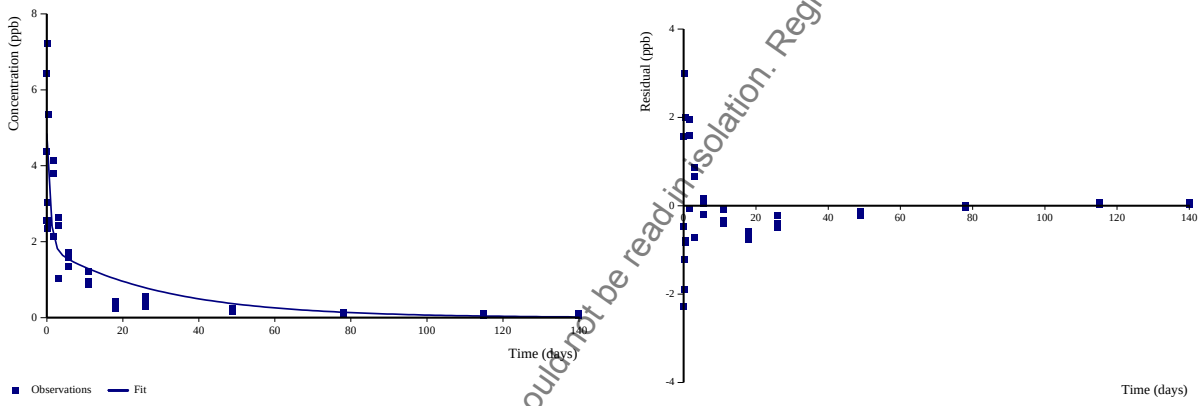
WARNING: This document forms part of an EU evaluation data package and should not be read in isolation. Registration must not be granted on the basis of this document.

Figure B.8.106 Statistics for kinetic fitting of UK, Autumn, parent + X11393729, all data, DFOP+SFO

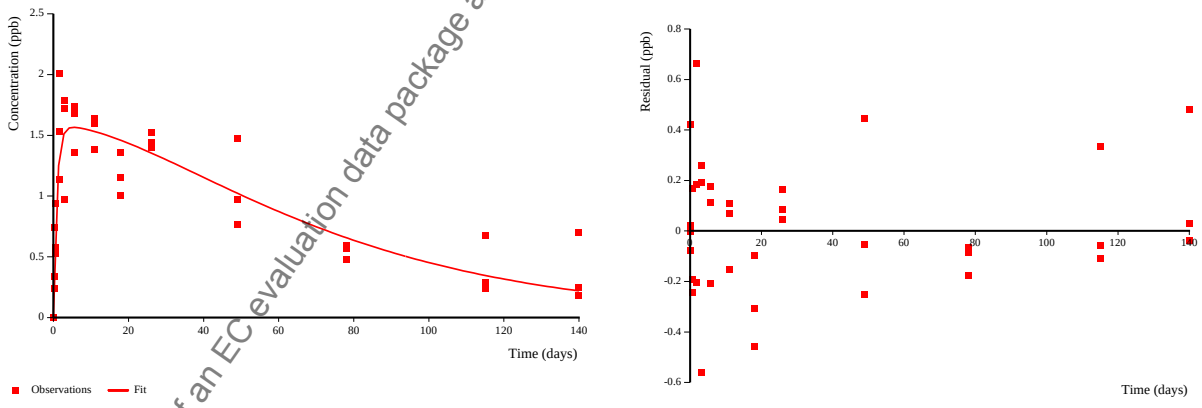
Parameter	Value	σ	Prob > t	Lower CI	Upper CI	DT50* (d)	X^2err (%)
M_0 (µg/kg)	4.848	0.4341	1.12E-17	3.983	5.714	-	22.6
k1 (d^{-1})	1.117	0.2879	0.0001146	0.5431	1.691	0.6	
k2 (d^{-1})	0.03293	0.01368	0.00930	0.00567	0.06	21.0	
g	0.6186	0.08345	9.48E-11	0.4523	0.785	-	
f_Par_to_A1	0.5188	0.09068	1.13E-07	0.3381	0.7	-	11.7
k_A1 (d^{-1})	0.02005	0.00340	5.47E-08	0.01327	0.025	34.6	

* DT50 for each rate constant calculated from ln2/k

Compartment Parent:



Compartment A1:



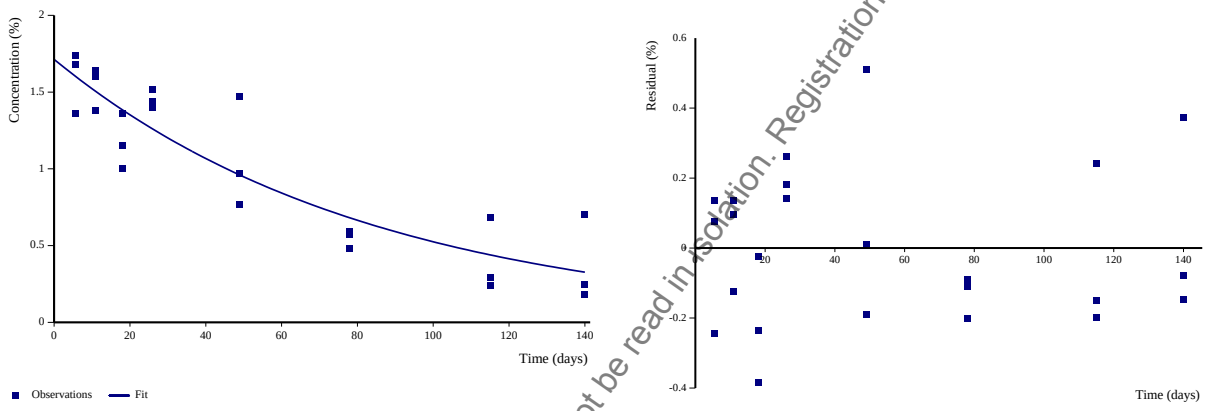
Using DFOP for parent in this sequential fit resulted in a better statistical and visual fit for the Parent compared with SFO. However, the RMS notes that the fitting of the parent in this sequential fit is significantly worsened compared to the DFOP fit for parent only (χ^2 error for DFOP parent only 9.4, compared to 22.6 for sequential fitting with metabolite DFOP+SFO). For the Acid, the visual fits were very similar using both models, with a lower DT50 of 35 days for the DFOP/SFO model being offset by an increased formation fraction. The RMS notes that the DFOP+SFO simulation gives a slightly lower peak concentration of X11393729.

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To complete the kinetics analysis for Acid, a top-down SFO fit was performed, starting at 5.6 DAT (29 DAT real time), the time of maximum formation. This gave 8 time points on the decline curve. The RMS notes that the peak observed was at the first sample time after 10mm of rainfall had occurred. An SFO fit was applied to the data and results are as follows:

Figure B.8.107 Statistics for kinetic fitting of UK, Autumn, X11393729, top down from peak (occurred after 10mm rainfall), SFO

Parameter	Value	σ	Prob > t	Lower CI	Upper CI	DT50 (d)	X^2 err (%)
k (d^{-1})	0.01183	0.00162	1.35E-07	0.00846	0.015	58.6	9.5



The top down SFO fit for the Acid gave a low χ^2 error (9.5%), acceptable t-test and confidence intervals, and a good visual fit.

The best fit for X11393729 was obtained with the top-down SFO model and the DT50 value of **59 days** can be proposed as a conservative estimate. The RMS can agree with this proposal. Alternatively, the SFO/SFO sequential fit with Parent could also be proposed as a valid approach. The degradation of Parent is over-predicted in this sequential model but this is a worst-case situation with respect to formation of X11393729. The visual and statistical fit for X11393729 is good and the advantage of using the sequential model is that it yields a formation fraction for X11393729, which is not possible with the top-down model. Therefore, a DegT50 of 1.1 days for parent together with a formation fraction of 0.36 and a DegT50 of 51 days for X11393729 is proposed as inputs for modelling X11393729 from this trial. The RMS considers his may be an acceptable approach if separate exposure modelling for the parent using parent only parameters is also conducted given that the sequential modelling gave shorter degradation parameters for parent than compared to the modelling of parent alone at this site..

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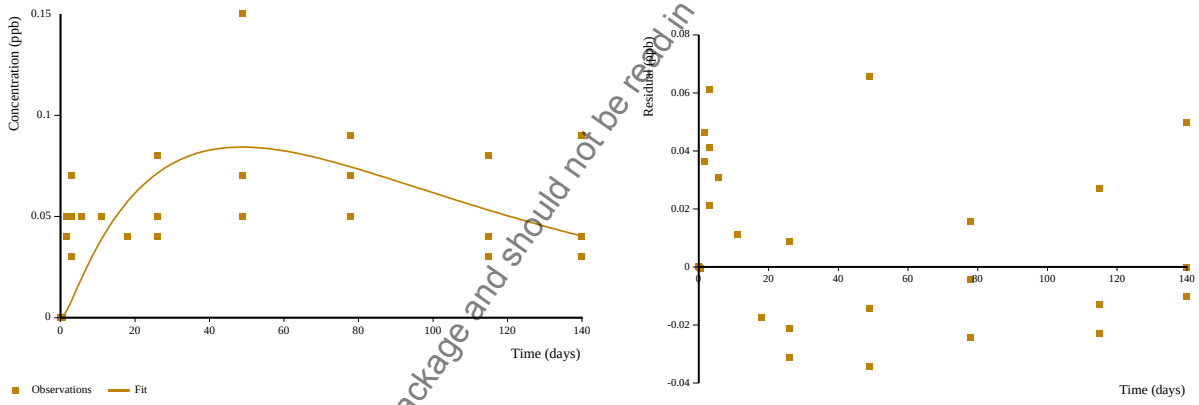
Parent + X11393729 + X11449757

The X11449757 data were added to the model and a sequential fit was performed for parent, X11393729 and X11449757 using SFO for the parent; X11449757 is designated A2. The optimised parameters are as follows:

Figure B.8.108 Statistics for kinetic fitting of UK, Autumn, parent + X11393729 + X11449757, all data, SFO+SFO+SFO

Parameter	Value	σ	Prob > t	Lower CI	Upper CI	DT50 (d)	X^2 err (%)
M_0 (µg/kg)	5.128	0.5164	2.61E-17	4.104	6.151		43.0
k_Parent (d^{-1})	0.7251	0.1252	3.33E-08	0.4769	0.973	0.96	
f_Par_to_A1	0.3495	0.04347	5.35E-13	0.2634	0.436		12.1
k_A1 (d^{-1})	0.0129	0.00193	4.97E-10	0.00907	0.017	53.7	
f_A1_to_A2	0.2169	0.06306	0.000411	0.09191	0.342		37.4
k_A2 (d^{-1})	0.0323	0.00954	0.000492	0.01339	0.051	21.5	

Compartment A2:



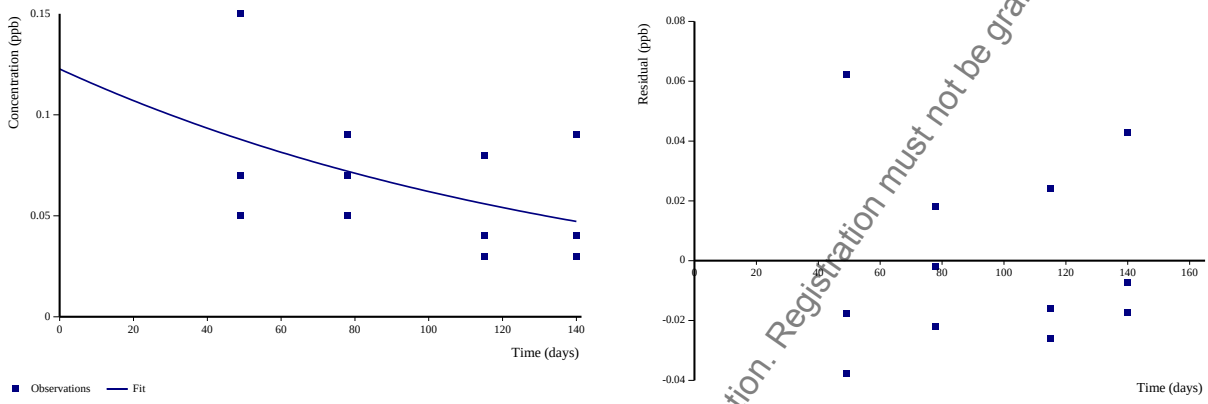
Only the X11449757 visual fit is shown here. The parameters for parent and X11393729 were very similar to those from the SFO+SFO fitting performed before addition of X11449757. There was a high χ^2 error for the X11449757 fit and a lot of scatter in the data although this is not unexpected given that the levels of X11449757 are close to or below the LOQ. Overall, the RMS considers that the model has performed reasonably well in attempting to describe the pattern of this metabolite in this study.

A top-down fit was attempted for the X11449757 metabolite despite only four time points being available. Results are shown in the following table:

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Figure B.8.109 Statistics for kinetic fitting of UK, Autumn, X11449757, top down from peak (occurred after 10mm rainfall), SFO

Parameter	Value	σ	Prob > t	Lower CI	Upper CI	DT50 (d)	X^2 err (%)
k (d^{-1})	0.00682	0.00418	0.06675	-0.00249	0.016	102	5.6



Although the χ^2 error was low, the t-test and confidence intervals were not acceptable. It is also reiterated by the RMS that the number of sample points was only 4, thus a reliable fit cannot be expected. The relatively low χ^2 error may simply be a reflection of the small number of sample times.

The Applicant concluded it was not possible to derive reliable top-down kinetics data for X11449757 from this data set. The Applicant considered that the sequential fit with the SFO model gave a reasonable fit for this metabolite and a DT50 of 22 days and a formation fraction of 0.22 (from X11393729) together with the optimised parameters for parent and X11393729 described above can be proposed as realistic inputs for modelling X11449757. In line with comments made on the fitting of X11393729 in this trial, the RMS considers this may be an acceptable approach if separate exposure modelling for the parent using parent only parameters is also conducted given that the sequential modelling gave shorter degradation parameters for parent than compared to the modelling of parent alone at this site.

Spain, Spring

Unnormalised data (Spain, Spring)

Parent

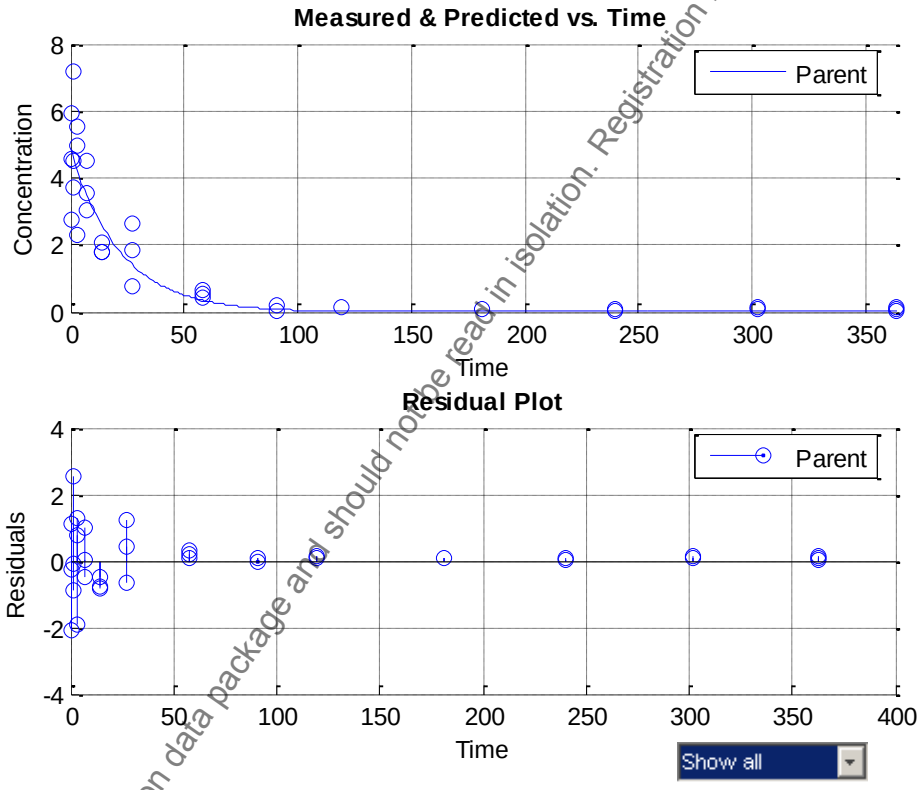
The kinetics fits for the measured data (*i.e.* not corrected for temperature and moisture) using the SFO and FOMC models for parent XDE-729 Methyl only are shown in the following table and figures.

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Table B.8.94 Statistics for SFO and FOMC fitting for Spain, Spring field dissipation data, XDE-729 methyl, all data

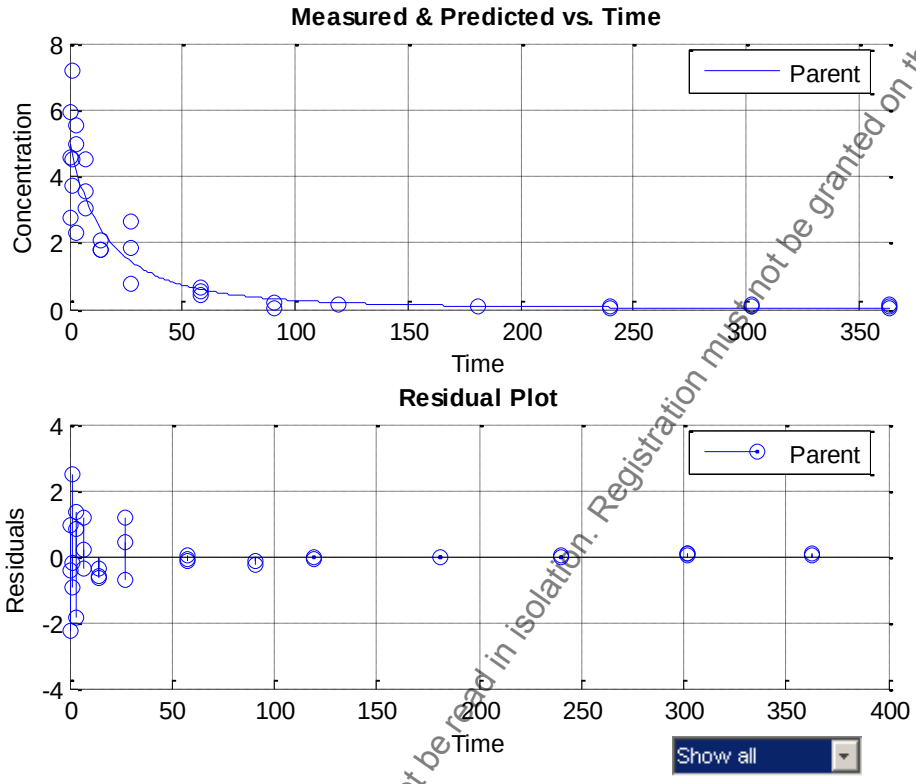
Model	Parameter	Value	Lower CI	Upper CI	Std Dev	Prob > t	DT_{50} (d)	DT_{90} (d)	% χ^2 error
SFO	M_0 (µg/kg)	4.83	4.24	5.43	0.29	-			
	k (d^{-1})	0.0454	0.0276	0.0631	0.0088	4.1e-06	15	51	14.1
FOMC	M_0 (µg/kg)	4.99	4.29	5.68	0.34	-			
	alpha	2.1869	-1.8304	6.2042	1.9808	0.1384	13	66	14.1
	beta	35.56	-51.63	122.8	42.99	0.2068			

Figure B.8.110 SFO fitting for Spain, Spring field dissipation data, XDE-729 methyl, all data



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Figure B.8.111 FOMC fitting for Spain, Spring field dissipation data, XDE-729 methyl, all data



The SFO model gave a DT50 of 15 days with a χ^2 error of 14% and acceptable t-test. The FOMC model gave the same χ^2 error but both the α and the β parameters showed unacceptable errors and lower CI less than zero. The Applicant proposed that the SFO model be accepted. As the fitting is virtually identical, the RMS can agree with this proposal. The best-fit DT50 and DT90 values for XDE-729 methyl at this site are 15 days and 51 days, respectively.

X11393729

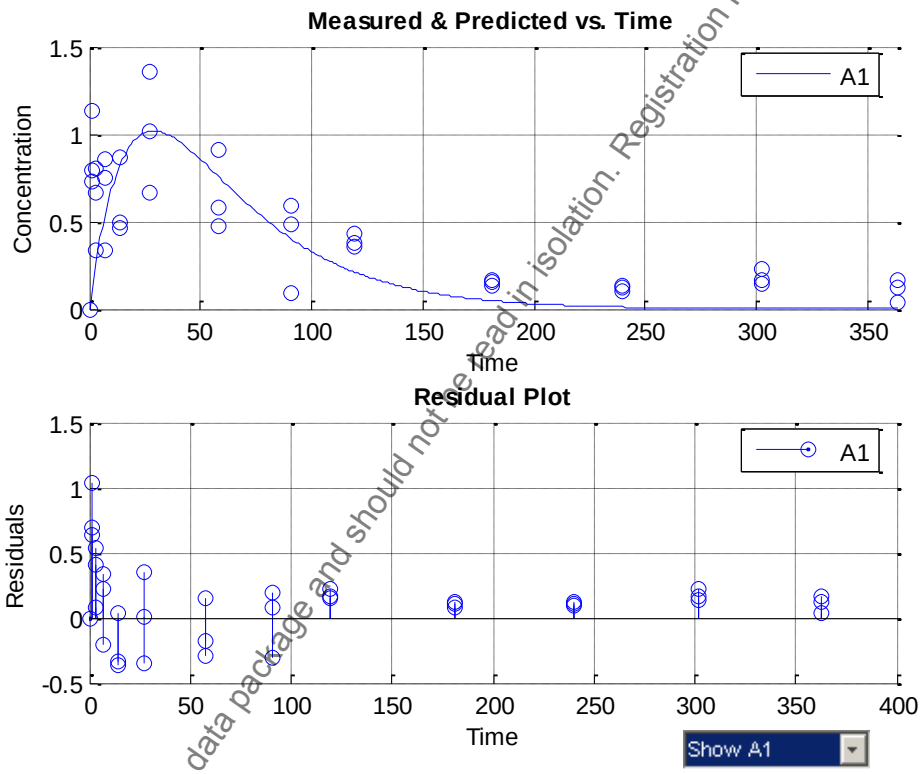
Using the optimised SFO parameters for parent XDE-729 methyl as initial values, X11393729 was added to the kinetics model with the formation fraction set to an initial value of 0.5. The optimised parameters for parent and metabolite are shown in the following table and figure. Only the X11393729 fit is shown as the parent fitting was not affected greatly.

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Table B.8.95 Statistics for SFO+SFO fitting for Spain, Spring field dissipation data, XDE-729 methyl+ X11393729, all data

Model	Parameter	Value	Lower CI	Upper CI	Std Dev	Prob > t	DT_{50} (d)	DT_{90} (d)	% χ^2 error
SFO Parent	M_0 (µg/kg)	4.84	4.39	5.28	0.22	-			
	k (d^{-1})	0.0458	0.0325	0.0592	0.0067	1.0e-09	15	50	14.1
SFO Acid	Form fraction	0.4378	0.1323	0.7433	0.1533	-			
	k (d^{-1})	0.0253	-3.3e-04	0.0509	0.0129	0.0265	27	91	50.5

Figure B.8.112 SFO+SFO fitting for Spain, Spring field dissipation data, XDE-729 methyl+ X11393729, all data



The DT50 for parent was essentially unchanged after addition of X11393729 to the model, and the χ^2 error was still less than 15%. The χ^2 error for X11393729 was high (51%) and the lower confidence interval for the k value is less than zero. Therefore, the Applicant considered a reliable DT50 for X11393729 could not be obtained at this trial site.

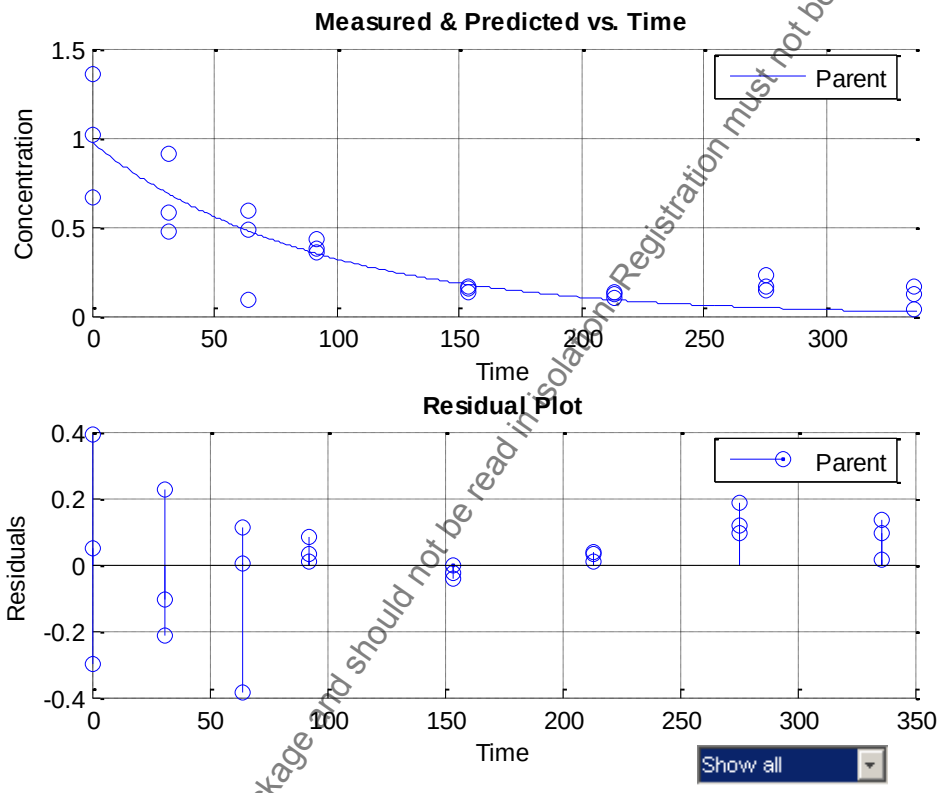
In order to obtain a "dissipation" rate for X11393729 that would be appropriate for a simple soil exposure assessment, a "top-down" fit was performed by the Applicant by running the SFO model to the decline data starting at Day 27, the time of maximum formation of XDE-729 Acid. The outputs are shown in the following table.

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Table B.8.96 Statistics for top-down SFO fit for X11393729, Spain, Spring, data from 27 DAT.

Model	Parameter	Value	Lower CI	Upper CI	Std Dev	Prob > t	DT_{50} (d)	DT_{90} (d)	% χ^2 error
SFO Acid (top-down)	M_0 (µg/kg) k (d^{-1})	0.97 0.0111	0.79 0.0071	4.15 0.0151	0.09 0.0019	- 4.5e-06	62	207	14.8

Figure 8.113 Top-down SFO fit for X11393729, Spain, Spring, data from 27 DAT.



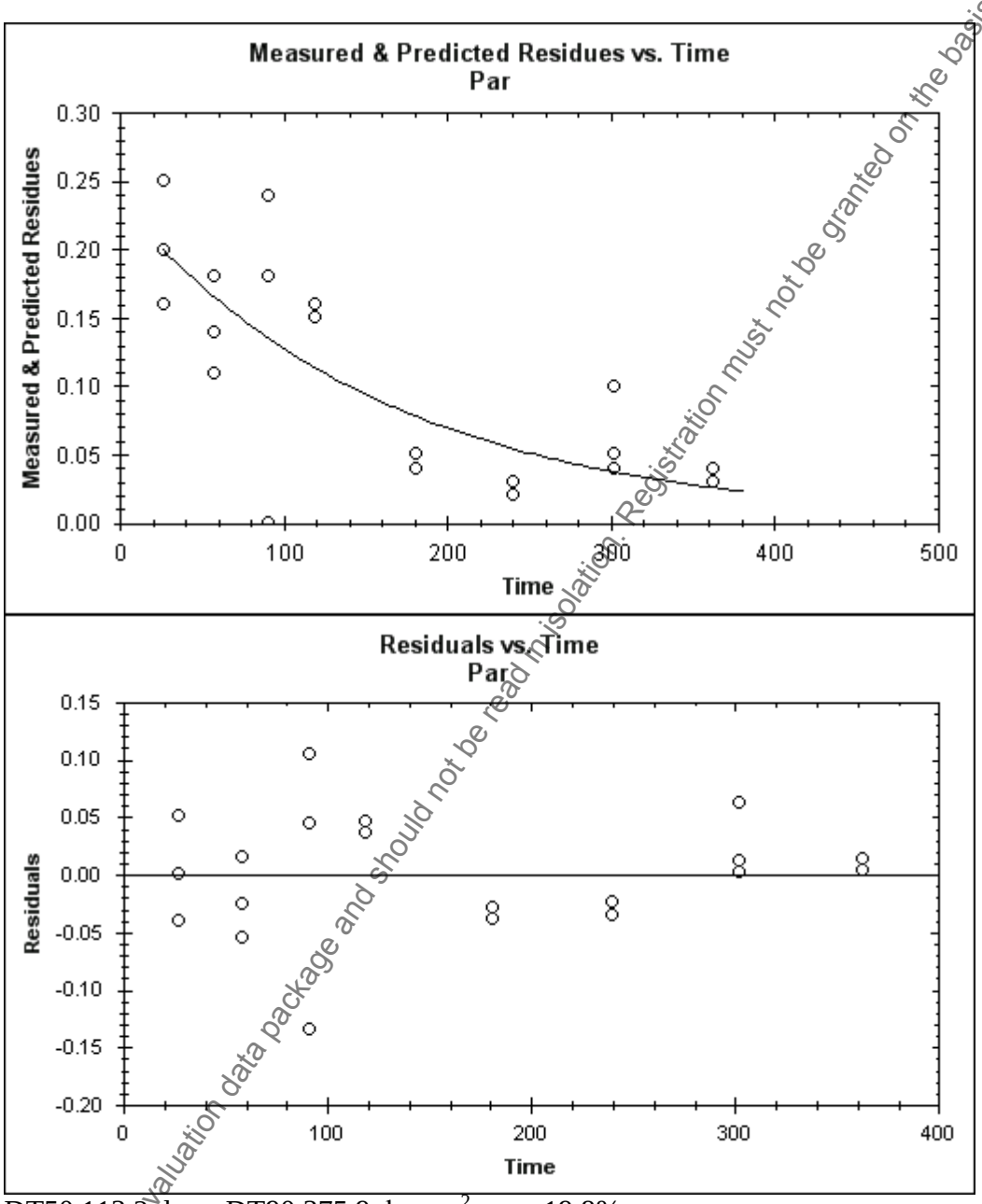
This top-down method was considered by the Applicant to give an acceptable χ^2 error of less than 15% and acceptable t-test. The calculated SFO DT50 of 62 days at this trials site can be accepted by the RMS for simple calculations such as PECsoil.

X11449757

The Applicant did not attempt to perform any fitting for X11449757 at this site. The RMS calculated a separate SFO top down DT50.

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Figure 8.114 RMS top-down SFO fit for X11449757, Spain, Spring, data from 27 DAT.



DT50 113.2 days, DT90 375.9 days, χ^2 error 19.8%

The RMS considers that the SFO top down DT50 is appropriate for use in simple calculations such as PECsoil calculation and proposes the DT50 value of 113.2 days for this trials site.

Data normalised to 20 °C and pF 2 (Spain, Spring)

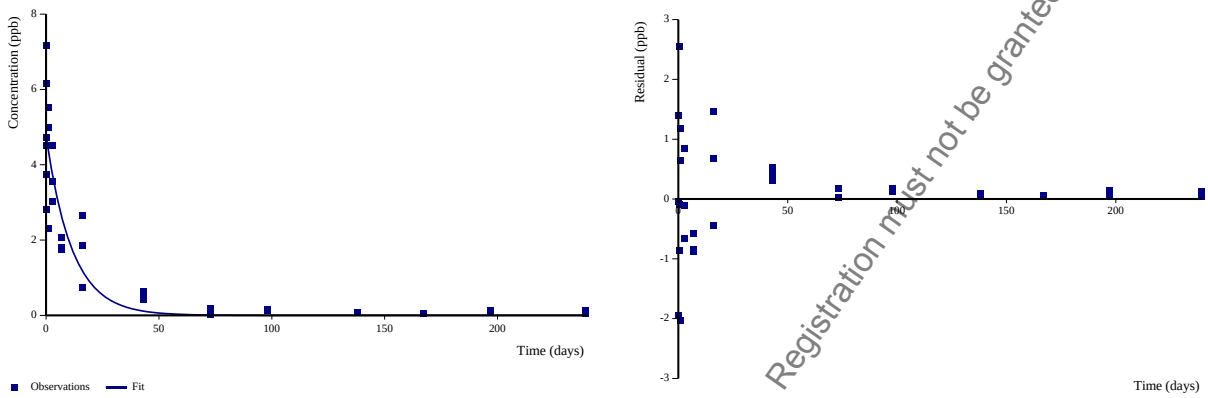
Parent

The results of fitting XDE-729 methyl (all data) to the SFO model are as follows:

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Figure B.8.115 Statistics for kinetic fitting of Spain, Spring, parent only, all data, SFO

Parameter	Value	σ	Prob > t	Lower CI	Upper CI	DT50 (d)	X^2 err (%)
M_0 (µg/kg)	4.766	0.2908	7.51E-19	4.177	5.355	8.0	15.9
k (d^{-1})	0.08682	0.01918	3.01E-05	0.04796	0.126		



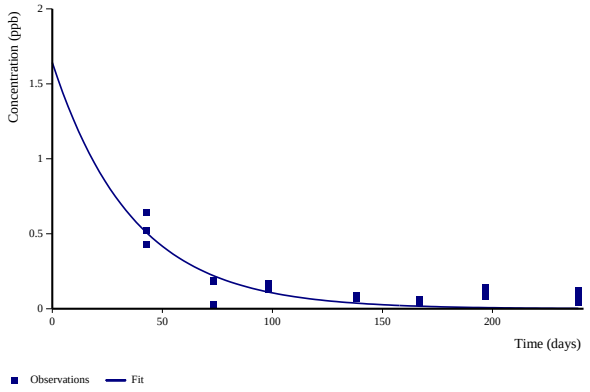
The SFO model gives a χ^2 error close to the target value and the visual fit is reasonable, although there is a tail of low residues above the predicted curve at later time points. The Applicant suggested that the residues in the tail were in the range 0.16 µg/kg to 0.03 µg/kg, which is less than 4% of the initial residue of 4.57 µg/kg. Therefore, the Applicant considered that 96% of the decline was described well by the SFO model. The RMS notes that the SFO curve also over predicts degradation at the 43 DAT time point where the average residue was 0.53 µg/kg, i.e. 11.6% of the initial residue.

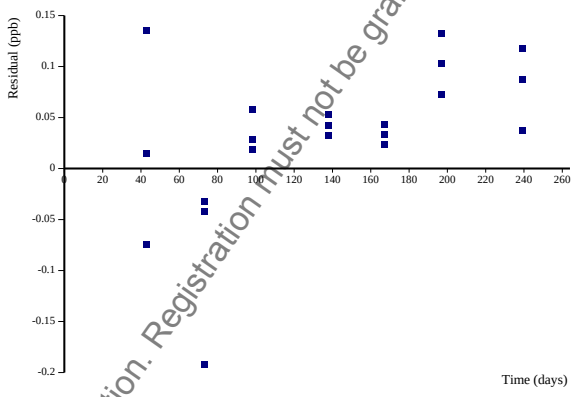
A further SFO fit was conducted after eliminating data points before 10 mm rainfall. Cumulative rainfall exceeded 10 mm (total = 12.7 mm) at 26 DAT (41 DAT real time). The first soil sampling time after this was 43 DAT (58 DAT real time), and the total rainfall at this time point was 12.9 mm. This gave 7 time points on the decline curve. The results of the SFO fit to these data are as follows:

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Figure B.8.116 Statistics for kinetic fitting of Spain, Spring, parent only, data after 10mm rainfall, SFO

Parameter	Value	σ	Prob > t	Lower CI	Upper CI	DT50 (d)	X^2err (%)
M_0 (µg/kg)	1.642	0.4606	0.001034	0.6778	2.606	25.3	32.0
k (d^{-1})	0.02742	0.00530	2.73E-05	0.01632	0.039		





The number of data points was low because of the relatively dry conditions at the start of the study which led to elimination of the first seven time points before 10 mm rain. Therefore, the initial residue was very low leading to high χ^2 error poor visual fit and residuals. The RMS notes that the residue at the first sample time included in the fitting represents on average 11.6% of the average initial residue. Therefore this part of the curve is mostly representing the tail of decline.

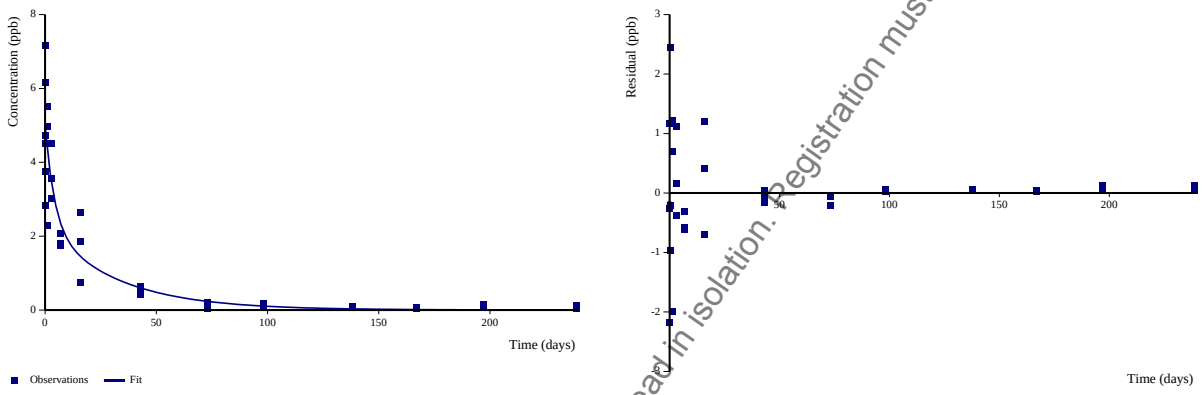
In line with EFSA guidance, the DFOP model was run with all the data. The results for the DFOP model for parent XDE-729 methyl are as follows:

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Figure B.8.117 Statistics for kinetic fitting of Spain, Spring, parent only, all data, DFOP

Parameter	Value	σ	Prob > t	Lower CI	Upper CI	DT50* (d)	X^2 err (%)
M_0 (µg/kg)	4.989	0.356	3.209E-16	4.266	5.712	-	12.9
k1 (d^{-1})	0.239	0.2125	0.1341	-0.1923	0.67	2.9	
k2 (d^{-1})	0.03114	0.02421	0.1033	-0.01799	0.08	22.3	
g	0.5427	0.3268	0.05287	-0.1208	1.206	-	

* DT50 for each rate constant calculated from ln2/k



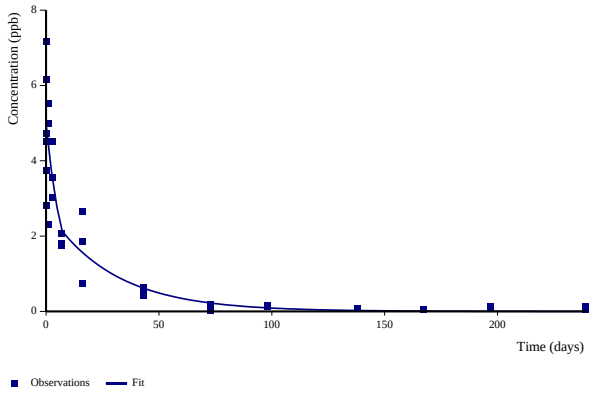
Although the χ^2 error was low, there were high errors on the k1 and k2 values, the t-test was failed and confidence intervals included zero. The g parameter was less than 0.75 and the k1 and k2 parameters were significantly different. According to EFSA guidance, the breakpoint is estimated from $t_b = (3 \times \ln 2)/k_{fast}$ giving a value of 8.7 days. This is much shorter than the 43 days before 10 mm rain. Therefore, the HS model was run. The results for the HS model for parent XDE-729 methyl are as follows:

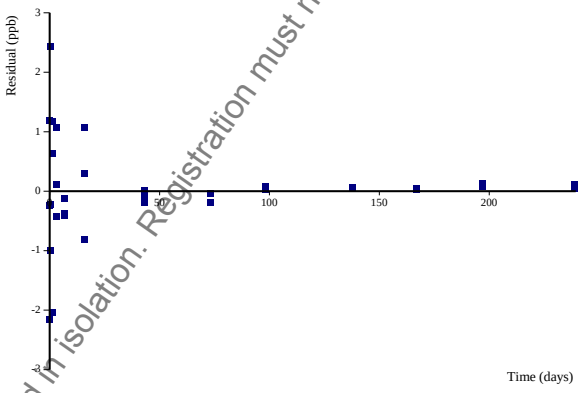
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Figure B.8.118 Statistics for kinetic fitting of Spain, Spring, parent only, all data, HS

Parameter	Value	σ	Prob > t	Lower CI	Upper CI	DT50* (d)	X^2 err (%)
M_0 (µg/kg)	4.969	0.3233	1.96E-17	4.312	5.625	-	10.5
k1 (d^{-1})	0.122	0.04079	0.00254	0.03915	0.205	5.7	
k2 (d^{-1})	0.03434	0.02101	0.05558	-0.00832	0.077	20.2	
t_b (days)	6.872	5.937	0.1275	-5.181	18.92	-	

* DT50 for each rate constant calculated from ln2/k





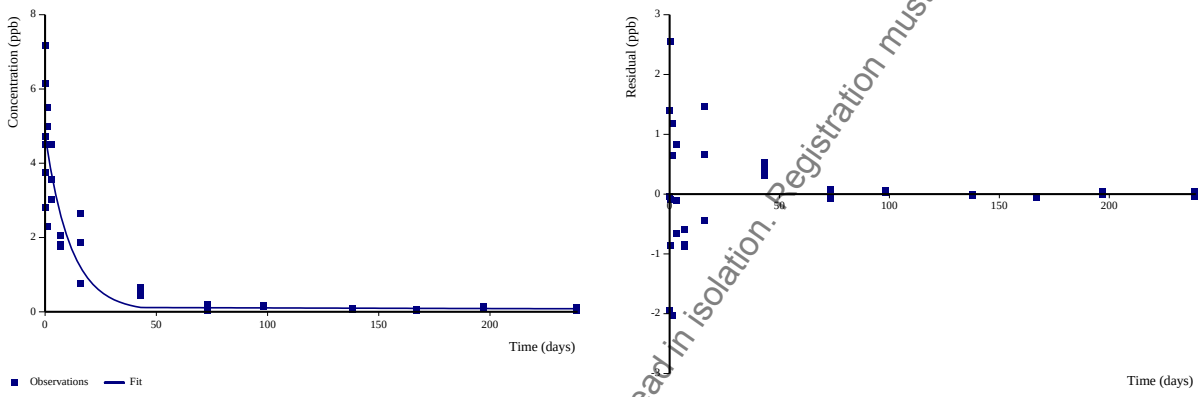
The calculated breakpoint of 6.9 days is a long way short of the 43 DAT point when 10 mm rainfall was reached. Therefore, the HS model was run again after fixing the breakpoint at 43 days.

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Figure B.8.119 Statistics for kinetic fitting of Spain, Spring, parent only, all data, HS, break point fixed at 43 DAT

Parameter	Value	σ	Prob > t	Lower CI	Upper CI	DT50* (d)	X^2err (%)
M_0 (µg/kg)	4.765	0.2928	1.78E-18	4.171	5.359	-	16.1
k1 (d^{-1})	0.08662	0.01906	2.99E-05	0.04797	0.125	8.0	
k2 (d^{-1})	0.00174	0.01904	0.4638	-0.03688	0.040	398	
t_b (days)	43 (fixed)	-	-	-	-	-	

* DT50 for each rate constant calculated from ln2/k



Although the χ^2 error was close to the target value, there was high error on the k2 parameter; in addition, the t-test failed and confidence interval included zero for k2. The RMS also notes that the fit was worsened by fixing the breakpoint

The Applicant considered that the problem with the Spain Spring data set is that there was a long period of time before 10 mm of rain was achieved at the test site. Therefore, almost half of the data points are eliminated and the initial residue of XDE-729 Methyl had decreased from 4.49 µg/kg to 0.53 µg/kg by this time. This results in only 12% of the initial residue in the soil at the start of the kinetic decline curve. The Applicant considered the most reliable parameters were derived from the SFO fit with all of the data, which gave a DT50 of **8.2 days**. However, taking into consideration the EFSA opinion, the DT50 of **25 days** derived from the SFO model after 10 mm rain is proposed as a conservative estimate for degradation in the soil bulk matrix. The RMS can agree with this selection of endpoint for the parent from this trial. The RMS also notes that the SFO DT50 after 10mm rainfall is very similar to the HS slow phase DT50 taking into account the whole database.

Parent + X11393729

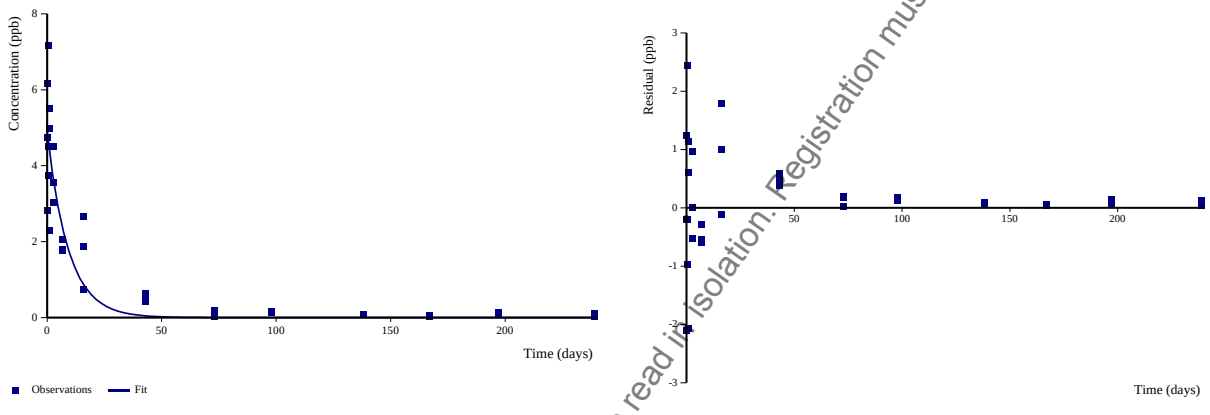
The Applicant considered that as the SFO model with all the data gave a reasonable fit for parent, a sequential fit was run using SFO for both parent and X11393729 (X11393729 is designated A1). The results are as follows:

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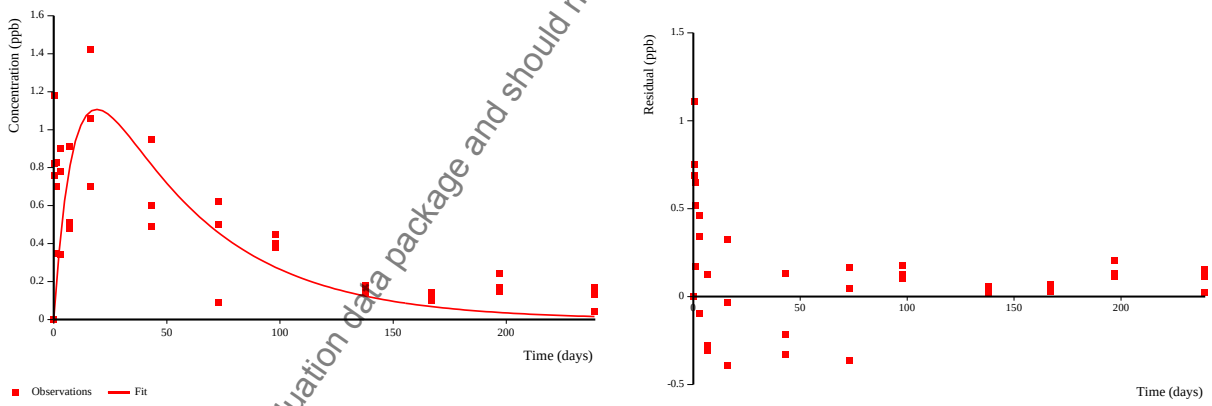
Figure B.8.120 Statistics for kinetic fitting of Spain, Spring, parent + X11393729, all data, SFO+SFO

Parameter	Value	σ	Prob > t	Lower CI	Upper CI	DT50 (d)	X^2err (%)
M_0 (µg/kg)	4.921	0.2991	9.84E-27	4.325	5.517	-	
k_Parent (d^{-1})	0.1086	0.02181	2.00E-06	0.0652	0.152	6.4	16.8
f_Par_to_A1	0.3303	0.06929	4.55E-06	0.1923	0.468	-	
k_A1 (d^{-1})	0.02023	0.00571	0.00034	0.00886	0.032	34.3	49.2

Compartment Parent:



Compartment A1:



After addition of X11393729 to the model, the DT50 for parent was similar to that obtained for parent alone (8.0 days and 6.4 days, respectively) and the χ^2 error was similar; the RMS notes that the SFO curve steepens slightly resulting a slightly worse fit for parent. The χ^2 error for X11393729 was high but other statistical parameters were considered acceptable by the Applicant, and the visual fit was considered by the Applicant to be good. The RMS notes that the increase in X11393729 residues was very steep initially which the SFO/SFO model could not quite match, but the peak in average residue was well simulated. There is also a significant amount of relative scatter in the X11393729 data which probably accounts for the high χ^2 error.

A kinetic fit using a DFOP/SFO sequential model for parent and X11393729 failed to complete successfully and since the DFOP model for parent XDE-729 methyl on its

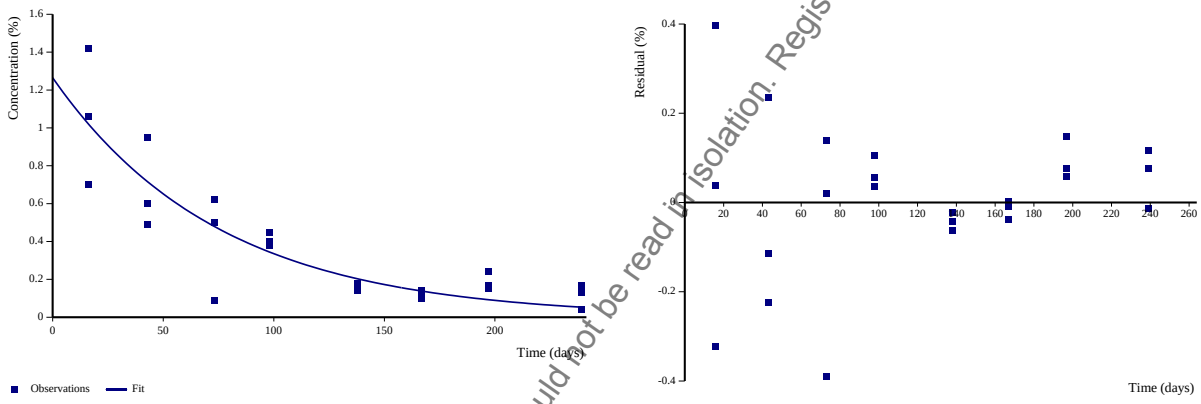
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own gave a poor fit, no more attempts were made by the Applicant to fit a biphasic model to parent.

To complete the kinetics analysis for X11393729, a top-down SFO fit was performed starting at 16 DAT (27 DAT real time), the time of maximum formation; the RMS notes that this is before 10mm rain has occurred. This gave 8 time points on the decline curve. An SFO fit was applied to the data and results are shown in the following table:

Figure B.8.121 Statistics for kinetic fitting of Spain, Spring, X11393729, top down from peak (occurred before 10mm rainfall), SFO

Parameter	Value	σ	Prob > t	Lower CI	Upper CI	DT50 (d)	X^2 err (%)
k (d^{-1})	0.01327	0.00204	7.80E-07	0.00903	0.018	52.3	11.9

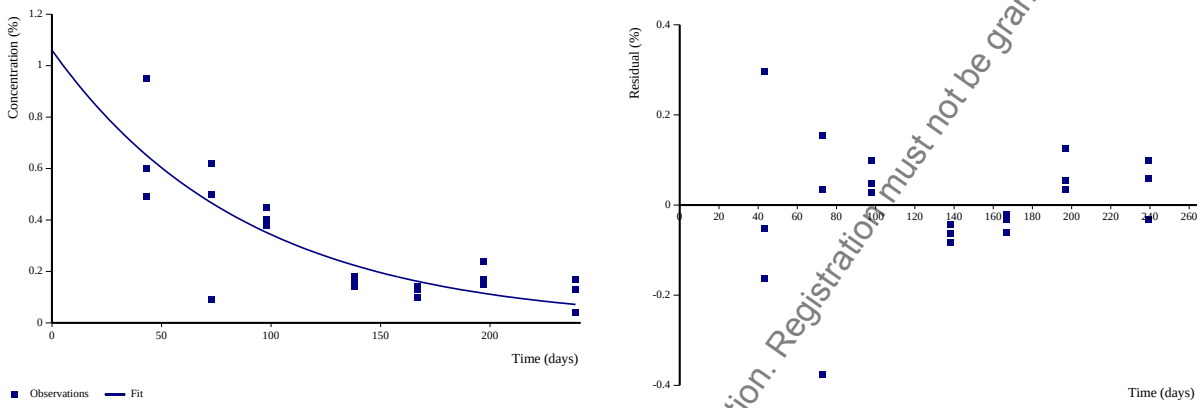


The top-down SFO fit gave a good visual fit, low χ^2 error (12%) and acceptable statistics, with a DT50 of 52 days. However, since 10 mm rain was not achieved until 43 DAT (58 DAT real time), a second top-down fit was performed on X11393729 using data from 43 DAT onwards (7 data points). The results are as follows:

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Figure B.8.122 Statistics for kinetic fitting of Spain, Spring, X11393729, top down from after 10mm rainfall, SFO

Parameter	Value	σ	Prob > t	Lower CI	Upper CI	DT50 (d)	X^2 err (%)
k (d^{-1})	0.01127	0.00222	3.29E-05	0.00663	0.016	61.5	14.5



The top down SFO fit with the shorter data set gave a slightly higher χ^2 error (15%) but the statistics were acceptable and the residuals were marginally improved.

The best fit for X11393729 was obtained with the top-down SFO model and the DT50 value of 62 days from SFO fitting after 10 mm rainfall was proposed by the Applicant as a conservative estimate. The alternative SFO/SFO sequential fit with parent gave poorer statistics but the visual fit for X11393729 was reasonable in terms of the maximum amount formed and the decline curve. Therefore, a DegT50 of 6.4 days for parent together with a formation fraction of 0.33 and a DegT50 of 34 days for X11393729 from this trial are proposed by the Applicant as inputs for modelling the X11393729 metabolite. The RMS can accept the parameters from sequential fitting as separate parent parameters are used for modelling X11393729 formed from parent compared to modelling parent alone.

Parent + X11393729 + X11449757

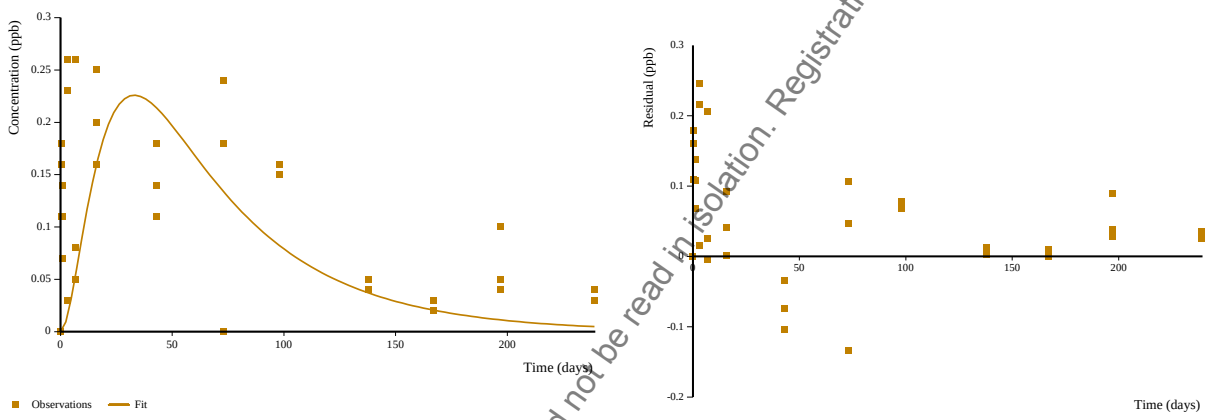
The X11449757 data were added to the model and a sequential fit was performed for parent, X11393729 and X11449757 using SFO for the parent (X11449757 is designated A2). The optimised parameters are as follows:

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Figure B.8.123 Statistics for kinetic fitting of Spain, Spring, parent + X11393729 + X11449757, all data, SFO+SFO+SFO

Parameter	Value	σ	Prob > t	Lower CI	Upper CI	DT50 (d)	χ^2 err (%)
M_0 (µg/kg)	4.98	0.3041	1.10E-31	4.377	5.583		17.6
k_Parent (d^{-1})	0.1181	0.02306	6.38E-07	0.07244	0.164	5.9	
f_Par_to_A1	0.328	0.06347	5.29E-07	0.2022	0.454		48.7
k_A1 (d^{-1})	0.02016	0.00506	6.04E-05	0.01014	0.03	34.4	
f_A1_to_A2	1	0.682	0.07271	-0.3515	2.351		58.8
k_A2 (d^{-1})	0.08675	0.05393	0.05526	-0.02011	0.194	8.0	

Compartment A2:



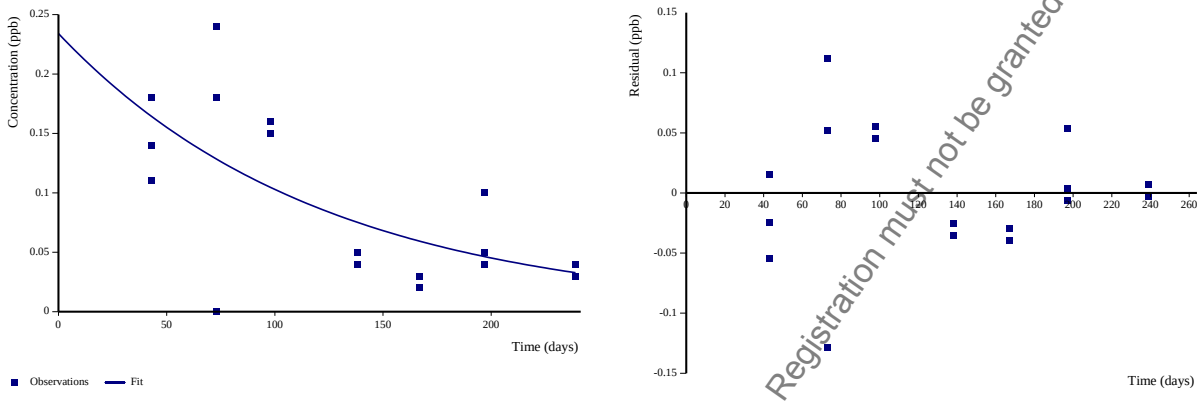
Only the X11449757 visual fit is shown here (full details in Appendix 6h). Visually and statistically, the fit for the X11449757 metabolite was considered by the Applicant to be poor. It was noted that there was a further reduction in the parent DT50 (from 8 days with SFO parent only modelling) but the X11393729 fitting was similar. The RMS agrees that the fitting to the X11449757 is poor, with the model failing to simulate the very early high formation, but it is also noted that the data are quite scattered and variable. It is unlikely that a suitable kinetic model could be found to fit this dataset.

A top-down fit was performed with X11449757. The time of maximum formation is 16 DAT (27 DAT real time), but 10 mm rain was not achieved until 43 DAT (58 DAT real time). Therefore, the top-down fit was performed using data from 43 DAT onwards (7 data points). The results are shown in the following table:

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Figure B.8.124 Statistics for kinetic fitting of Spain, Spring, X11449757, top down from after 10mm rainfall, SFO

Parameter	Value	σ	Prob > t	Lower CI	Upper CI	DT50 (d)	X^2 err (%)
k (d^{-1})	0.00822	0.00255	0.00223	0.00289	0.014	84.3	26.2



Although the χ^2 error of 26% is higher than would be normally accepted, the visual fit is reasonably good and considering the low residue levels involved, the results can be accepted.

The top-down DT50 of 84 days is proposed by the Applicant as a conservative estimate for X11449757. The RMS can accept this value.

Spain, Autumn

Unnormalised data (Spain, Autumn)

Parent

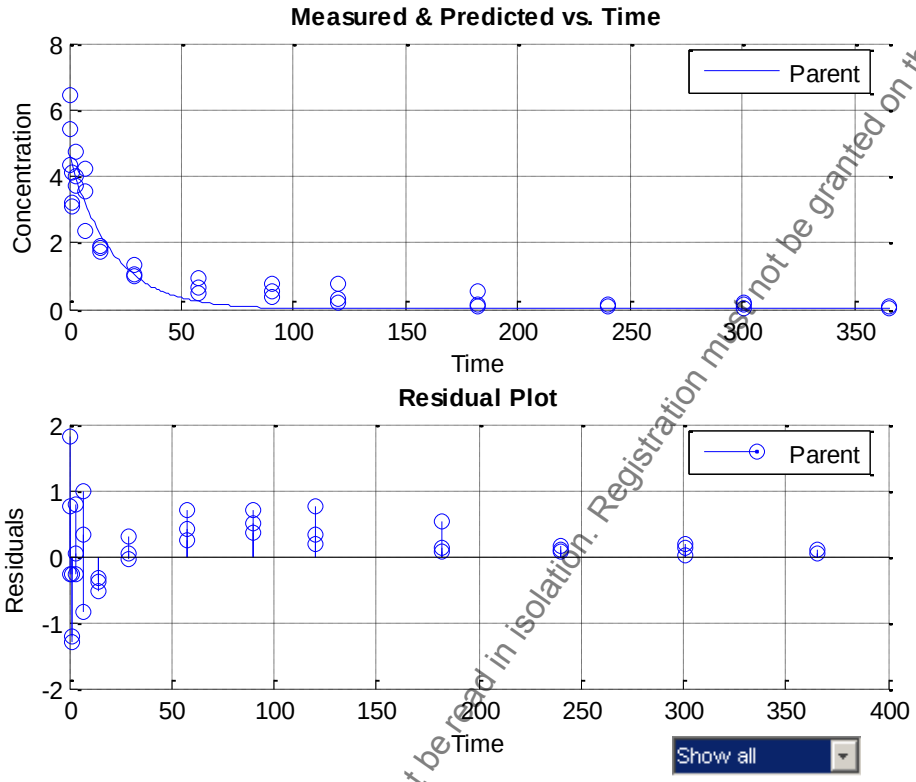
The kinetics fits for the measured data (i.e. not corrected for temperature and moisture) using the SFO and FOMC models for parent XDE-729 methyl only are shown in the following table and figures.

Table B.8.97 Statistics for SFO and FOMC fitting for Spain, Autumn field dissipation data, XDE-729 methyl, all data

Model	Parameter	Value	Lower CI	Upper CI	Std Dev	Prob > t	DT_{50} (d)	DT_{90} (d)	% χ^2 error
SFO	M_0 (µg/kg)	4.63	4.19	5.08	0.22	-			
	k (d^{-1})	0.0520	0.0361	0.0678	0.0078	4.2e-08	13	44	21.3
FOMC	M_0 (µg/kg)	4.86	4.36	5.37	0.25	-			
	alpha	1.1553	0.3674	1.9432	0.3885	0.0026	11	83	18.3
	beta	13.05	-2.22	28.32	7.5300	0.0458			

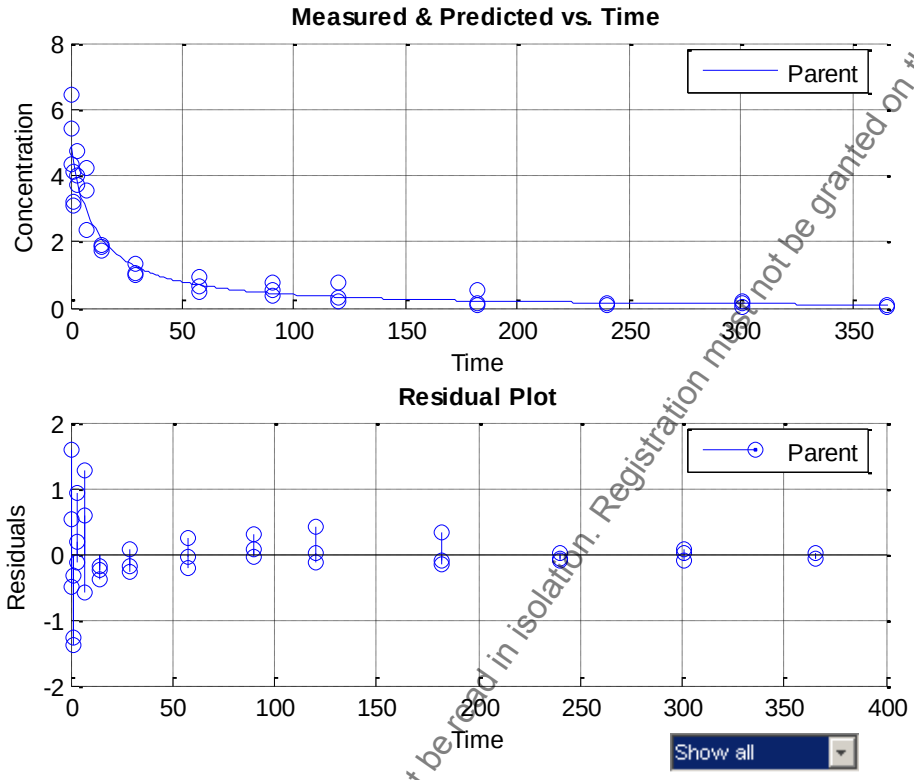
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Figure B.8.125 SFO fitting for Spain, Autumn field dissipation data, XDE-729 methyl, all data



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Figure B.8.126 FOMC fitting for Spain, Autumn field dissipation data, XDE-729 methyl, all data



The SFO model gave a DT50 of 13 days with a χ^2 error of 21% and acceptable t-test. The FOMC model gave a slightly lower χ^2 error (18%) but the lower CI for the β parameter was less than zero. The Applicant considered the SFO model to be more appropriate even though the χ^2 error is greater than 15%. The visual fit and residuals for the SFO model shows a slight over-prediction of residues from 58 days onwards.

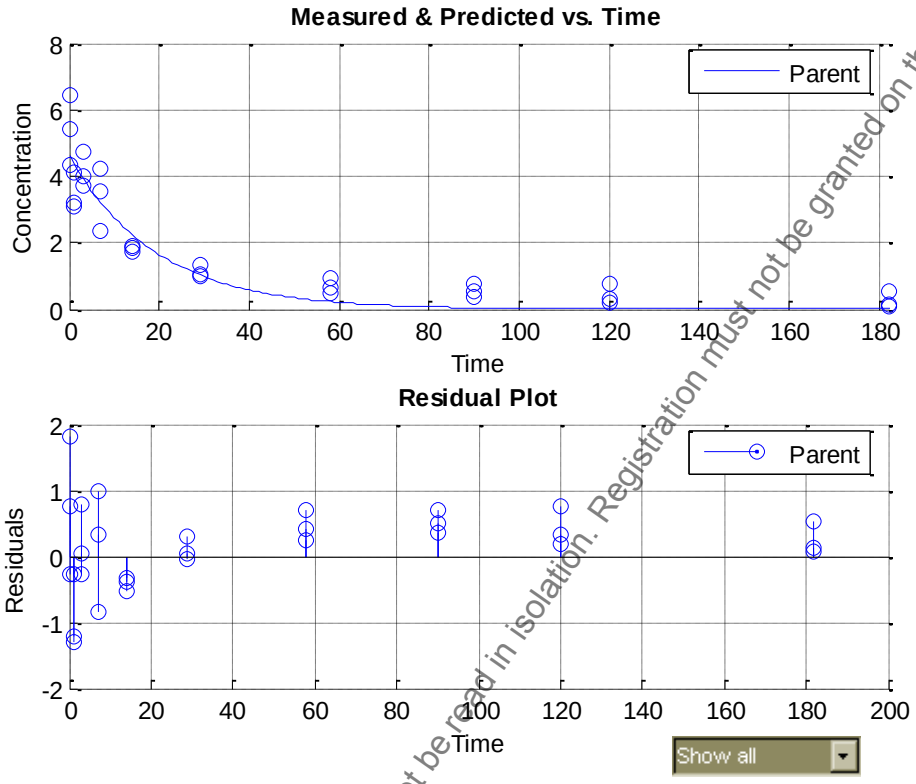
The Applicant considered that the residues of XDE-729 methyl decreased from an initial concentration of 5.39 µg/kg (average of parent and X11393729 combined) to less than 8% after 120 days and less than 5% after 182 days. Since greater than 95% of the residue was dissipated over the first 6 months the Applicant re-ran the SFO and FOMC models using the data up to Day 182. The optimised parameters are as follows.

Table B.8.98 Statistics for SFO and FOMC fitting for Spain, Autumn field dissipation data, XDE-729 methyl, 0 – 182 DAT data

Model	Parameter	Value	Lower CI	Upper CI	Std Dev	Prob > t	DT_{50} (d)	DT_{90} (d)	% χ^2 error
SFO (Day 0-182)	M_0 (µg/kg)	4.63	4.11	5.15	0.25	-			
	k (d^{-1})	0.0520	0.0336	0.0703	0.0090	1.5e-06	13	44	18.5
FOMC (Day 0-182)	M_0 (µg/kg)	4.87	4.28	5.47	0.29	-			
	alpha	1.0936	0.1669	2.0204	0.4517	0.0112	11	86	16.3
	beta	11.957	-5.462	29.376	8.490	0.085			

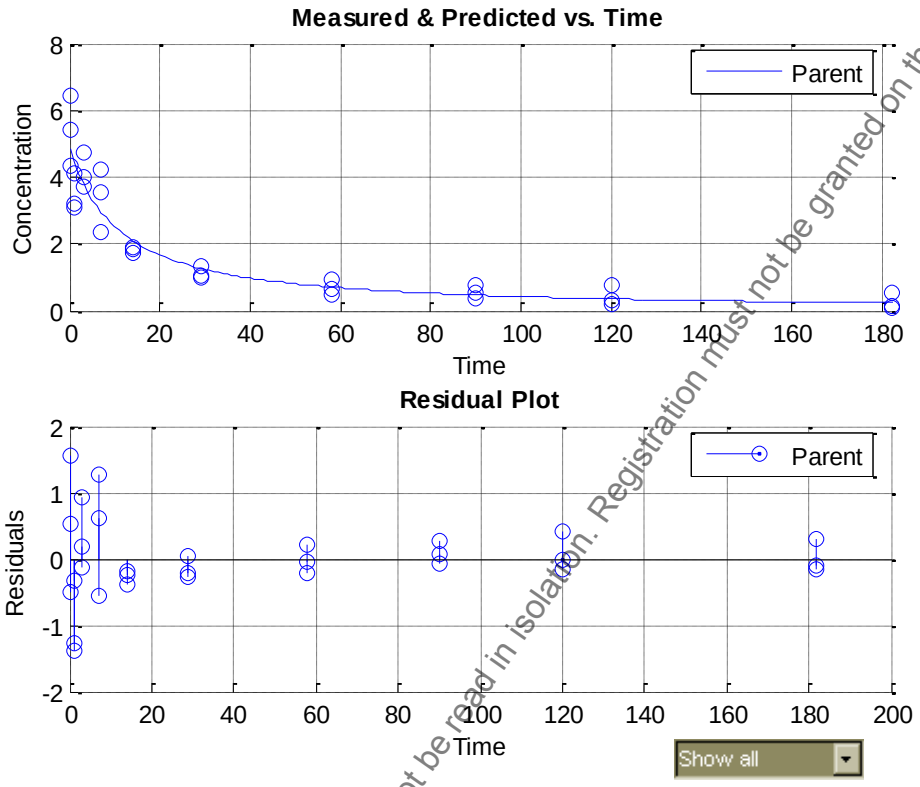
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Figure B.8.127 SFO fitting for Spain, Autumn field dissipation data, XDE-729 methyl, 0 – 182 DAT data



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Figure B.8.128 DFOP fitting for Spain, Autumn field dissipation data, XDE-729 methyl, 0 – 182 DAT data



Using the data up to Day 182, the χ^2 error was reduced from 21% to 19% for the SFO model and the kinetics parameters are essentially identical to those derived using the whole data set. The FOMC fit still gave a lower CI less than zero, so was rejected by the Applicant; the SFO fitting was accepted by the Applicant.

The RMS considers that the FOMC model is a better overall fit to this dataset and prefers to use these parameters for persistence purposes. Therefore the RMS proposed FOMC DT50 of 11 days and DT90 of 86 days for this trials site.

X11393729

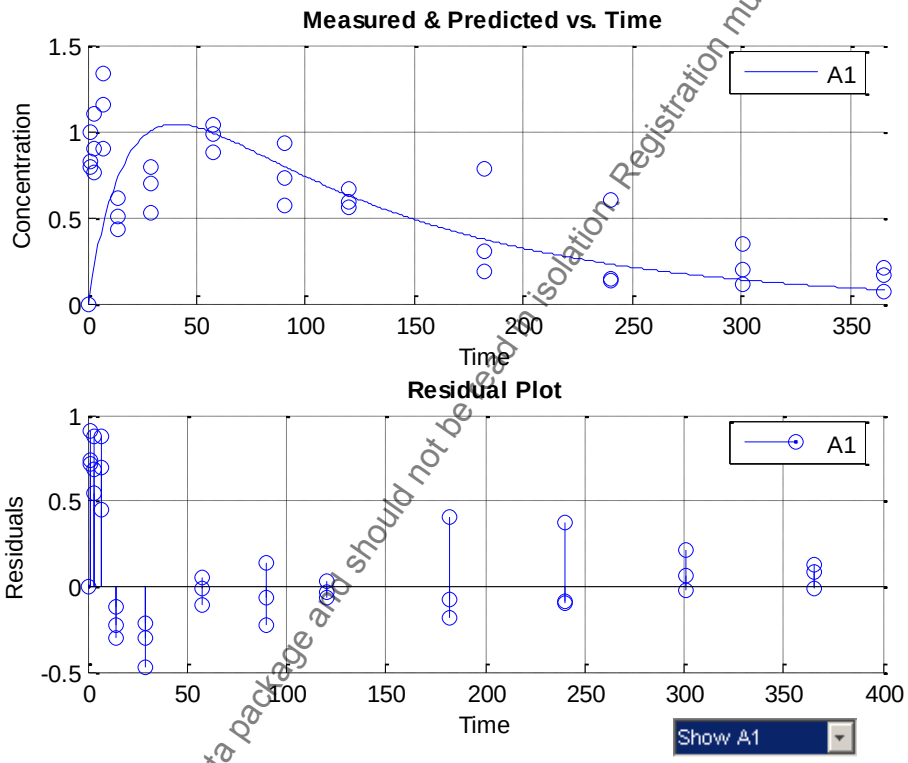
Using the optimised SFO parameters for parent XDE-729 methyl as initial values, X11393729 was added to the kinetics model with the formation fraction set to an initial value of 0.5. The optimised parameters for parent and metabolite are shown in the following table and figure. Only the X11393729 fit is shown as the parent fitting was not affected greatly.

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Table B.8.99 Statistics for SFO+SFO fitting for Spain, Autumn field dissipation data, XDE-729 methyl+ X11393729, all data

Model	Parameter	Value	Lower CI	Upper CI	Std Dev	Prob > t	DT_{50} (d)	DT_{90} (d)	% χ^2 error
SFO Parent (all data)	M_0 (µg/kg)	4.68	4.30	5.06	0.19	-			
	k (d^{-1})	0.0549	0.0412	0.0687	0.0069	7.7e-12	13	42	21.3
SFO Acid (all data)	Form fraction	0.3127	0.1730	0.4524	0.0701				
	k (d^{-1})	0.0084	0.0020	0.0149	0.0032	0.0056	82	273	53.5

Figure B.8.129 SFO+SFO fitting for Spain, Autumn field dissipation data, XDE-729 methyl+ X11393729, all data



The parameters for parent were similar to those obtained with parent alone. The fit for X11393729 gave a high χ^2 error (54%) but both the formation fraction and rate constant parameters showed acceptable error and t-test. The residuals were high at the very early time points due to some high residues at the first few sampling points which the model could not fit but the visual fit and residuals during the main decline part of the curve from 58 days to one year appeared. Therefore, the DT50 value of 82 days with a formation fraction of 0.313 was proposed by the Applicant for this trials site.

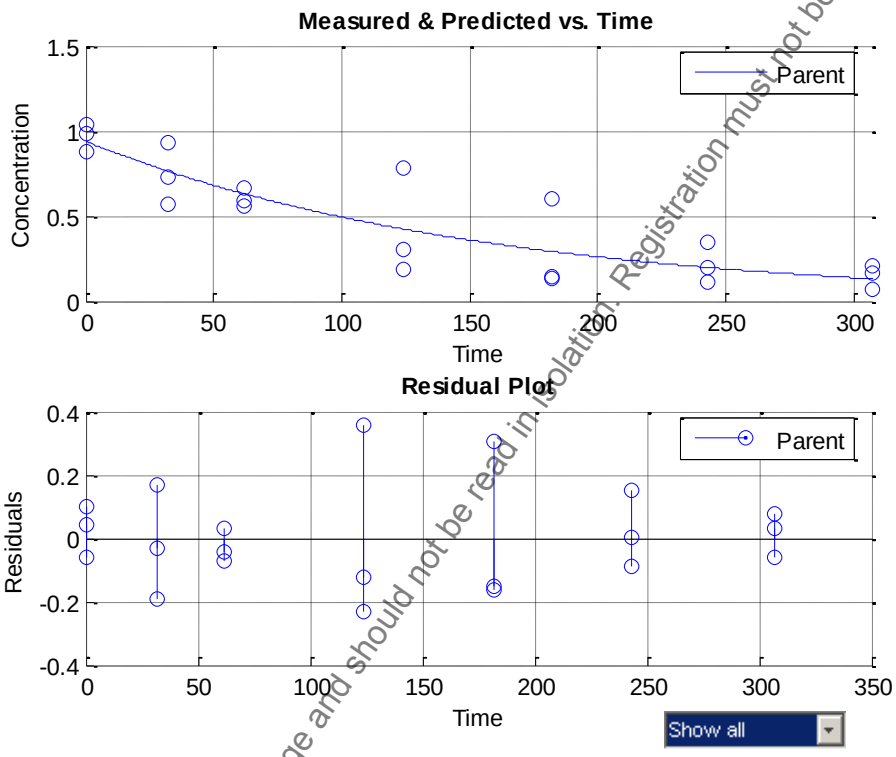
In order to obtain a "dissipation" rate for X11393729 that would be appropriate for a soil exposure assessment, a "top-down" fit was performed by the Applicant by running the SFO model to the decline data starting at Day 58. Although there was a higher residue at Day 7 (based on average values) the Applicant considers there was high variability in the data at the earlier time points and the Day 58 point appeared to be the start of the true decline phase for the acid.

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Table B.8.100 Statistics for top-down SFO fit for X11393729, Spain Autumn, data from 58 DAT.

Model	Parameter	Value	Lower CI	Upper CI	Std Dev	Prob > t	DT_{50} (d)	DT_{90} (d)	% χ^2 error
SFO Acid (top-down)	M_0 (µg/kg)	0.94	0.79	1.09	0.07	-			
	k (d^{-1})	0.0064	0.0042	0.0086	0.0011	3.9e-06	108	359	3.2

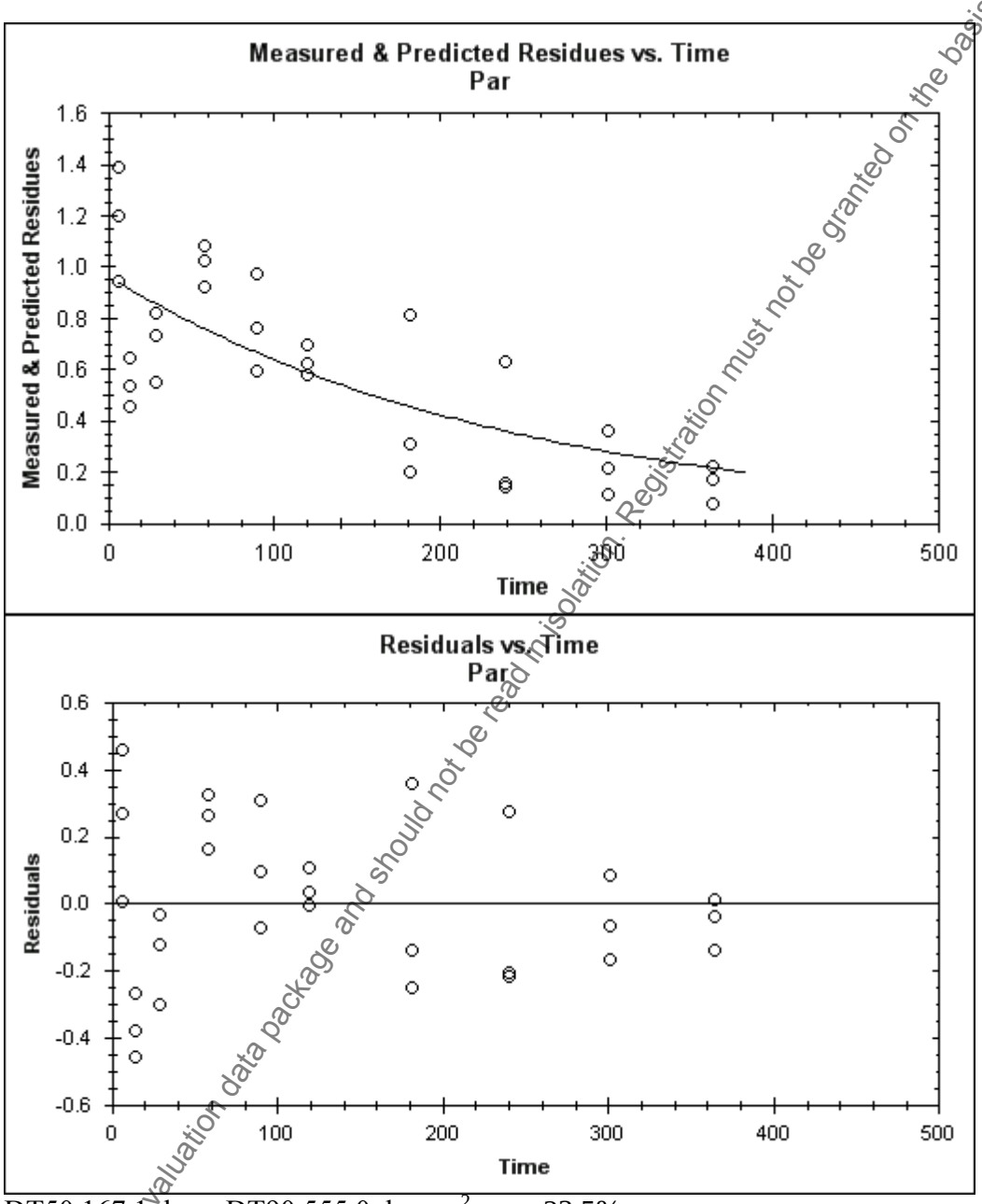
Figure 8.130 Top-down SFO fit for X11393729, Spain Autumn, data from 29 DAT.



The RMS re-ran the top down fit including data from the peak residue at 7 DAT.

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Figure 8.131 RMS top-down SFO fit for X11393729, Spain Autumn, data from 29 DAT.



DT50 167.1 days, DT90 555.0 days, χ^2 error 23.5%

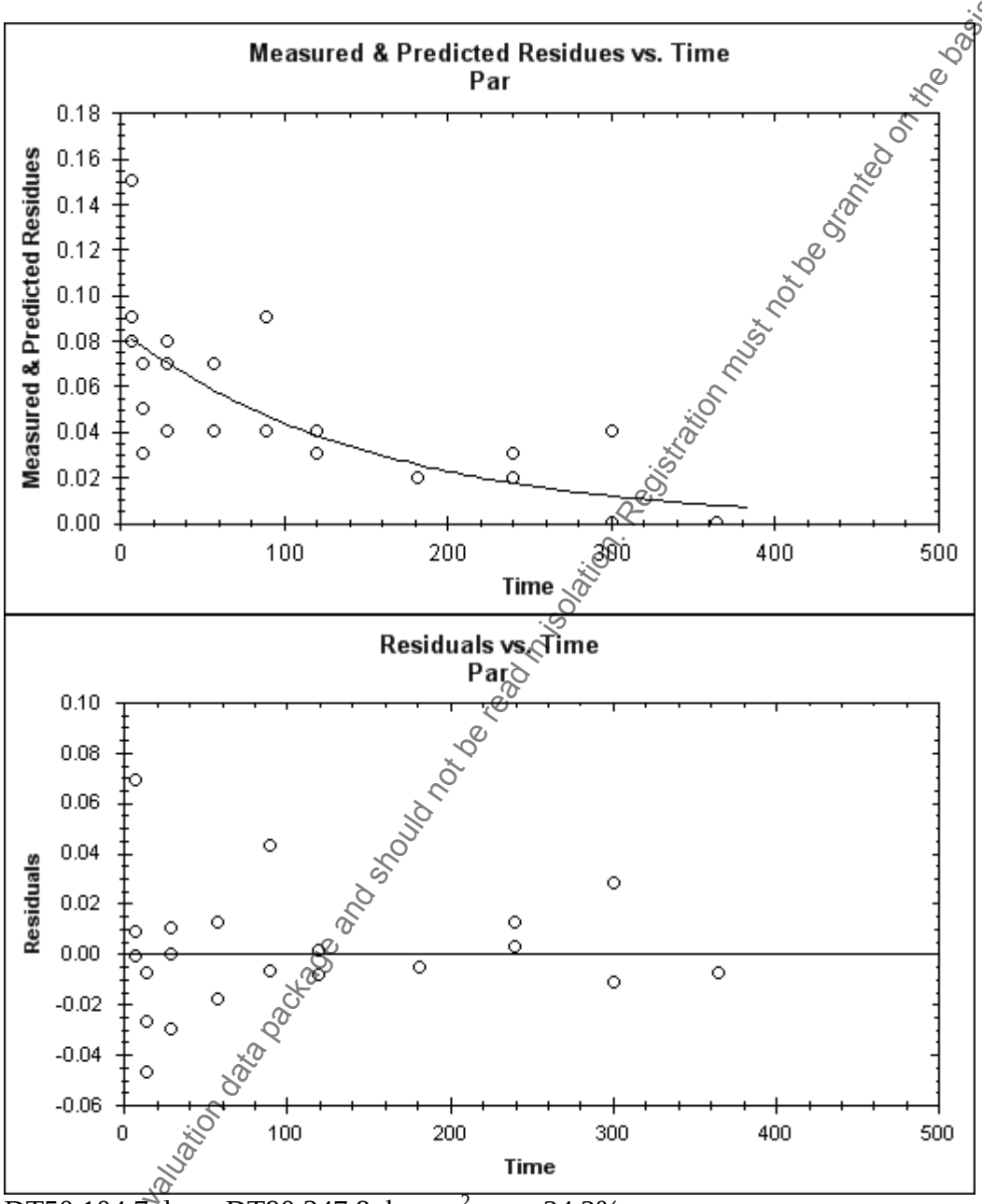
The RMS agrees that including the data from the peak residue increased variability of the dataset, resulting in significant worsening of the fit. Clearly the SFO model would not be able to simulate such variability. Therefore the RMS accepts the top down SFO DT50 of 108 days from this trials site for use in simple PECsoil calculation.

X11449757

The Applicant did not attempt any fitting with X11449757. The RMS calculated a separate SFO top down DT50.

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Figure 8.132 RMS top-down SFO fit for X11449757, Spain, Autumn, data from 7 DAT.



DT50 104.7 days, DT90 347.8 days, χ^2 error 24.2%

The RMS considers that the SFO top down DT50 is appropriate for use in simple calculations such as PECsoil calculation and proposes the DT50 value of 104.7 days for this trials site.

Data normalised to 20 °C and pF 2 (Spain, Autumn)

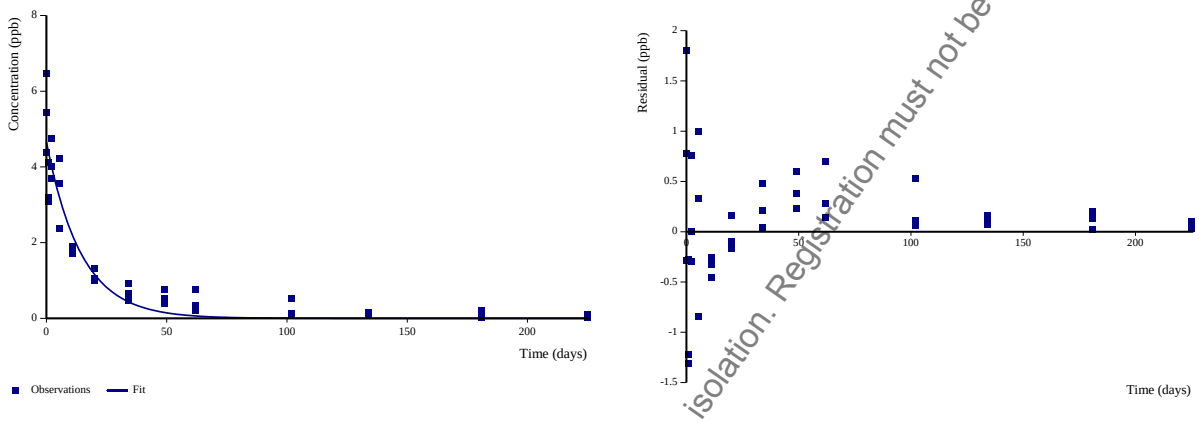
Parent

The results of fitting XDE-729 methyl (all data) to the SFO model are as follows:

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Figure B.8.133 Statistics for kinetic fitting of Spain, Autumn, parent only, all data, SFO

Parameter	Value	σ	Prob > t	Lower CI	Upper CI	DT50 (d)	X^2 err (%)
M_0 (µg/kg)	4.654	0.2101	2.99E-23	4.228	5.079	10.0	19.6
k (d^{-1})	0.06949	0.00918	2.48E-09	0.05089	0.088		



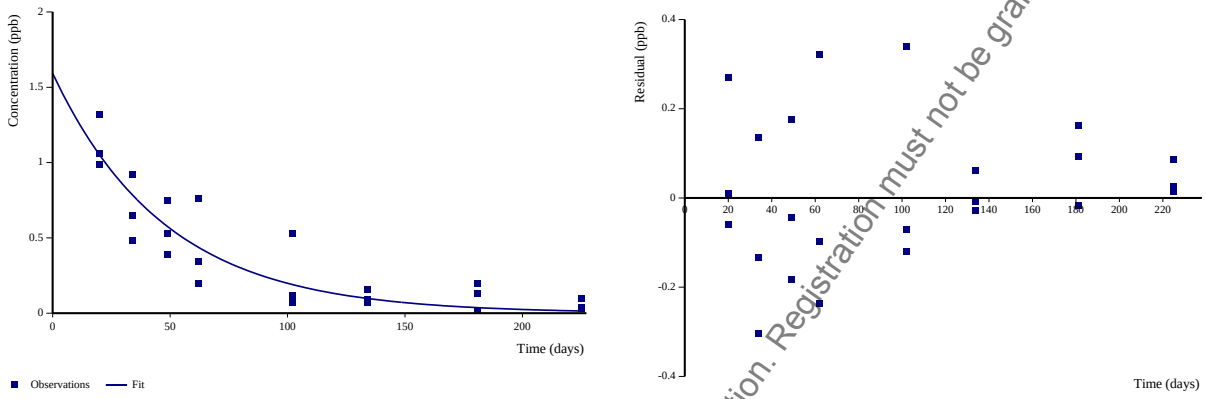
The SFO model gives a χ^2 error close to the target value of 15% and the visual fit is reasonable, particularly at the early time points. The Applicant considered there was evidence of biphasic behaviour with a tail of low residues above the predicted curve at later time points. These average residues decreased from 0.68 µg/kg at 34 DAT to 0.06 µg/kg at the end of the study and, based on the initial average residue of 5.42 µg/kg, this represents 13% to 1% of the applied material. The Applicant considered that most (i.e. 87%) of the decline was described well by the SFO model.

A further SFO fit was conducted after eliminating data points before 10 mm rainfall. Cumulative rainfall exceeded 10 mm (total = 14.1 mm) at 16.4 DAT (22 DAT real time). The first soil sampling time after this was 20 DAT (29 DAT real time), and the total rainfall at this time point was 14.1 mm. This gave 8 time points on the decline curve. The results of the SFO fit to these data are as follows:

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Figure B.8.134 Statistics for kinetic fitting of Spain, Autumn, parent only, data after 10mm rainfall, SFO

Parameter	Value	σ	Prob > t	Lower CI	Upper CI	DT50 (d)	X^2err (%)
M_0 (µg/kg)	1.593	0.2161	1.12E-07	1.144	2.041	33.3	11.1
k (d^{-1})	0.02083	0.003581	3.74E-06	0.01341	0.028		



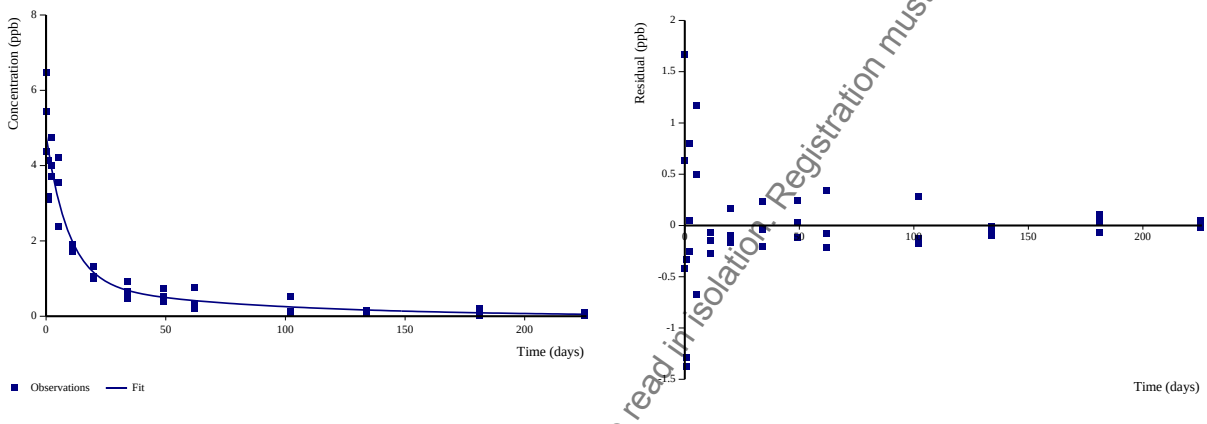
The χ^2 error was acceptable (11%) and the visual fit was good with only a slight positive bias to the residuals at the last two time points. The RMS agrees that this is a good fit. Although the Applicant considered this fit could be accepted, to be consistent with the other data sets, the DFOP model was run. The results for the DFOP model for parent XDE-729 methyl are as follows:

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Figure B.8.135 Statistics for kinetic fitting of Spain, Autumn, parent only, all data, DFOP

Parameter	Value	σ	Prob. > t	Lower CI	Upper CI	DT50* (d)	X^2err (%)
M_0 (µg/kg)	4.794	0.2281	9.74E-22	4.332	5.257	-	18.4
k1 (d^{-1})	0.1069	0.03457	0.00194	0.03677	0.177	6.5	
k2 (d^{-1})	0.01263	0.01308	0.1704	-0.01393	0.039	54.9	
g	0.8131	0.1617	7.33E-06	0.4849	1.141	-	

* DT50 for each rate constant calculated from ln2/k



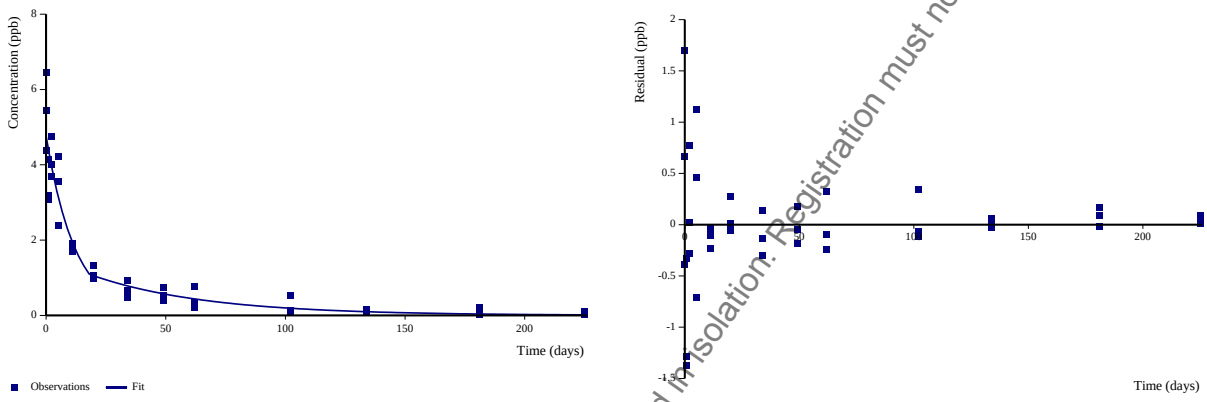
The RMS notes that the DFOP fit to the complete data set was slightly better than SFO, particularly the tail of residues. However, the Applicant observed that the g parameter was > 0.75 and there was high error on the k2 parameter and that the lower confidence interval was less than zero. Therefore, the HS model was run. The results for the HS model for parent XDE-729 Methyl are as follows:

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Figure B.8.136 Statistics for kinetic fitting of Spain, Autumn, parent only, all data, HS

Parameter	Value	σ	Prob > t	Lower CI	Upper CI	DT50* (d)	X^2 err (%)
M_0 (µg/kg)	4.764	0.2201	3.77E-22	4.317	5.211	-	18.4
k1 (d^{-1})	0.08146	0.01371	4.593E-07	0.05363	0.109	8.5	
k2 (d^{-1})	0.02083	0.01162	0.0408	-0.00275	0.044	33.3	
t_b (days)	18.07	5.844	0.001942	6.208	29.94	-	

* DT50 for each rate constant calculated from ln2/k



The RMS again notes an improvement of fit over SFO with all data and identical χ^2 error to the DFOP fit. However, there was high error on the k2 parameter. The breakpoint of 18.1 days was just after 16.4 days when 10 mm rain was reached.

The Applicant concluded that the DT50 value of 33 days derived from the SFO model after 10 mm rain is accepted as the best fit for parent XDE-729 methyl. The RMS notes that this value is identical to that from the HS slow phase DT50.

Parent + X11393729

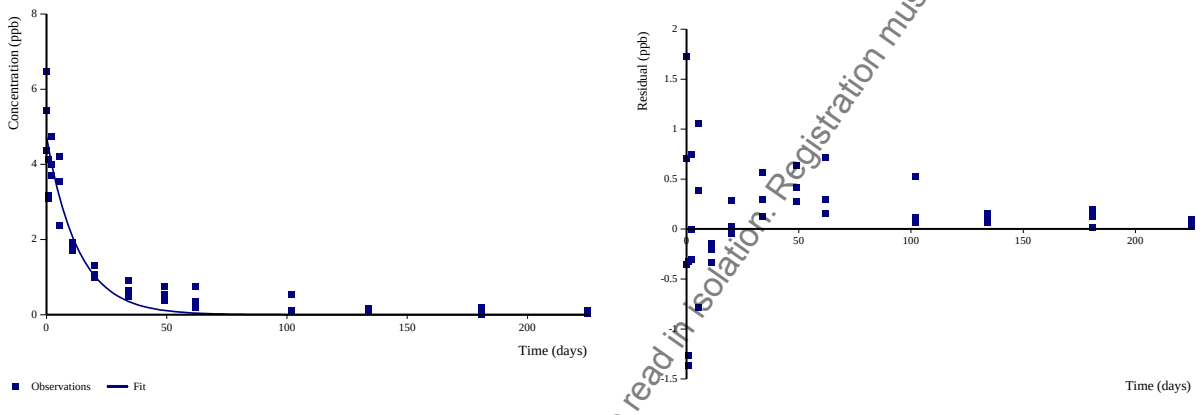
Since the SFO model with all the data gave a reasonable fit for parent, a sequential fit was run using SFO for both parent and X11393729; X11393729 is designated A1. The results are as follows:

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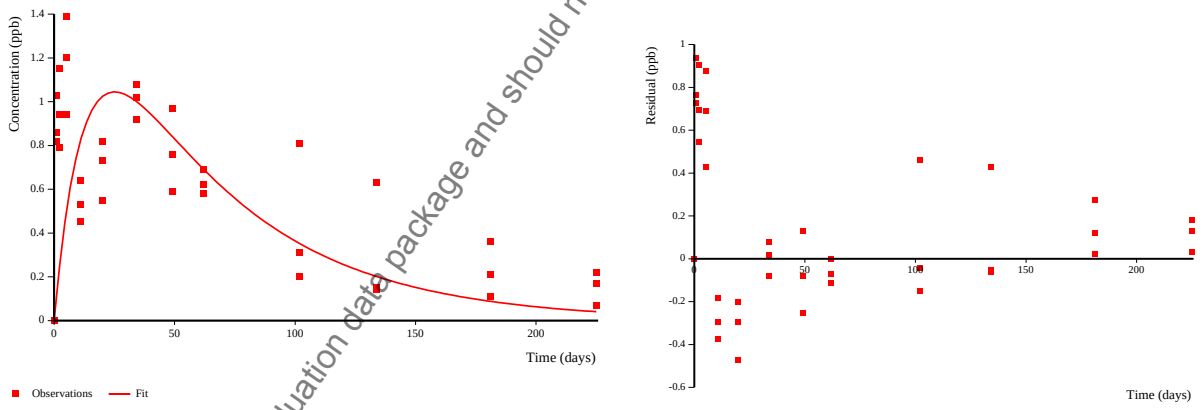
Figure B.8.137 Statistics for kinetic fitting of Spain, Autumn, parent + X11393729, all data, SFO+SFO

Parameter	Value	σ	Prob > t	Lower CI	Upper CI	DT50 (d)	X^2err (%)
M_0 (µg/kg)	4.729	0.2137	1.16E-34	4.303	5.155	-	
k_Parent (d^{-1})	0.07603	0.00988	2.42E-11	0.05635	0.096	9.1	19.8
f_Par_to_A1	0.3428	0.06828	1.72E-06	0.2068	0.479	-	
k_A1 (d^{-1})	0.01753	0.00575	0.00160	0.00607	0.029	39.5	49.4

Compartment Parent:



Compartment A1:



After addition of X11393729 to the model, the DT50 for Parent was similar to that obtained for Parent alone (9.1 days and 10 days, respectively) and the χ^2 error was similar; the RMS notes that that the speed of degradation increased slightly and the fit was worsened slightly. The χ^2 error for the X11393729 was high but other statistical parameters were acceptable. The Applicant considered that the visual fit was good except for the very early time points where the model could not predict the very high residues of X11393729 that were detected in the first few time points after application. The RMS notes that the X11393729 residues in the initial part of the study were quite variable between time points and this is likely to have influences the shape of the curve for the metabolite, but it may also be that the SFO/SFO is simply unable to simulate such rapid formation.

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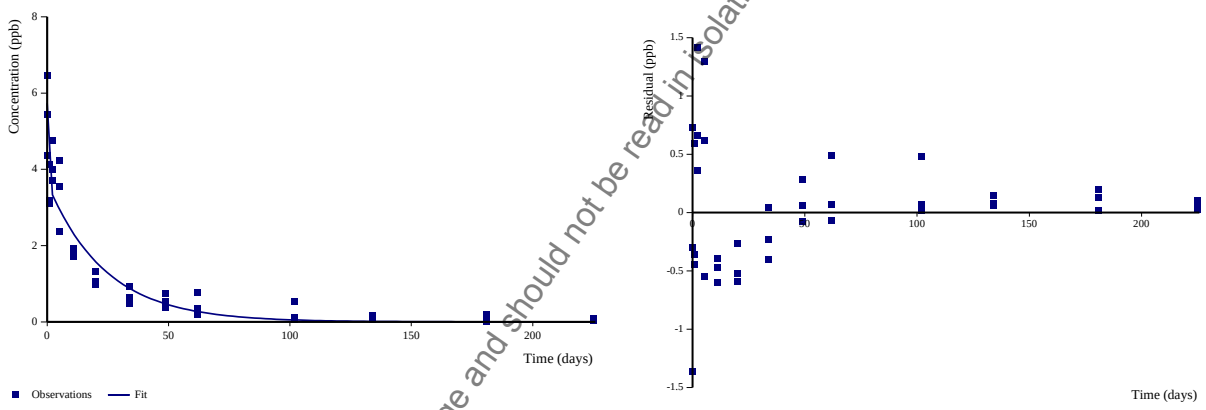
To check if the fit for X11393729 could be improved, a further kinetics fit was run using the DFOP/SFO sequential model. The results are as follows:

Figure B.8.138 Statistics for kinetic fitting of Spain, Autumn, parent + X11393729, all data, DFOP+SFO

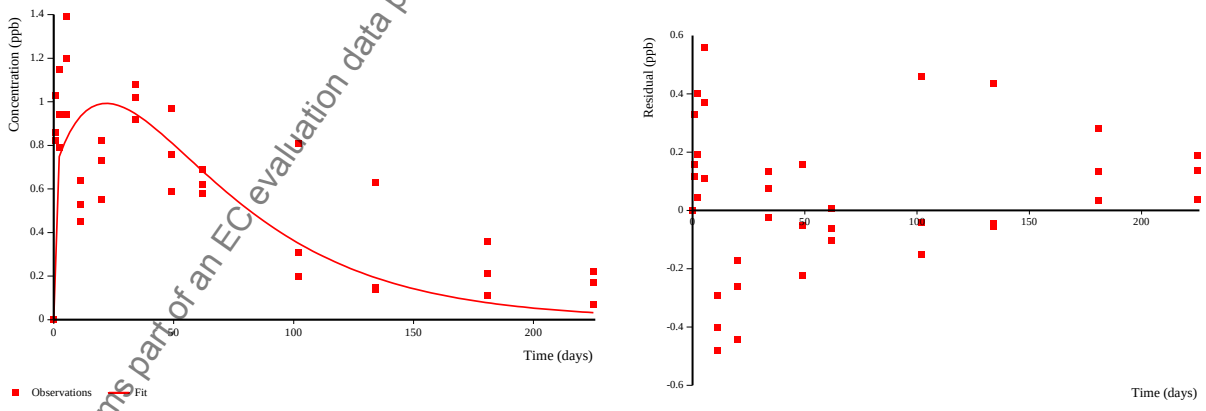
Parameter	Value	σ	Prob > t	Lower CI	Upper CI	DT50* (d)	X^2 err (%)
M_0 (µg/kg)	5.734	0.2987	2.48E-30	5.138	6.329	-	18.3
k1 (d^{-1})	10.82	1103	0.4961	-2187	2209	0.06	
k2 (d^{-1})	0.04195	0.00600	5.78E-10	0.02999	0.054	16.5	
g	0.3619	0.04769	4.45E-11	0.2669	0.457	-	
f_Par_to_A1	0.324	0.06002	4.10E-07	0.2044	0.444	-	28.9
k_A1 (d^{-1})	0.02	0.00413	3.49E-06	0.01177	0.028	34.7	

* DT50 for each rate constant calculated from ln2/k

Compartment Parent:



Compartment A1:



Using DFOP for parent in this sequential fit, the Applicant considered that the initial high residues of X11393729 were better predicted which resulted in a lower χ^2 error compared with the SFO/SFO fit. However, if these first few time points are excluded, the visual fit and residuals for the X11393729 were very similar for both models. The RMS notes that whilst the χ^2 error was indeed reduced for X11393729, the peak

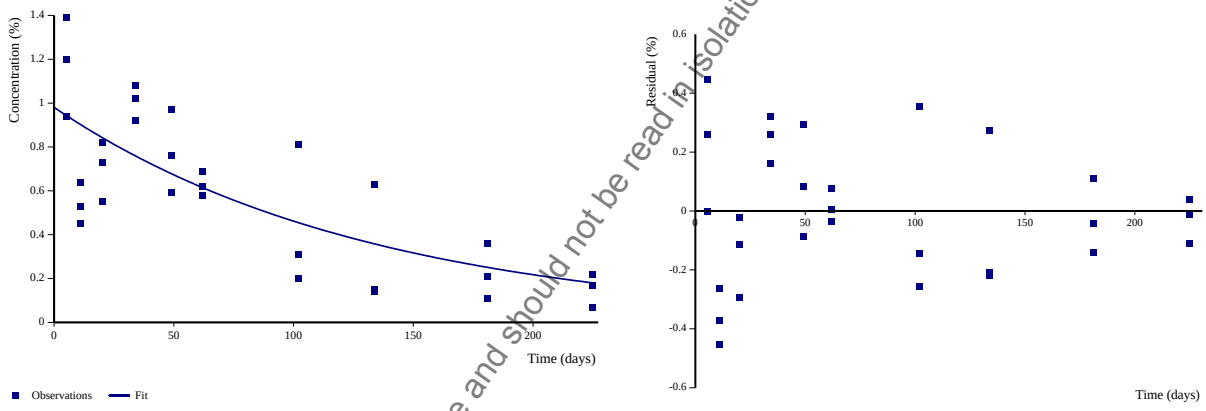
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residues could still not be predicted, and the SFO/SFO fit predicted a slightly higher peak concentration. In the opinion of the Applicant, the lower DT50 of 35 days for X11393729 using the DFOP/SFO model is offset by a slightly higher formation fraction. Since the results for X11393729 were similar for both models, the SFO/SFO model is preferred by the Applicant since it is preferred in simulation models. Whilst not ideal, the RMS agrees that this is a pragmatic interpretation of guidance and choice of endpoints for X11393729.

To complete the kinetics analysis for X11393729, a top-down SFO fit was performed starting at 5.3 DAT (7 DAT real time), the time of maximum formation. This gave 10 time points on the decline curve. The results are shown in the following table:

Figure B.8.139 Statistics for kinetic fitting of Spain, Autumn, X11393729, top down from peak (occurred before 10mm rainfall), SFO

Parameter	Value	σ	Prob > t	Lower CI	Upper CI	DT50 (d)	X^2 err (%)
k (d^{-1})	0.00753	0.00167	5.12E-05	0.00412	0.011	92.1	22.6

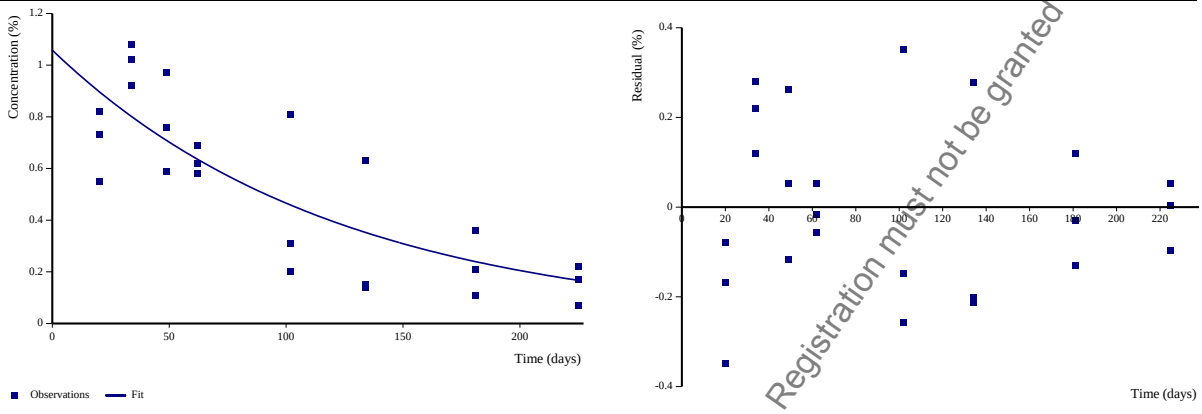


Since 10 mm rain was not achieved until 16.4 DAT (22 DAT real time) a second top-down fit was performed using data from 20 DAT onwards (8 data points).

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Figure B.8.140 Statistics for kinetic fitting of Spain, Autumn, X11393729, top down from after 10mm rainfall, SFO

Parameter	Value	σ	Prob > t	Lower CI	Upper CI	DT50 (d)	X^2 err (%)
k (d^{-1})	0.00820	0.00170	4.06E-05	0.00468	0.012	84.5	15.9



The top down SFO fit with the shorter data set gave a slightly lower χ^2 error (16%) and the visual fit was good.

The Applicant concluded that the best fit for X11393729 in this trial was obtained with the top-down SFO model and the DT50 value of 85 days was proposed as a conservative estimate. The alternative SFO/SFO sequential fit with parent gave poorer statistics but the visual fit for X11393729 was considered by the Applicant as reasonably good. Therefore, a DegT50 of 9.1 days for parent together with a formation fraction of 0.34 and a DegT50 of 40 days for X11393729 is proposed by the Applicant as modelling inputs for X11393729 from this trial. The RMS can agree with this choice depending on how exposure modelling of parent and metabolites is conducted.

Parent + X11393729 + X11449757

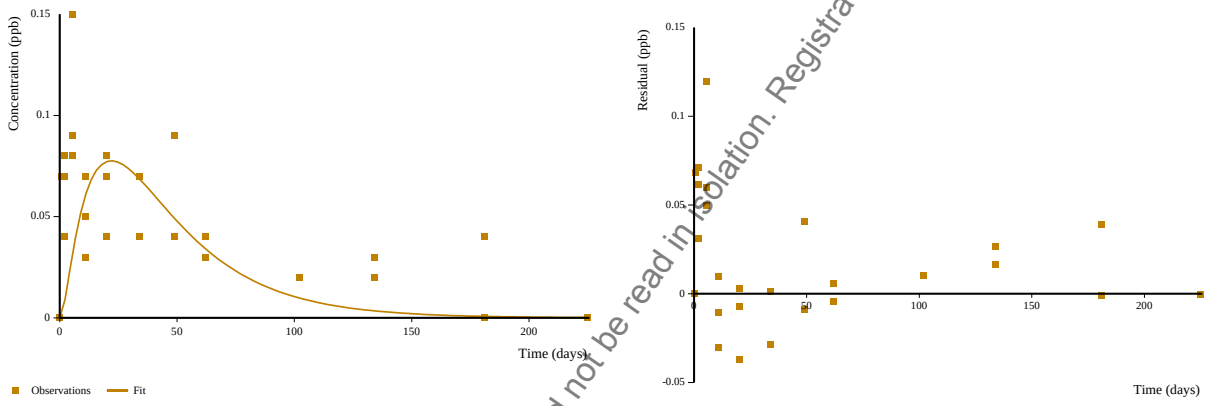
The X11449757 data were added to the model and a sequential fit was performed for Parent, X11393729 and X11449757 using SFO for the parent; X11449757 is designated A2. The optimised parameters are as follows:

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Figure B.8.141 Statistics for kinetic fitting of Spain, Autumn, parent + X11393729 + X11449757, all data, SFO+SFO+SFO

Parameter	Value	σ	Prob > t	Lower CI	Upper CI	DT50 (d)	χ^2 err (%)
M_0 (µg/kg)	4.702	0.2121	7.07E-43	4.281	5.122		19.7
k_Parent (d^{-1})	0.07359	0.00960	3.57E-12	0.05458	0.093	9.4	
f_Par_to_A1	0.4735	0.1001	3.29E-06	0.2753	0.672		51.0
k_A1 (d^{-1})	0.03304	0.00907	0.000206	0.01507	0.051	21.0	
f_A1_to_A2	1	1.092	0.1808	-1.163	3.163		60.9
k_A2 (d^{-1})	0.4909	0.4998	0.1641	-0.4996	1.481	1.4	

Compartment A2:

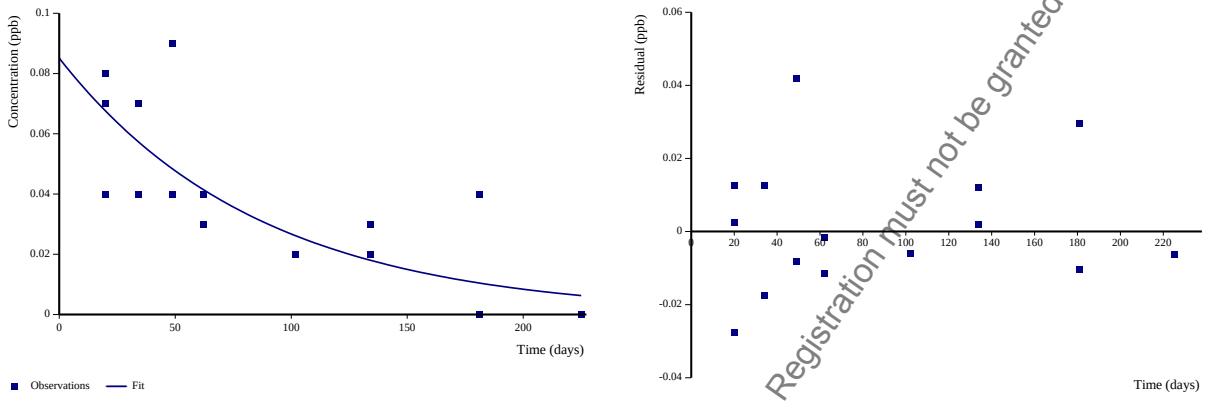


Only the X11449757 visual fit is shown here (might have to show parent and acid as acid parameters have change by quite a lot but chi2 stay relatively the same). The Applicant considered the visual and statistical fits for X11449757 to be poor using this sequential model. The RMS agrees, noting the relative scatter of replicate data and variability in data at sample times towards the end of the trial. Therefore, a top-down fit was performed. Since 10 mm rain was not achieved until 16.4 DAT (22 DAT real time) the top-down fit was performed using data from 20 DAT (29 DAT real time) onwards (8 data points).

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Figure B.8.142 Statistics for kinetic fitting of Spain, Autumn, X11449757, top down from after 10mm rainfall, SFO

Parameter	Value	σ	Prob > t	Lower CI	Upper CI	DT50 (d)	X^2 err (%)
k (d^{-1})	0.01158	0.00254	7.58E-05	0.00632	0.017	59.8	12.6



Considering the very low residue levels present, the visual and statistical fits were considered by the Applicant to be good with a χ^2 error of 13%. As before, the RMS notes that the data are quite variable.

The best fit for the X11449757 metabolite was obtained with the top-down SFO model and the DT50 value of 60 days is proposed by the Applicant. The RMS can agree with this endpoint.

France, Spring

Unnormalised data (France, Spring)

Parent

The kinetics fits for the measured data (i.e. not corrected for temperature and moisture) using the SFO and FOMC models for parent XDE-729 methyl only are shown in the following table and figures.

Table B.8.101 Statistics for SFO and FOMC fitting for France, Spring field dissipation data, XDE-729 methyl, all data

Model	Parameter	Value	Lower CI	Upper CI	Std Dev	Prob > t	DT_{50} (d)	DT_{90} (d)	% χ^2 error
SFO	M_0 (µg/kg)	2.79	2.31	3.27	0.24	-			
	k (d^{-1})	0.0469	0.0214	0.0724	0.0126	3.2e-04	15	49	36.6
FOMC	M_0 (µg/kg)	3.43	2.76	4.11	0.33	-			
	Alpha	0.6268	0.2060	1.0475	0.2075	0.0023	4.9	93	33.2
	Beta	2.4138	-1.5980	6.4257	1.9781	0.1152			

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Figure B.8.143 SFO fitting for France, Spring field dissipation data, XDE-729 methyl, all data

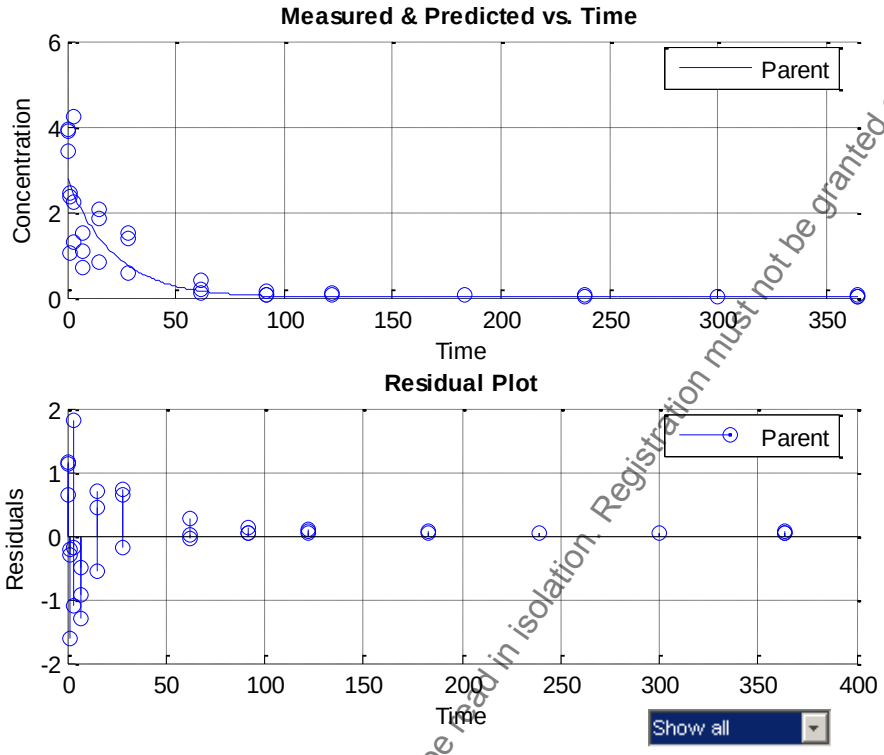
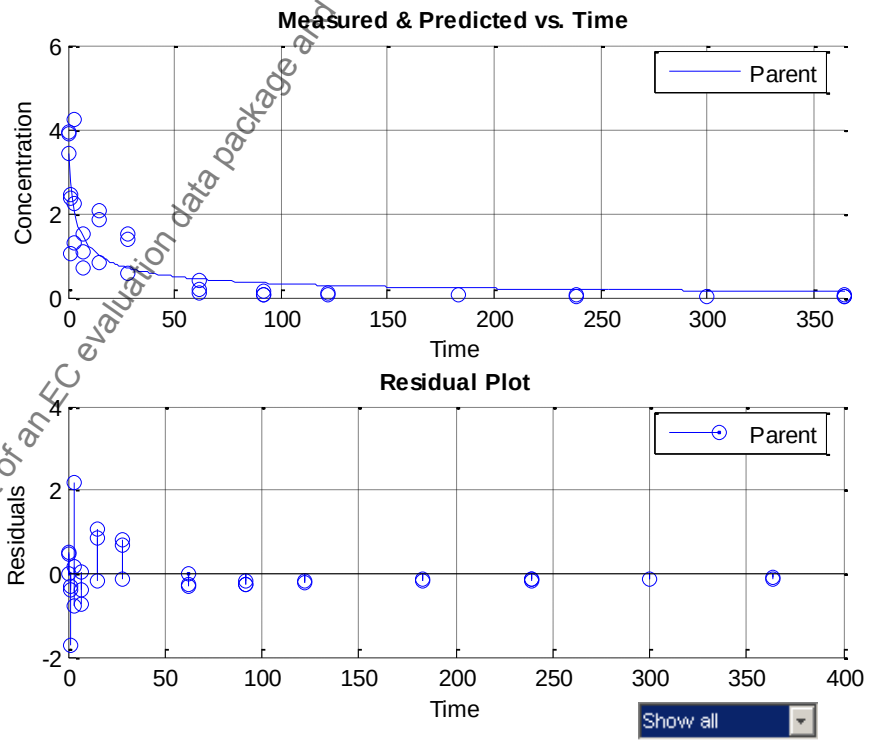


Figure B.8.144 FOMC fitting for France, Spring field dissipation data, XDE-729 methyl, all data



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The SFO model gave a DT50 of 15 days with a χ^2 error of 37% and acceptable t-test. The FOMC model gave a slightly lower χ^2 error of 33% but the β parameter showed unacceptable errors and lower CI less than zero. The high error for the SFO fit is most likely due to the scatter in the data at earlier time points and it is clear from the visual assessment that XDE-729 methyl is rapidly dissipated with more than 90% of the initial residue dissipated within 62 days. The Applicant proposed the SFO parameters as the best fit and the RMS can accept this. Therefore the SFO DT50 of 15 days is proposed as the persistence endpoint for this trials site.

X11393729

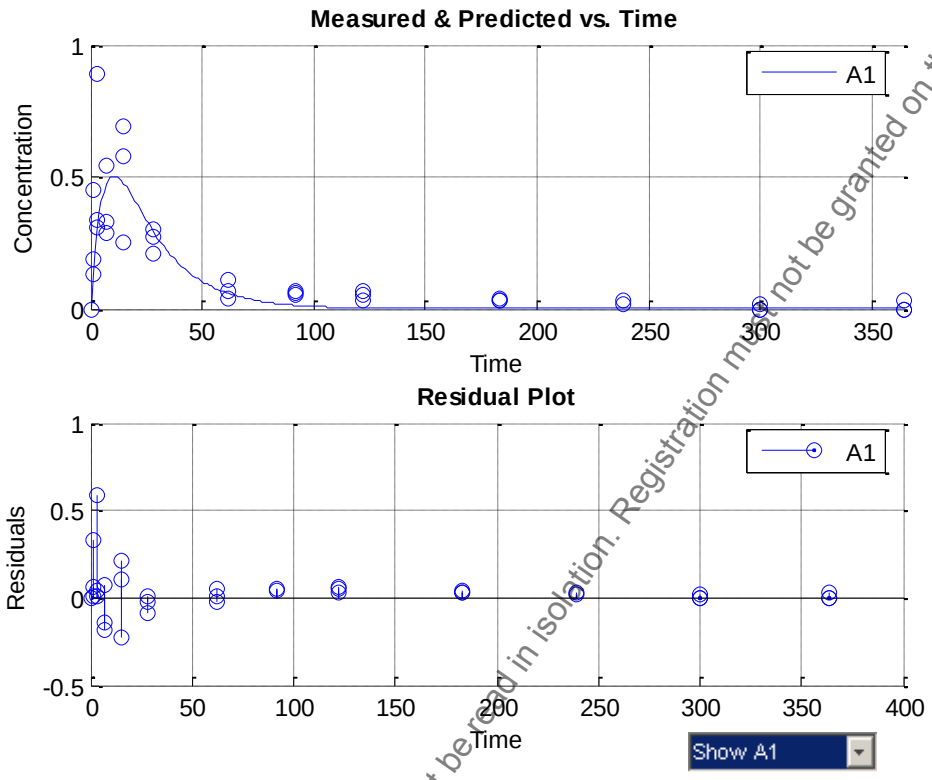
Using the optimised SFO parameters for parent XDE-729 methyl as initial values, X11393729 was added to the kinetics model with the formation fraction set to an initial value of 0.5. The optimised parameters for parent and metabolite are shown in the following table and figure. Only the X11393729 fit is shown as the parent fitting was not affected greatly.

Table B.8.102 Statistics for SFO+SFO fitting for France, Spring field dissipation data, XDE-729 methyl+ X11393729, all data

Model	Parameter	Value	Lower CI	Upper CI	Std Dev	Prob > t	DT_{50} (d)	DT_{90} (d)	% χ^2 error
SFO Parent	M_0 (µg/kg)	2.81	2.47	3.15	0.17				
	k (d^{-1})	0.0489	0.0302	0.0676	0.0094	8.0e-07	14	47	36.7
SFO Acid	Form fraction	1.0000	-0.6404	2.6403	0.8232				
	k (d^{-1})	0.1630	-0.1714	0.4974	0.1678	0.1673	4.3	14	38.9

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Figure B.8.145 SFO+SFO fitting for France, Spring field dissipation data, XDE-729-methyl+ X11393729, all data



The parameters for parent were essentially unchanged after addition of X11393729 to the model. The χ^2 error for X11393729 was high (39%) and the lower confidence interval for the k value and the formation fraction is less than zero. Therefore the Applicant considered that a reliable DT50 for X11393729 could not be obtained.

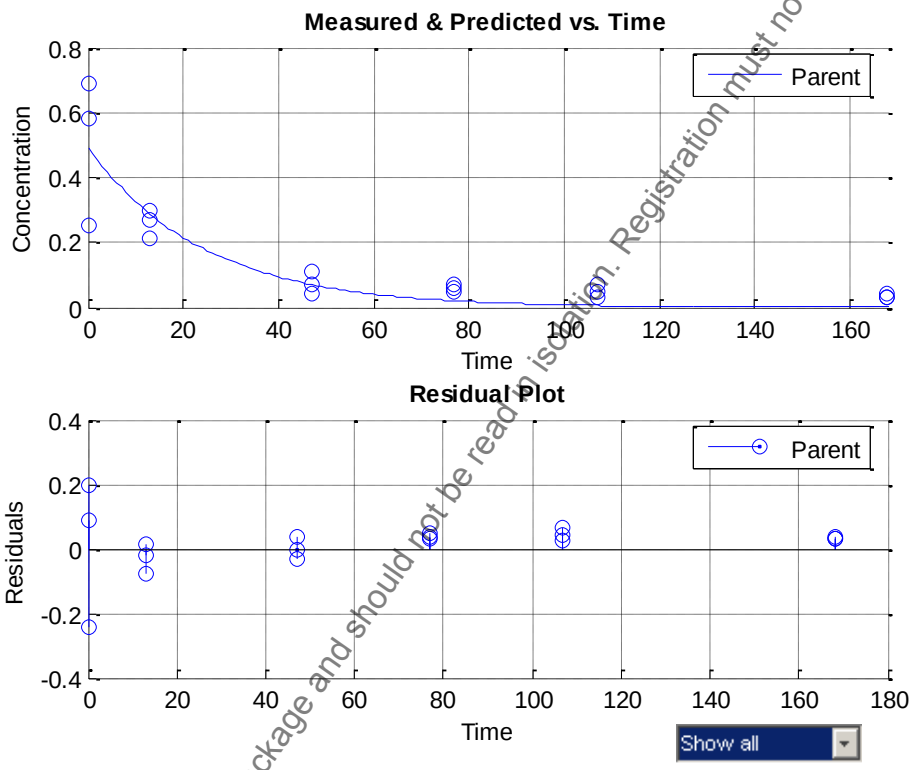
In order to obtain a "dissipation" rate for X11393729 that would be appropriate for a soil exposure assessment, a "top-down" fit was performed by the Applicant by running the SFO model to the decline data starting at Day 15, which was considered to be the start of the clear decline phase for X11393729. The RMS notes that there is a slightly higher average data point at 3 DAT, 0.54 µg/kg molar equivalent which falls to 0.40 µg/kg at 7 DAT before increasing again to 0.53 µg/kg at 15 DAT. Therefore the RMS can accept the use of the 15 DAT data point as the start of the decline curve. The RMS also notes that the Applicant excluded the final three sample times between 239-364 DAT. As the average residues were 0.02 µg/kg, 0.01 µg/kg and 0.01 µg/kg at these sample times, i.e. represent a long tail just above the LOQ, with the 0.02 µg/kg representing 4% of the peak observe concentration of X11393729, The RMS can accept the exclusion of these data.

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Table B.8.103 Statistics for top-down SFO fit for X11393729, France, Spring, data from 15 – 183 DAT.

Model	Parameter	Value	Lower CI	Upper CI	Std Dev	Prob > t	DT_{50} (d)	DT_{90} (d)	% χ^2 error
SFO Acid (top-down)	M_0 (µg/kg)	0.49	0.39	0.60	0.05	-			
	k (d^{-1})	0.0414	0.0181	0.0647	0.0110	8.4e-04	17	56	14.8

Figure 8.146 Top-down SFO fit for X11393729, France, Spring, data from 15 – 183 DAT.



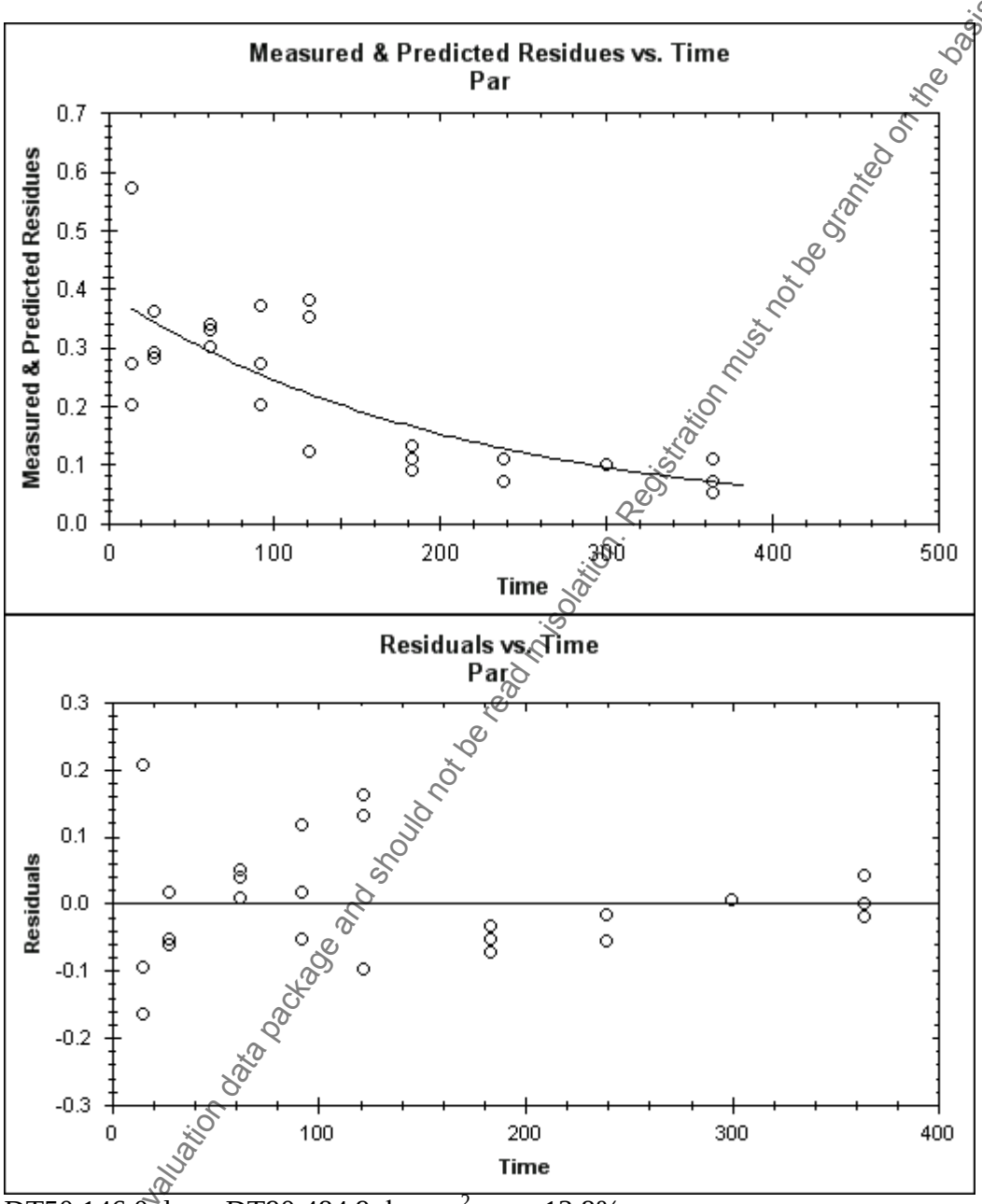
This top-down method gave a χ^2 error less than 15% and acceptable t-test. The Applicant considered the calculated DT50 of 17 days can be taken as a good estimate of dissipation rate of X11393729 for environmental risk assessment but since no formation fraction or formation rate are calculated, it is not suitable for use as model input. The RMS agrees to the use of this top down DT50 as a persistence endpoint for X11393729 from this trials site, and it can be used in simple PEC soil calculation.

X11449757

The Applicant did not attempt any fitting with X11449757. The RMS calculated a separate SFO top down DT50.

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Figure 8.147 RMS top-down SFO fit for X11449757, France, Spring, data from 15 DAT.



DT50 146.0 days, DT90 484.9 days, χ^2 error 13.8%

The RMS considers that the SFO top down DT50 is appropriate for use in simple calculations such as PECsoil calculation and proposes the DT50 value of 146.0 days for this trials site.

Data normalised to 20 °C and pF 2 (France, Spring)

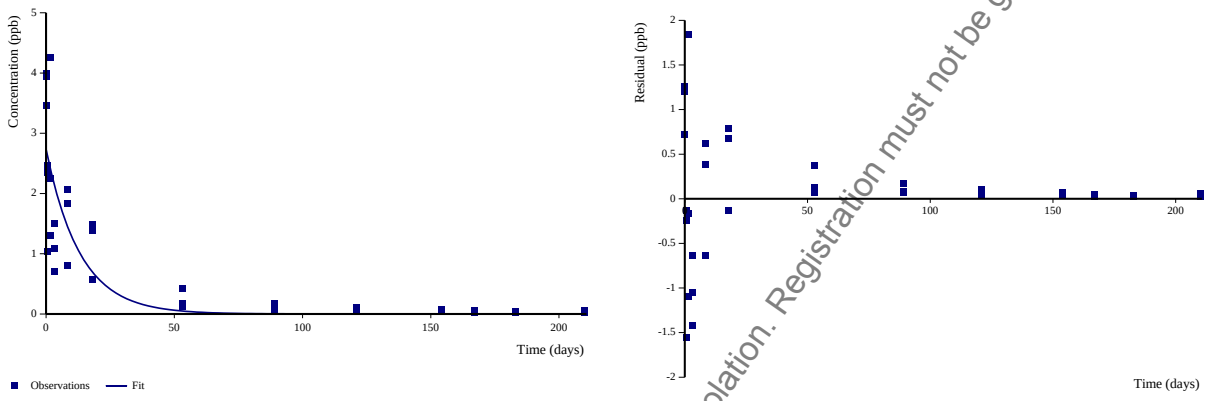
Parent

The results of fitting XDE-729 methyl (all data) to the SFO model are as follows:

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Figure B.8.148 Statistics for kinetic fitting of France, Spring, parent only, all data, SFO

Parameter	Value	σ	Prob > t	Lower CI	Upper CI	DT50 (d)	X^2 err (%)
M_0 (µg/kg)	2.735	0.2423	7.67E-14	2.244	3.226	9.2	39.3
k (d^{-1})	0.07568	0.02357	0.00137	0.02793	0.123		



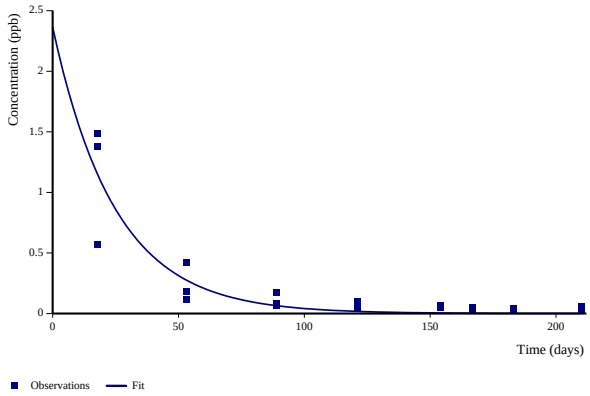
The SFO model gave a high χ^2 error and this is most likely due to the high scatter in the data at early time points; the RMS agrees with this statement. The RMS considered there was some evidence of biphasic behaviour with a tail of low residues above the predicted curve at later time points (from 53 DAT onwards). However, since residues of parent had declined to 0.24 µg/kg at this time from an initial value of 3.80 µg/kg, this slow phase decline represented only 6% of the residues of XDE-729 methyl.

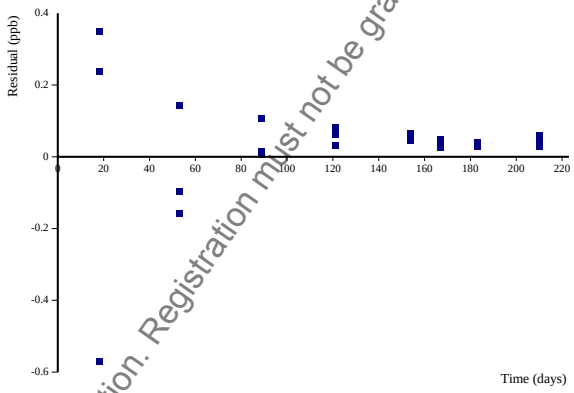
A further SFO fit was conducted after eliminating data points before 10 mm rainfall. Cumulative rainfall exceeded 10 mm (total = 10.2 mm) at 11.3 DAT (19 DAT real time). The first soil sampling time after this was 18 DAT (28 DAT real time), and the total rainfall at this time point was 29.0 mm. This gave 8 time points on the decline curve. The results of the SFO fit to these data are as follows:

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Figure B.8.149 Statistics for kinetic fitting of France, Spring, parent only, data after 10mm rainfall, SFO

Parameter	Value	σ	Prob > t	Lower CI	Upper CI	DT50 (d)	X^2err (%)
M_0 (µg/kg)	2.363	0.4714	2.56E-05	1.385	3.341	17.1	15.2
k (d^{-1})	0.04043	0.00902	9.32E-05	0.02172	0.059		





The χ^2 error was just above 15% and the visual fit was considered reasonable by the Applicant although there was high variability in the first time point. As for most of the other data sets, there was evidence of some biphasic behaviour, but this only involved a very small fraction of the applied substance.

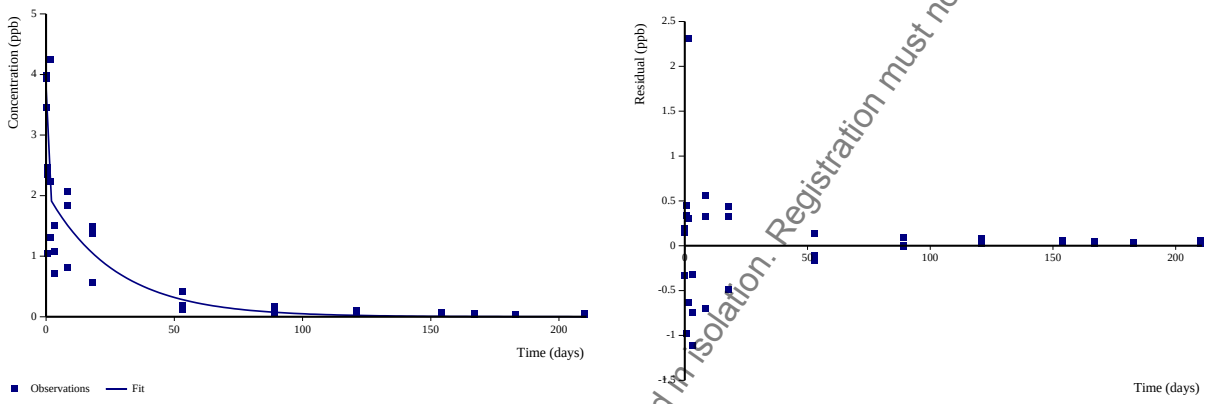
The Applicant attempted to run the DFOP model with parent data but it was stated that statistical outputs could not be generated. The RMS remarks that depending on data set, it can be very difficult to get some biphasic models to optimise. To complete the analysis, the HS model was run and results are as follows:

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Figure B.8.150 Statistics for kinetic fitting of France, Spring, parent only, all data, HS

Parameter	Value	σ	Prob > t	Lower CI	Upper CI	DT50* (d)	X^2 err (%)
M_0 (µg/kg)	3.797	0.3193	3.79E-14	3.148	4.445	-	24.8
k1 (d^{-1})	7.698	4016	0.4992	-8145	8160	0.09	
k2 (d^{-1})	0.03739	0.01423	0.00633	0.00851	0.066	18.5	
t_b (days)	0.01928	75.99	0.4999	-154.2	154.3	-	

* DT50 for each rate constant calculated from ln2/k



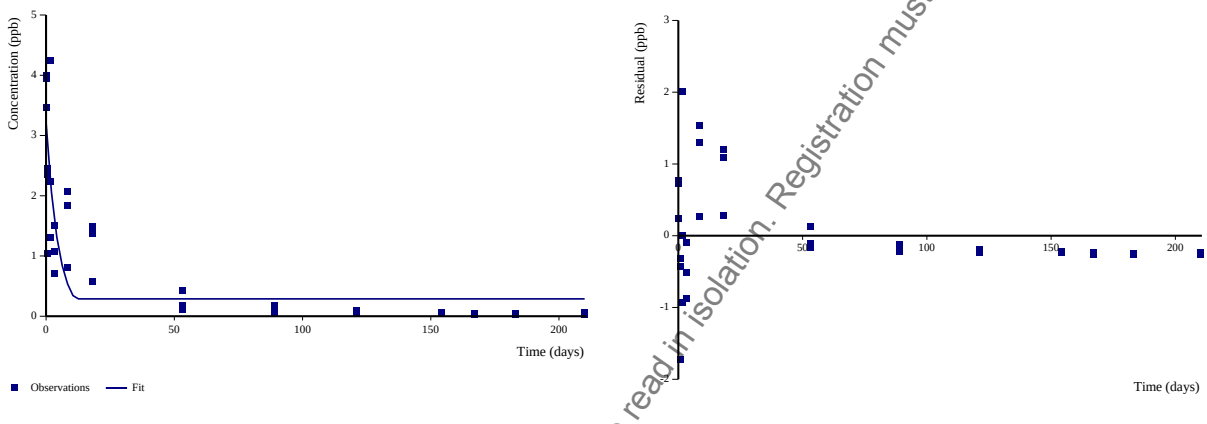
There was an extremely large error on the k1 parameter and the predicted break point was extremely short and also gave a high error. A final fit was attempted by fixing the break point to 11.3 days, the time at which 10 mm rain was reached.

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Figure B.8.151 Statistics for kinetic fitting of France, Spring, parent only, all data, HS, breakpoint fixed at 11.3 days

Parameter	Value	σ	Prob > t	Lower CI	Upper CI	DT50* (d)	χ^2 err (%)
M_0 (µg/kg)	3.218	0.3124	1.39E-12	2.585	3.852	-	44.6
k1 (d^{-1})	0.2135	0.05334	0.00015	0.1053	0.322	3.2	
k2 (d^{-1})	1.8E-103	0.00544	0.50	-0.01103	0.011	NC	
t_b (days)	11.3 (fixed)	-	-	-	-	-	

* DT50 for each rate constant calculated from ln2/k NC = not calculated



An acceptable fit was not achieved with a high χ^2 error and high error and a lower confidence interval less than zero on the k2 parameter.

The DT50 value of **17 days** derived from the SFO model after 10 mm rain was proposed as best parameter for parent XDE-729 methyl at this trial. The RMS agrees with this proposal.

Parent + X11393729

The optimised parameters for parent and X11393729 (designated A1) fitted sequentially with the SFO/SFO model are as follows:

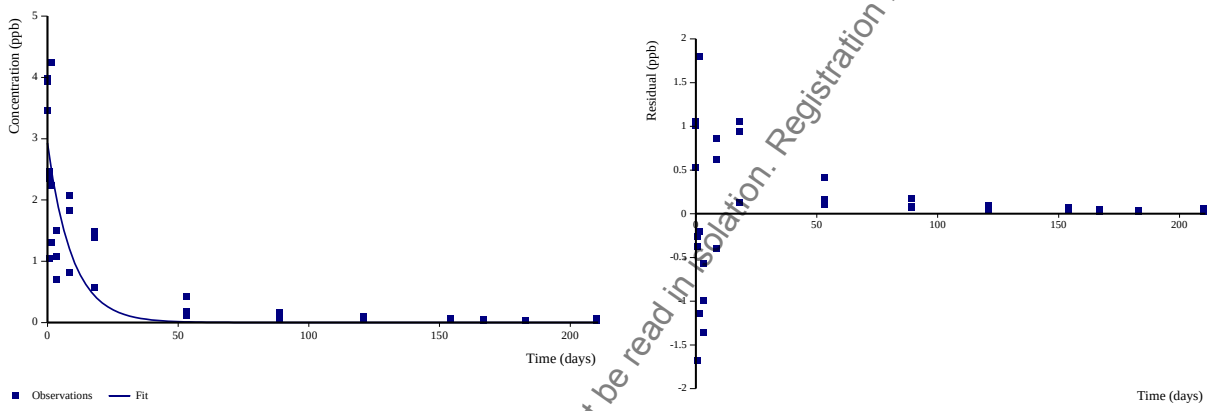
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Figure B.8.152 Statistics for kinetic fitting of France, Spring, parent + X11393729, all data, SFO+SFO

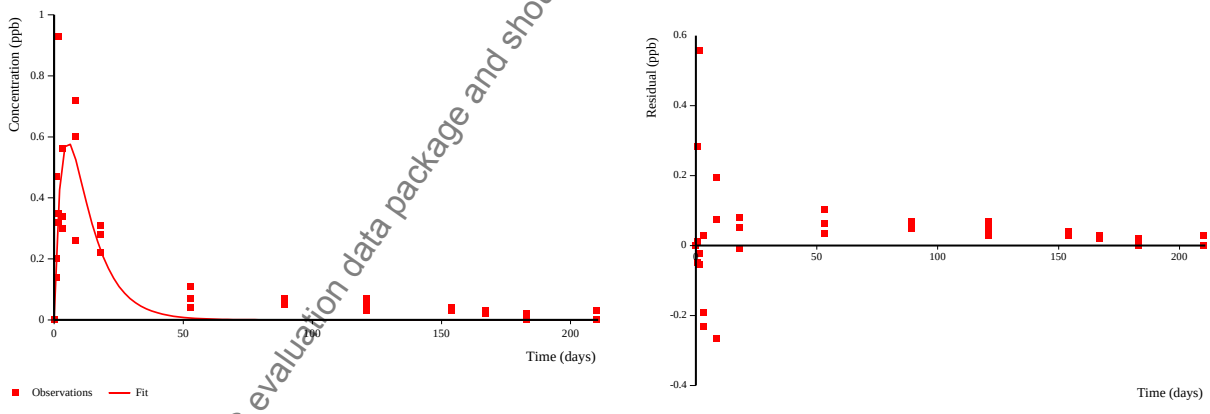
Parameter	Value	σ	Prob > t	Lower CI	Upper CI	DT50* (d)	X^2err (%)
M_0 (µg/kg)	2.929	0.2545	1.87E-18	2.422	3.436	-	
k_Parent (d^{-1})	0.1056	0.02852	0.00020	0.04874	0.162	6.6	39.9
f_Par_to_A1	1	0.4169	0.0095	0.1694	1.831	-	
k_A1 (d^{-1})	0.3017	0.106	0.00286	0.09049	0.513	2.3	31.6

* DT50 for each rate constant calculated from ln2/k

Compartment Parent:



Compartment A1:



After addition of the X11393729 to the model, the DT50 for parent was shorter than that obtained for parent alone (6.6 days and 9.2 days, respectively). The χ^2 error values for parent and X11393729 were high but other statistical parameters were acceptable. The visual fit for X11393729 was good during the formation and initial decline but there was a tail of residues that was under-predicted. The RMS agrees with this assessment of the SFO/SFO fitting.

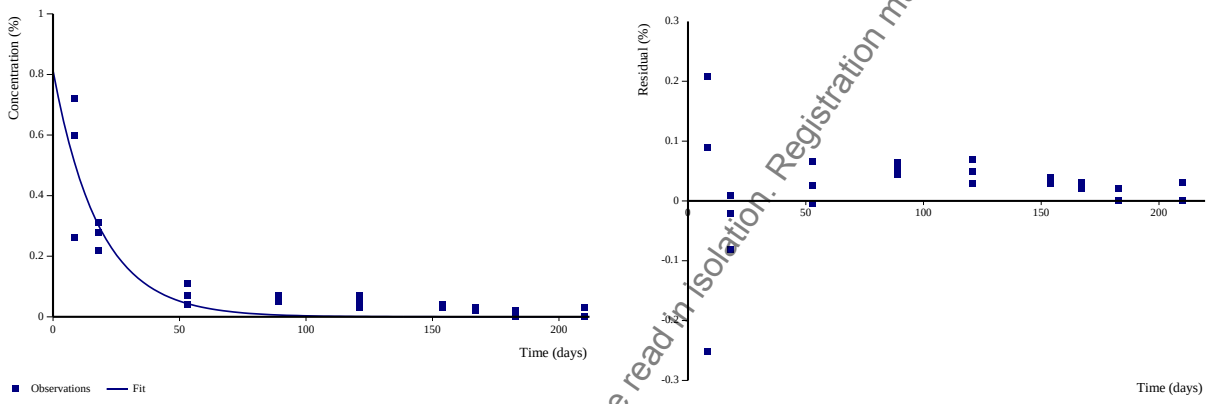
Since the DFOP and HS models for parent gave very poor fits, no attempt was made to run a DFOP/SFO fit for parent and X11393729. The RMS agrees that in this case there was probably little point in running sequential fitting for parent and metabolite with biphasic kinetics for the parent.

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To complete the kinetics analysis for the X11393729, a top-down SFO fit was performed starting at 8.4 DAT (15 DAT real time), the time of maximum formation. This gave 9 time points on the decline curve. An SFO fit was applied to the data and results are shown in the following table:

Figure B.8.153 Statistics for kinetic fitting of France, Spring, X11393729, top down from peak (occurred before 10mm rainfall), SFO

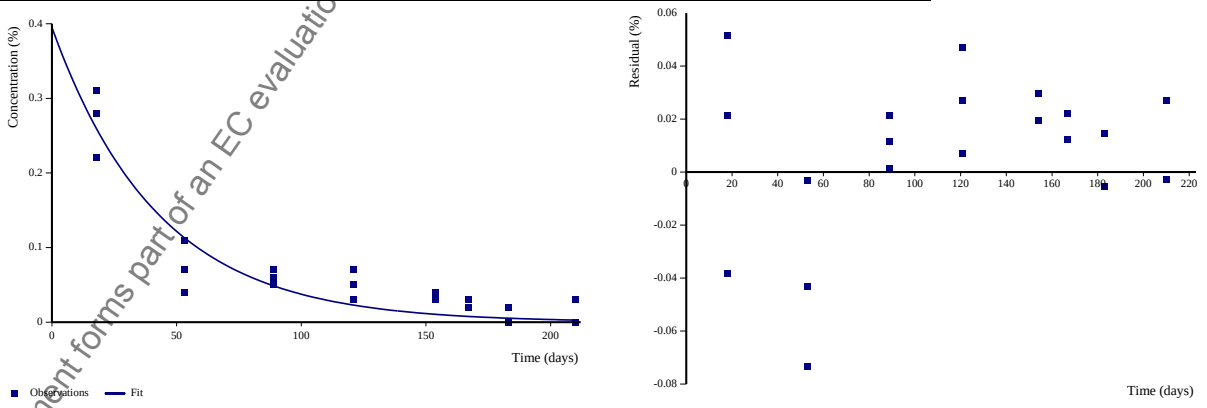
Parameter	Value	σ	Prob > t	Lower CI	Upper CI	DT50 (d)	X^2 err (%)
k (d^{-1})	0.05509	0.01426	0.00035	0.02572	0.084	12.6	21.8



Since 10 mm rain was not achieved until 18 DAT (28 DAT real time) a second top-down fit was performed using data from 18 DAT onwards (8 data points).

Figure B.8.154 Statistics for kinetic fitting of France, Spring, X11393729, top down from after 10mm rainfall, SFO

Parameter	Value	σ	Prob > t	Lower CI	Upper CI	DT50 (d)	X^2 err (%)
k (d^{-1})	0.02354	0.00301	4.27E-08	0.0173	0.03	29.4	25.0



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In the view of the Applicant, the top-down model for the X11393729 gave a reasonable visual fit although there was a slight over-prediction of degradation rate towards the end.

The best fit for the X11393729 proposed by the Applicant to have been obtained with the top-down SFO model from after 10mm rainfall and the DT50 value of **29 days** was proposed. An alternative proposal was made for the SFO/SFO sequential fit with parent which was not as good as for some of the other data sets but a DT50 of **6.6 days** for parent together with a formation fraction of **1** and a DT50 of **2.3 days** for X11393729 could be considered as reasonable inputs for modelling the X11393729 metabolite. The RMS considers that the later proposal could be reasonable for metabolite modelling.

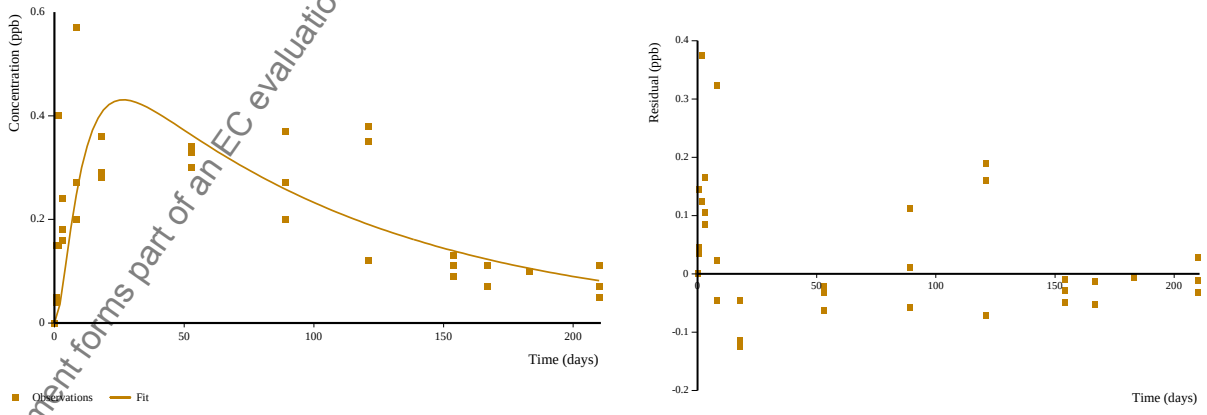
Parent + X11393729 + X11449757

The X11449757 data were added to the model and a sequential fit was performed for Parent, X11393729 and X11449757 using SFO for the parent; X11449757 is designated A2. The optimised parameters are as follows:

Figure B.8.155 Statistics for kinetic fitting of France, Spring, parent + X11393729 + X11449757, all data, SFO+SFO+SFO

Parameter	Value	σ	Prob >t	Lower CI	Upper CI	DT50 (d)	X^2 err (%)
M_0 (µg/kg)	2.997	0.2586	3.83E-21	2.485	3.51		40.5
k_Parent (d^{-1})	0.119	0.02999	6.43E-05	0.05958	0.178	5.8	
f_Par_to_A1	1	0.4073	0.00782	0.1929	1.807		32.4
k_A1 (d^{-1})	0.3565	0.1245	0.00250	0.1099	0.603	1.9	
f_A1_to_A2	0.1801	0.06432	0.00302	0.0526	0.308		36.1
k_A2 (d^{-1})	0.00952	0.00201	3.11E-06	0.00555	0.014	72.8	

Compartment A2:



Only the X11449757 visual fit is shown here. The parameters for parent and X11393729 were considered by the Applicant to be essentially unchanged after

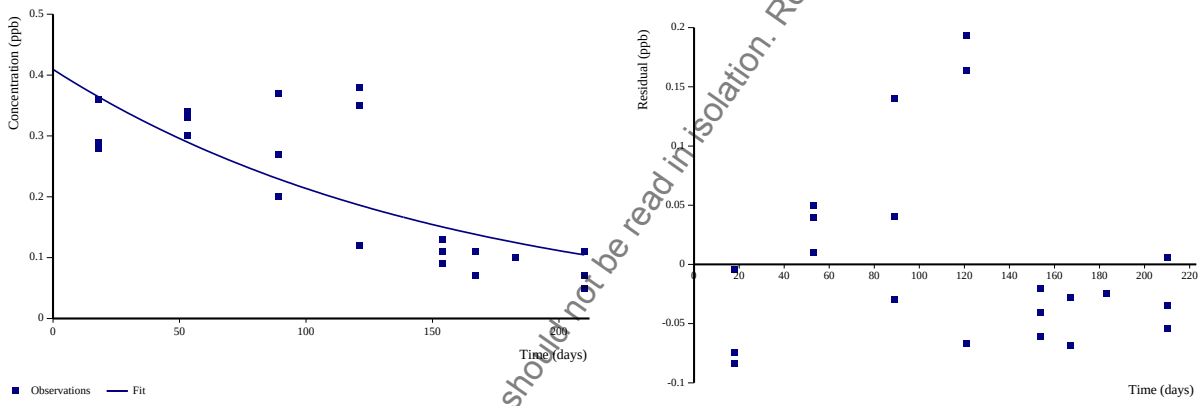
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addition of X11449757. The visual fit for X11449757 was considered by the Applicant to be good particularly at later time points although χ^2 error for all compartments was high.

A top-down fit was attempted for the X11449757 metabolite. The maximum residue of X11449757 was seen at 8.4 DAT (15 DAT real time) but rainfall did not exceed 10 mm until the 18 DAT time point (28 DAT real time). Therefore, the top-down fit was performed starting at 18 DAT. This gave 8 time points on the decline curve. Results are shown in the following table:

Figure B.8.156 Statistics for kinetic fitting of France, Spring, X11449757, top down from after 10mm rainfall, SFO

Parameter	Value	σ	Prob > t	Lower CI	Upper CI	DT50 (d)	X^2 err (%)
k (d^{-1})	0.00650	0.00126	1.78E-05	0.00389	0.009	107	21.4



Although the χ^2 error of 21% is slightly higher than would be normally accepted, the visual fit was considered by the Applicant to be reasonably good.

The best fit for X11449757 was obtained with the top-down SFO model and the DT50 value of 107 days can be proposed as a conservative estimate. The Applicant considered that the sequential fit with the SFO model gave a reasonable visual fit for this metabolite and a DT50 of 73 days and a formation fraction of 0.18 (from X11393729) together with the optimised parameters for parent and X11393729 described above can be proposed as realistic inputs for modelling X11449757 from this trial. The RMS considers that this a reasonable approach for metabolite exposure modelling.

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France, Autumn

Unnormalised data (France, Autumn)

Parent

For this data set, only the data up to Day 239 were used by the Applicant since all residues were non-detected beyond this time point; the RMS agrees with this. The kinetic fits for the measured data (*i.e.* not corrected for temperature and moisture) using the SFO and FOMC models for parent XDE-729 methyl only are shown in the following table and figures. In addition, because FOMC gave a better fit than SFO (as described below), the DFOP model was run. The outputs are shown in the following table.

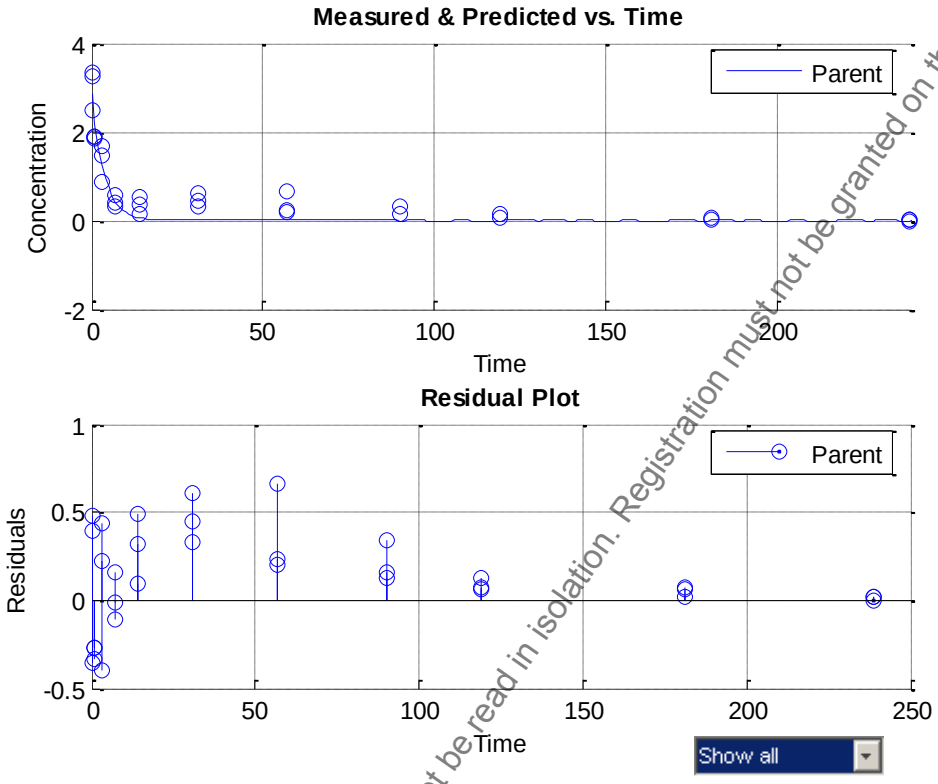
Table B.8.104 Statistics for SFO, FOMC and DFOP fitting for France, Autumn field dissipation data, XDE-729 methyl, 0 – 239 DAT data

Model	Parameter	Value	Lower CI	Upper CI	Std Dev	Prob > t	DT_{50} (d)	DT_{90} (d)	% χ^2 error
SFO	M_0 (µg/kg)	2.87	2.56	3.19	0.16	-			
	k (d^{-1})	0.2737	0.1935	0.3539	0.0393	4.1e-08	2.5	8.4	25.3
FOMC	M_0 (µg/kg)	3.05	2.77	3.33	0.14	-			
	alpha	0.6875	0.4324	0.9427	0.1249	2.8e-06	1.7	27	15.3
	beta	0.9974	0.1615	1.8332	0.4093	0.0105	(8.1)*		
DFOP	M_0 (µg/kg)	2.97	2.71	3.22	0.13	-			
	k1 (d^{-1})	0.4403	0.2879	0.5926	0.0745	1.0e-06	2.1	51	13.0
	k2 (d^{-1})	0.0099	-4.1e-04	0.0201	0.0050	0.0296			
	g	0.8351	0.7493	0.9210	0.0420	9.5e-19			

* pseudo SFO DT50 derived from FOMC DT90/3.32

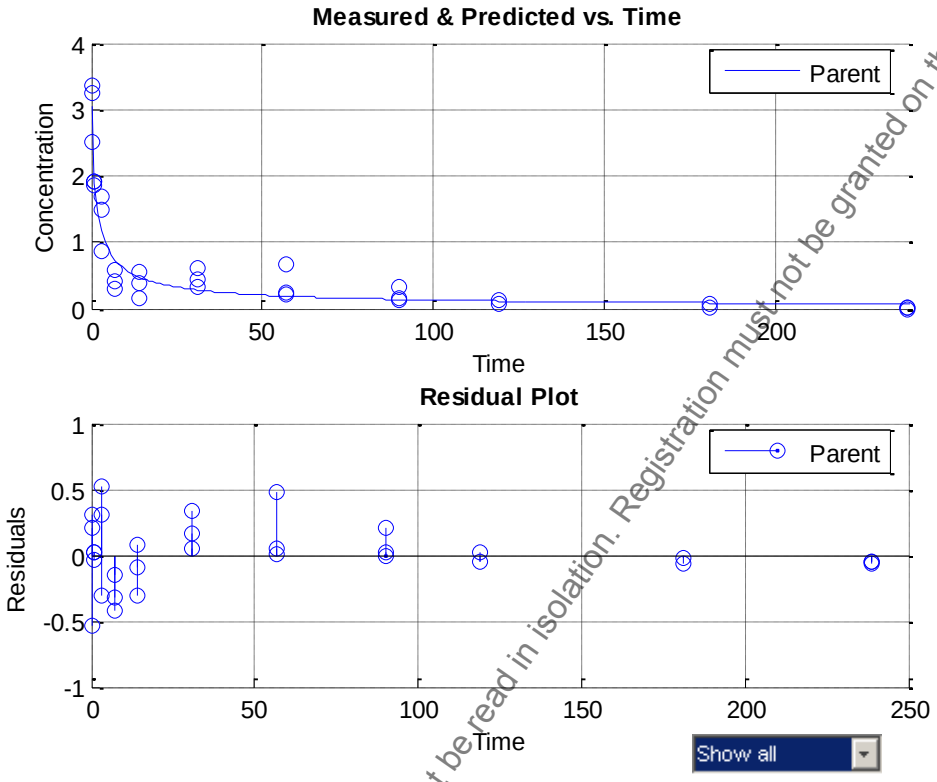
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Figure B.8.157 SFO fitting for France, Autumn field dissipation data, XDE-729 methyl, 0 – 239 DAT data



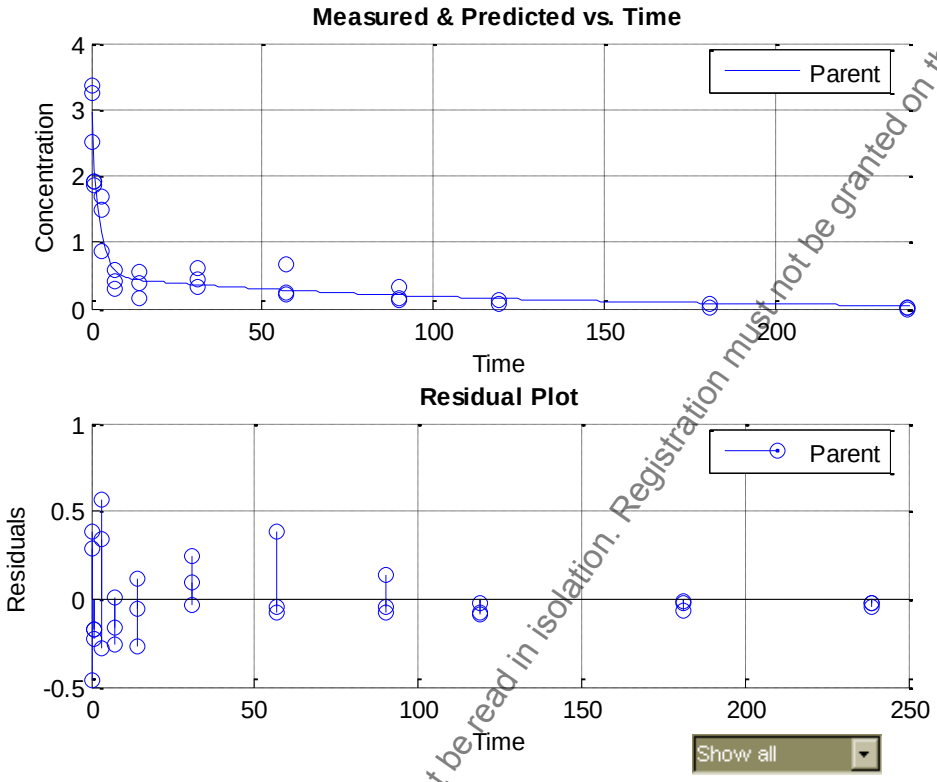
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Figure B.8.158 FOMC fitting for France, Autumn field dissipation data, XDE-729 methyl, 0 – 239 DAT data



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Figure B.8.159 DFOP fitting for France, Autumn field dissipation data, XDE-729 methyl, 0 – 239 DAT data



The FOMC model gave a better fit than SFO (χ^2 error of 15% and 25%, respectively) and the statistical outputs from the FOMC model were acceptable. The DFOP model gave a lower confidence interval less than zero, and was therefore considered by the Applicant to be not accepted. The RMS notes that whilst the statistical output is not optimal, DFOP gives a slightly better representation of the measured residues and prefers the DFOP parameters. The RMS proposes to used the DFOP parameters as persistence endpoints from this trial site, i.e. DT50 2.1 days, DT90 51 days.

X11393729

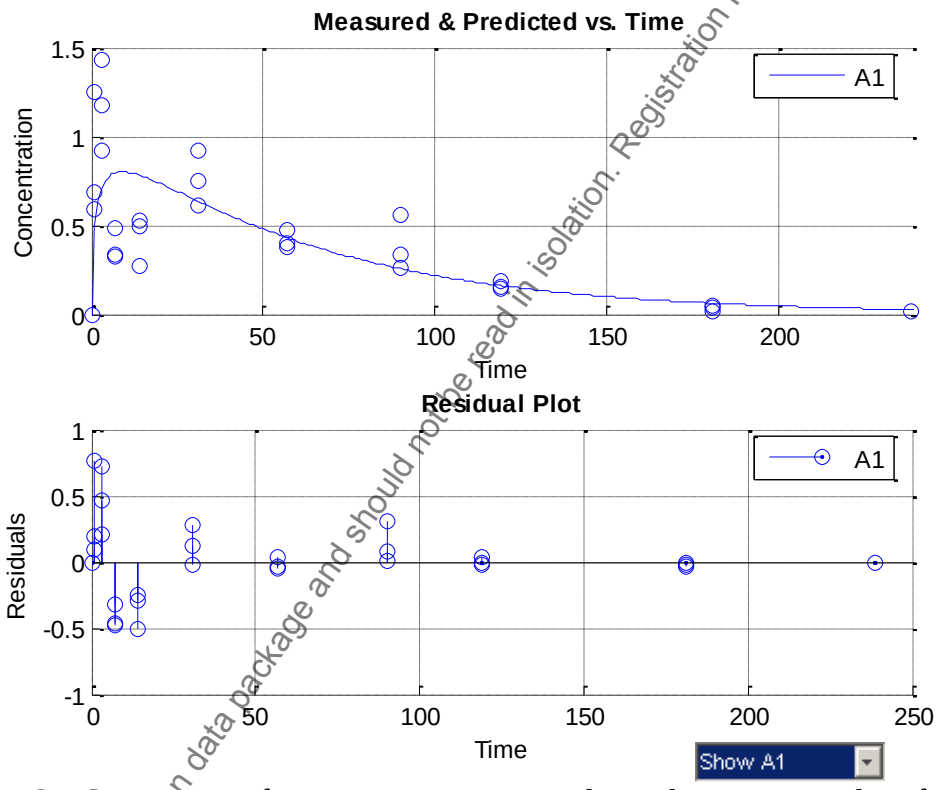
The Applicant used the optimised FOMC parameters for XDE-729 methyl as initial values, and added X11393729 to the kinetic model as the first metabolite (with SFO kinetics for the metabolite). The formation fraction was set to an initial value of 0.5 and all parameters for parent and metabolite were optimised. The outputs are shown in the following table and figure. Only the X11393729 fit is shown as the parent fitting was not affected greatly.

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Table B.8.105 Statistics for FOMC+SFO fitting for France, Autumn field dissipation data, XDE-729 methyl+ X11393729, all data

Model	Parameter	Value	Lower CI	Upper CI	Std Dev	Prob > t	DT_{50} (d)	DT_{90} (d)	% χ^2 error
FOMC Parent	M_0 (µg/kg)	3.13	2.82	3.44	0.15	-			
	alpha	0.5731	0.3737	0.7724	0.0997	1.5e-07	1.4	32	16.5
	beta	0.5846	0.0667	1.1025	0.2590	0.0138			
SFO Acid	Form fraction	0.3644	0.2598	0.4691	0.0523	-			
	k (d^{-1})	0.0174	0.0078	0.0271	0.0048	3.1e-04	40	132	49.9

Figure B.8.160 FOMC+SFO fitting for France, Autumn field dissipation data, XDE-729 methyl+ X11393729, all data



The FOMC parameters for parent ester were similar to the previous values for parent ester alone after addition of X11393729 to the model. The χ^2 error for X11393729 was high (50%) but the statistical outputs were acceptable. The residuals were high at the very early time points due to some high residues at the first few sampling points but the visual fit and residuals during the main decline part of the curve from 31 days onwards was considered by the Applicant to be reasonable. Therefore, the Applicant proposed the endpoints for X11393729 from this fitting. The RMS notes that the model is not able to simulate the peak residues. In any case, for persistence endpoints, for use in simple PECsoil calculations, top down parameters are probably more appropriate. Therefore the RMS does not agree to the FOMC/SFO generated endpoints for X11393729 at this trials site.

In order to obtain a "dissipation" rate for X11393729 that would be appropriate for a soil exposure assessment, a "top-down" fit was performed by the Applicant by running the SFO model to the decline data starting at Day 31. Although there were some

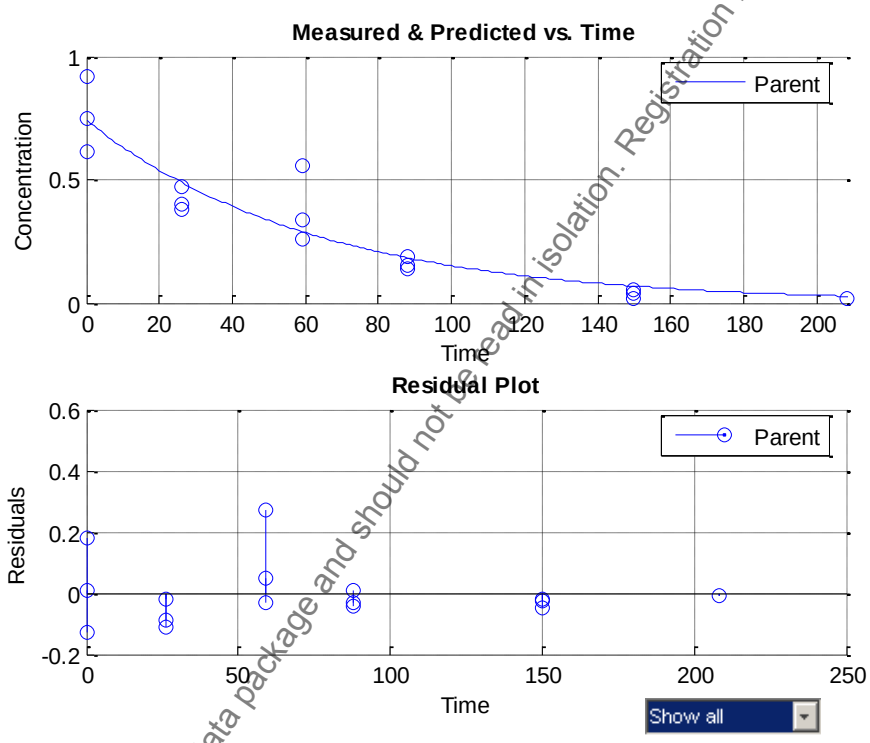
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higher residues at earlier time points there was not a clear picture of formation and decline, and the Day 58 point appears to be the start of the true decline phase for the X11393729.

Table B.8.106 Statistics for top-down SFO fit for X11393729, France Autumn, data from 31 DAT.

Model	Parameter	Value	Lower CI	Upper CI	Std Dev	Prob > t	DT_{50} (d)	DT_{90} (d)	% χ^2 error
SFO Acid (top-down)	M_0 (µg/kg)	0.74	0.63	0.85	0.05	-			
	k (d^{-1})	0.0159	0.0110	0.0208	0.0023	1.7e-06	44	145	14.1

Figure 8.161 Top-down SFO fit for X11393729, France Autumn, data from 31 DAT.



The RMS re-ran the top down fit including data from 3 DAT, the date of the highest residue. As noted by the Applicant, the data between 3 and 31 DAT were variable, with average residues at each time point following the sequence 1.23 µg/kg, 0.39 µg/kg, 0.45 µg/kg, 0.79 µg/kg. The χ^2 error was relatively poor at 45.8%, mainly caused by the scattered initial data points but also because these data points affected subsequent fitting through remaining data points. Therefore the RMS can accept the Applicant's use of data from 31 DAT in this fitting.

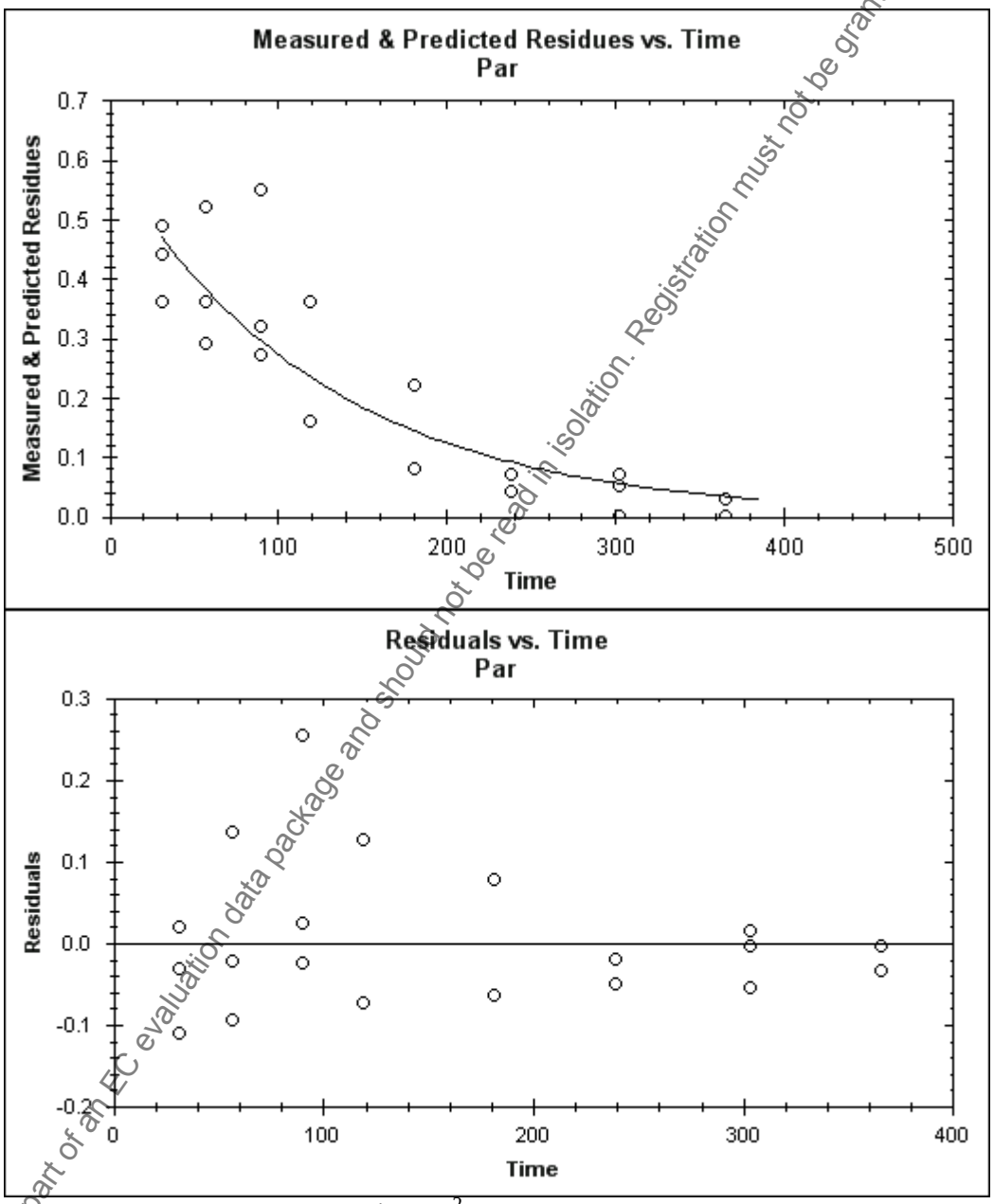
The Applicants top-down method gave a χ^2 error less than 15% and acceptable t-test. The calculated DT50 and DT90 values are only slightly higher than those derived above from the parent + metabolite model. Therefore, the top down SFO DT50 of 44 days can be accepted by the RMS as the persistence endpoint for X11393729 at this trials site and for use in simple PECsoil calculation.

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X11449757

The Applicant did not attempt any fitting with X11449757. The RMS calculated a separate SFO top down DT50.

Figure 8.162 RMS top-down SFO fit for X11449757, France, Autumn, data from 31 DAT.



DT50 87.3 days, DT90 290.2 days, χ^2 error 14.2%

The RMS considers that the SFO top down DT50 is appropriate for use in simple calculations such as PECsoil calculation and proposes the DT50 value of 87.3 days for this trials site.

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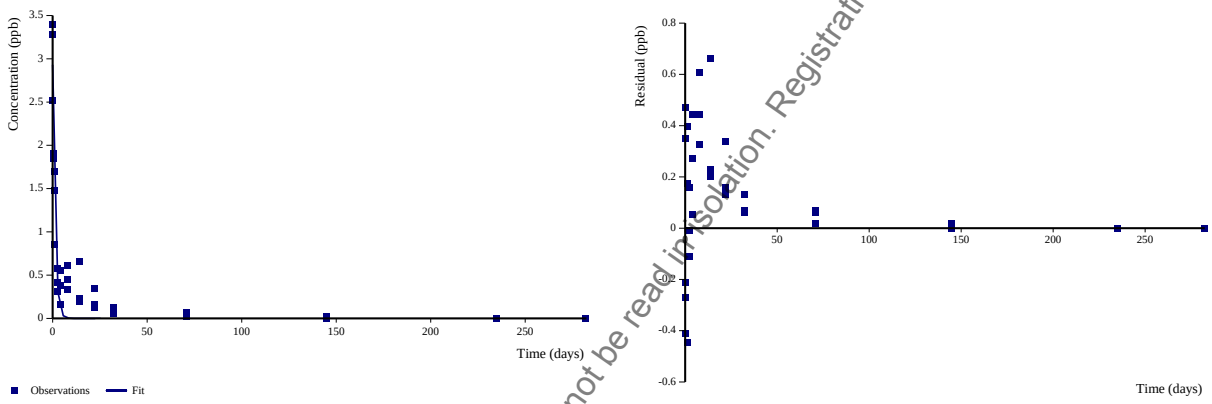
Data normalised to 20 °C and pF 2 (France, Autumn)

Parent

The results of fitting XDE-729 methyl (all data) to the SFO model are as follows:

Figure B.8.163 Statistics for kinetic fitting of France, Autumn, parent only, all data, SFO

Parameter	Value	σ	Prob > t	Lower CI	Upper CI	DT50 (d)	X^2 err (%)
M_0 (µg/kg)	2.93	0.1418	3.24E-22	2.643	3.217	0.9	25.9
k (d^{-1})	0.8085	0.0982	3.45E-10	0.6096	1.008		



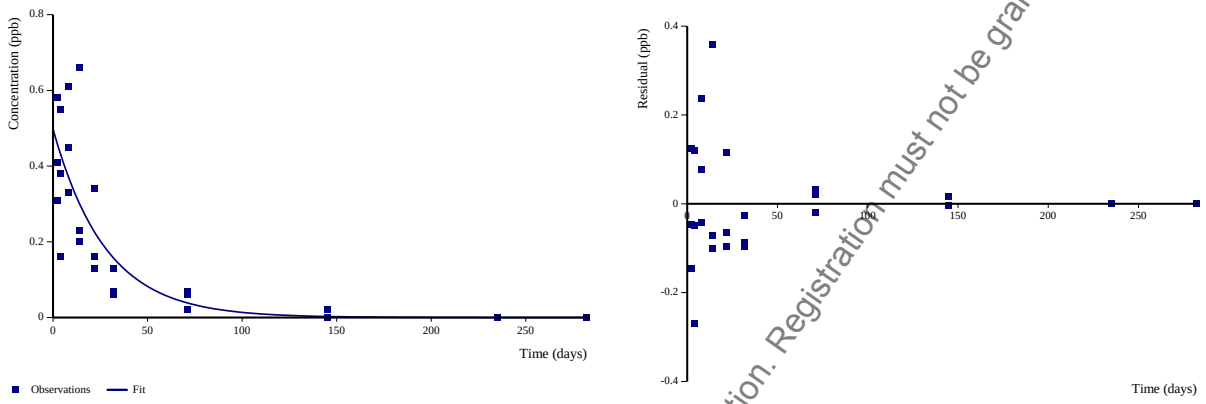
There was very rapid decline of XDE-729 methyl at this site and the χ^2 error was high with a clear biphasic profile. Residues of parent declined from 3.07 µg/kg to 0.43 µg/kg between the day of application and 7 DAT real time (2.4 DAT normalised). This means that approximately 86% of the parent had dissipated during this very short period.

A further SFO fit was conducted after eliminating data points before 10 mm rainfall. Cumulative rainfall exceeded 10 mm (total = 12.4 mm) at 1.4 DAT (4 DAT real time). The first soil sampling time after this was 2.4 DAT (7 DAT real time), and the total rainfall at this time point was 21.0 mm. This gave 10 time points on the decline curve. The results of the SFO fit to these data are as follows:

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Figure B.8.164 Statistics for kinetic fitting of France, Autumn, parent only, data after 10mm rainfall, SFO

Parameter	Value	σ	Prob > t	Lower CI	Upper CI	DT50 (d)	X^2err (%)
M_0 (µg/kg)	0.4974	0.05778	1.18E-09	0.379	0.616	19.3	19.2
k (d^{-1})	0.03601	0.01033	0.00082	0.01486	0.057		



Although the χ^2 error was slightly higher than the target value, the visual fit was good with an even distribution of residuals. The very rapid decline in residues that resulted in the extremely short DT50 from using all of the data has been eliminated and the resulting DT50 is significantly longer (19 days vs 0.9 days). However, as noted above, only 14% of the initial applied XDE-729 methyl is included in this kinetics fit, with the great majority having dissipated during the initial rapid decline period.

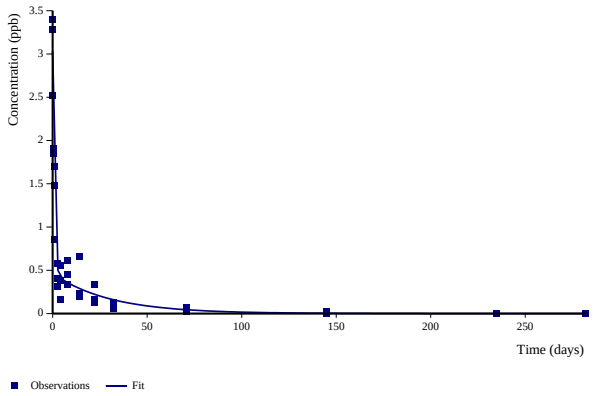
To complete the kinetics analysis, the DFOP model was run for parent XDE-729 methyl and results are as follows:

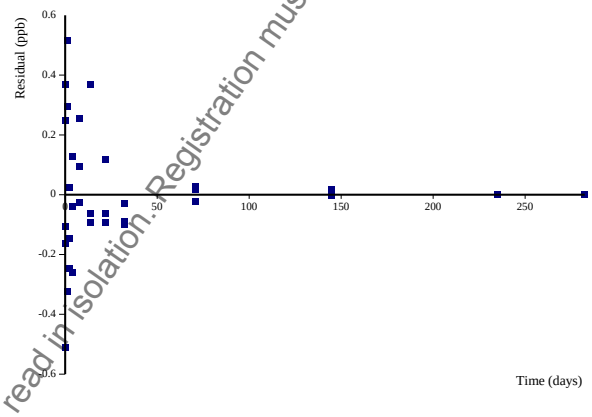
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Figure B.8.165 Statistics for kinetic fitting of France, Autumn, parent only, all data, DFOP

Parameter	Value	σ	Prob. > t	Lower CI	Upper CI	DT50* (d)	χ^2 err (%)
M_0 (µg/kg)	3.031	0.1113	1.876E-25	2.805	3.257	-	11.1
k1 (d^{-1})	1.251	0.1756	1.335E-08	0.894	1.607	0.55	
k2 (d^{-1})	0.03325	0.01893	0.04386	-0.00517	0.072	20.8	
g	0.8466	0.03814	1.661E-22	0.7691	0.924	-	

* DT50 for each rate constant calculated from ln2/k





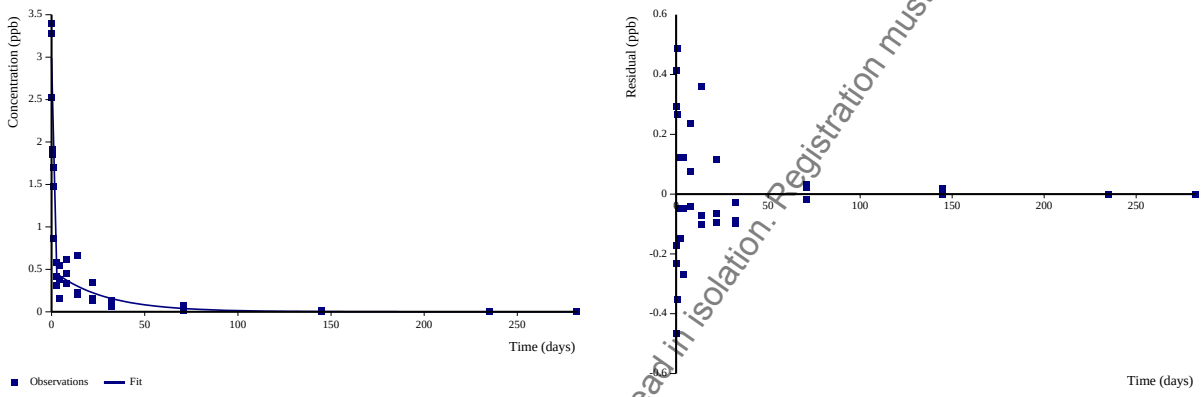
Although the χ^2 error was acceptable, the Applicant considered there to be high error on the k2 (although the RMS notes that k2 passed the t-test) and the g parameter was > 0.75. The RMS also notes that the lower confidence interval for k2 is lower than zero. Therefore, the HS model was run. Results are as follows:

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Figure B.8.166 Statistics for kinetic fitting of France, Autumn, parent only, all data, HS

Parameter	Value	σ	Prob > t	Lower CI	Upper CI	DT50* (d)	X^2err (%)
M_0 (µg/kg)	2.986	0.1094	1.73E-25	2.764	3.208	-	11.1
k1 (d^{-1})	0.9004	0.09547	1.91E-11	0.7066	1.094	0.77	
k2 (d^{-1})	0.03598	0.01779	0.0254	-0.00013	0.072	19.3	
t_b (days)	2.074	0.2943	1.66E-08	1.477	2.672	-	

* DT50 for each rate constant calculated from ln2/k



As observed for the DFOP, the χ^2 error was low but there was high error on the k2 parameter (the RMS notes that the t-test passes but the lower confidence interval includes zero).

The DT50 values derived from SFO (after 10 mm rain) and the slow phase degradation of the two biphasic models are very similar. Since the lower CI from the biphasic models was less than zero, the DT50 value of 19 days derived from the SFO model after 10 mm rain is accepted as the best fit. The RMS notes that that the HS fit gives virtually the same slow phase DT50 as the SFO model after 10mm rainfall.

Parent + X11393729

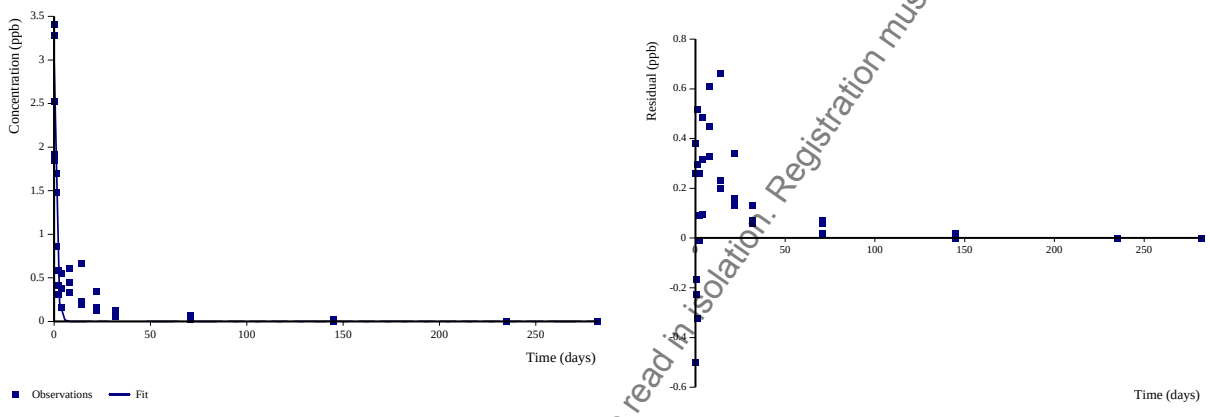
The Applicant indicated that as they considered the SFO model with all the data gave a reasonable fit for the initial rapid decline of parent, a sequential fit was run using SFO for both parent and X11393729; X11393729 is designated A1. The RMS notes that the SFO fit to the whole dataset was actually quite poor. The results are as follows:

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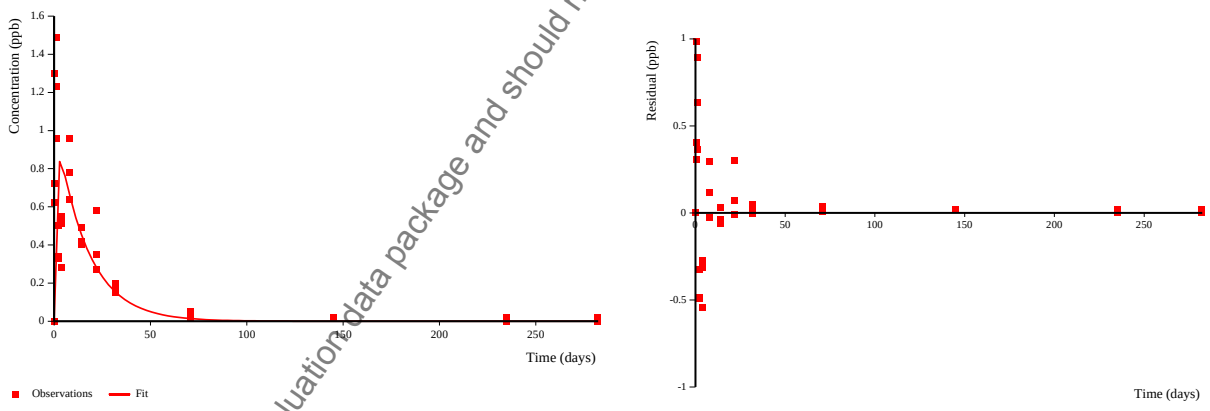
Figure B.8.167 Statistics for kinetic fitting of France, Autumn, parent + X11393729, all data, SFO+SFO

Parameter	Value	σ	Prob > t	Lower CI	Upper CI	DT50 (d)	X^2err (%)
M_0 (µg/kg)	3.021	0.1466	1.10E-32	2.729	3.313	-	
k_Parent (d^{-1})	0.9372	0.1114	1.07E-12	0.7153	1.159	0.7	26.6
f_Par_to_A1	0.3365	0.0571	5.2E-08	0.2227	0.45	-	
k_A1 (d^{-1})	0.06163	0.02252	0.00388	0.01676	0.107	11.3	61.2

Compartment Parent:



Compartment A1:



After addition of X11393729 to the model, the fit for parent was similar to that observed for parent alone; the RMS notes that the parent DT is further shortened and the fit is worsened compared to fitting parent data alone. The χ^2 error for the X11393729 was very high and visually, the model predicted the decline at later time points, although it did not predict the high residues at early time points. The RMS notes that the maximum predicted concentration was just over 0.8 µg/kg whereas the maximum concentration was average 1.23 µg/kg.

A further kinetics fit was run using the DFOP/SFO sequential model. The results are as follows:

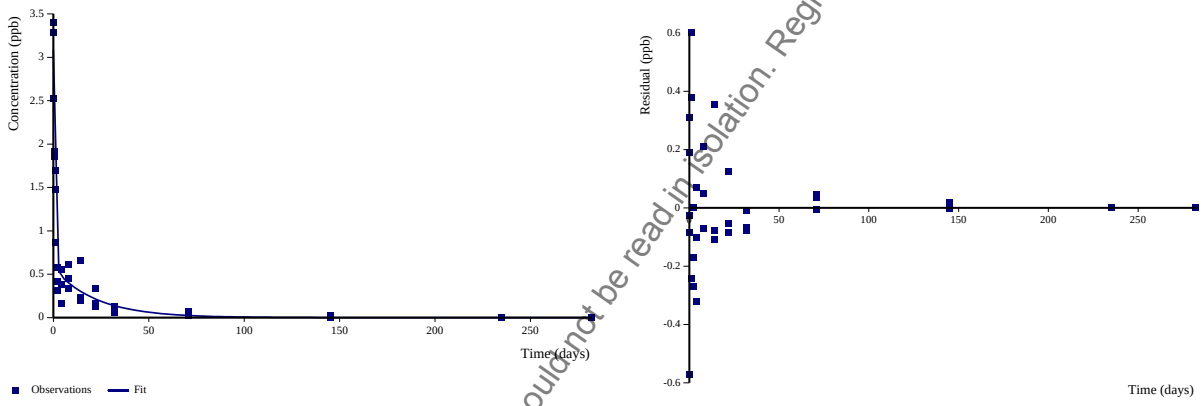
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Figure B.8.168 Statistics for kinetic fitting of France, Autumn, parent + X11393729, all data, DFOP+SFO

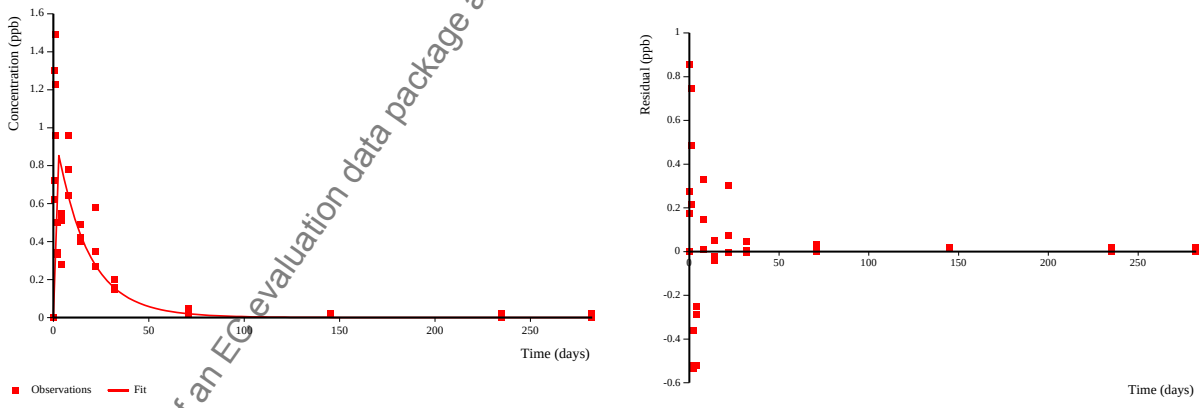
Parameter	Value	σ	Prob > t	Lower CI	Upper CI	DT50* (d)	X^2err (%)
M_0 (µg/kg)	3.091	0.1136	6.16E-40	2.865	3.318	-	12.6
k1 (d^{-1})	1.514	0.2132	3.60E-10	1.089	1.939	0.5	
k2 (d^{-1})	0.04438	0.02012	0.01531	0.00427	0.085	15.6	
g	0.8155	0.03917	1.72E-32	0.7374	0.894	-	
f_Par_to_A1	0.39	0.05683	9.87E-10	0.2767	0.503	-	59.3
k_A1 (d^{-1})	0.07151	0.02225	0.00098	0.02717	0.116	9.7	

* DT50 for each rate constant calculated from ln2/k

Compartment Parent:



Compartment A1:



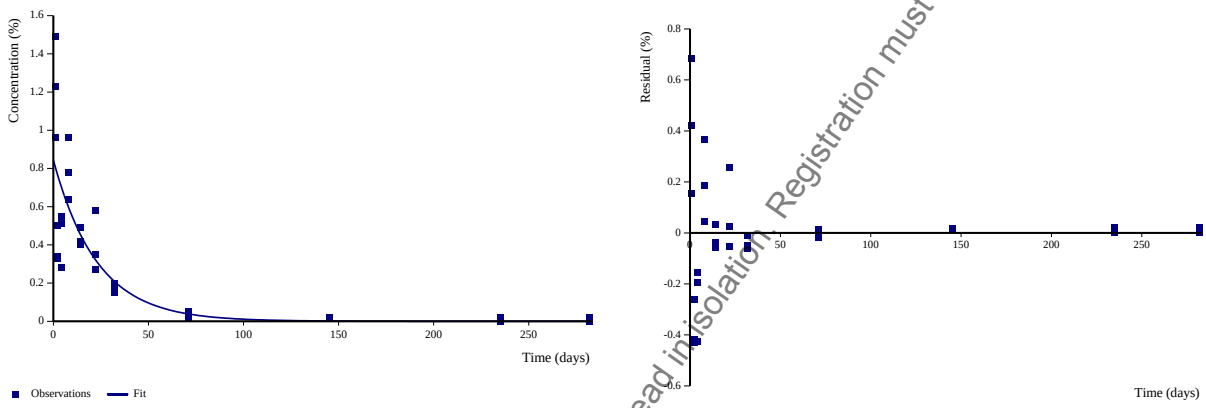
For the X11393729, the Applicant considered the DFOP/SFO model gave a very similar fit to the SFO/SFO model with similar DT50 and formation fraction values. Since the results for X11393729 were similar for both models, the SFO/SFO model was preferred by the Applicant since it is compatible with the kinetics routines in simulation models. However, the RMS notes that neither SFO/SFO or DFOP/SFO models could accurately predict the formation behaviour of X11393729.

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To complete the kinetics evaluation for X11393729 , a top-down SFO fit was performed starting at 1.0 DAT (3 DAT real time), the time of maximum formation. This gave 11 time points on the decline curve. An SFO fit was applied to the data and results are shown in the following table:

Figure B.8.169 Statistics for kinetic fitting of France, Autumn, X11393729, top down from peak (occurred before 10mm rainfall), SFO

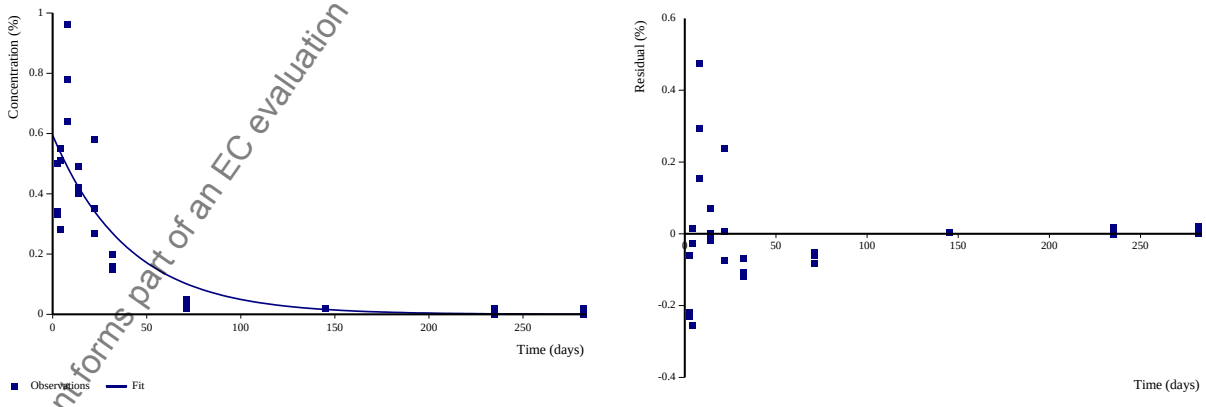
Parameter	Value	σ	Prob > t	Lower CI	Upper CI	DT50 (d)	X^2 err (%)
k (d^{-1})	0.04352	0.01291	0.001008	0.0172	0.07	15.9	44.4



Since 10 mm rain was not achieved until 2.4 DAT (7 DAT real time) a second top-down fit was performed using data from 2.4 DAT onwards (10 data points).

Figure B.8.170 Statistics for kinetic fitting of France, Autumn, X11393729, top down from after 10mm rainfall, SFO

Parameter	Value	σ	Prob > t	Lower CI	Upper CI	DT50 (d)	X^2 err (%)
k (d^{-1})	0.02488	0.00760	0.00141	0.00932	0.04	27.9	36.1



The Applicant considered that the top-down model for the X11393729 gave a reasonable visual fit although the χ^2 error was high, which is most likely due to the high scatter in the data at early time points. The RMS concurs that the between sample

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time variability appears large at the earlier time points which may be driving the large χ^2 error.

The best fit for the X11393729 was obtained with the top-down SFO model after 10mm rainfall had occurred and the DT50 value of 28 days was proposed by the Applicant as a conservative estimate. The high χ^2 error for all the kinetics models is most likely due to the high scatter in the data at early time points but it is clear that both parent and the X11393729 were rapidly dissipated at this site; the RMS can concur with this statement. The SFO/SFO sequential fit with parent was not as good as for some of the other data sets but a DT50 of 0.7 days for parent together with a formation fraction of 0.34 and a DT50 of 11 days for X11393729 could be considered as reasonable inputs for modelling X11393729.

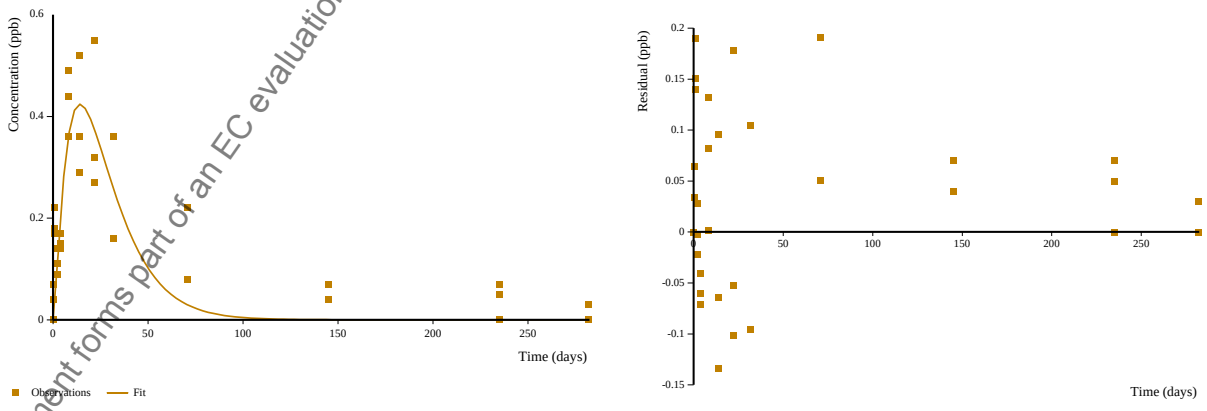
Parent + X11393729 + X11449757

The X11449757 data were added to the model and a sequential fit was performed for Parent, X11393729 and X11449757 using SFO for the parent; X11449757 is designated A2. The optimised parameters are as follows:

Figure B.8.171 Statistics for kinetic fitting of France, Autumn, parent + X11393729 + X11449757, all data, SFO+SFO+SFO

Parameter	Value	σ	Prob >t	Lower CI	Upper CI	DT50 (d)	X^2 err (%)
M_0 (µg/kg)	3.032	0.1406	8.67E-42	2.753	3.31		26.8
k_Parent (d^{-1})	0.9544	0.1064	4.16E-15	0.7436	1.165	0.73	
f_Par_to_A1	0.3648	0.06136	1.63E-08	0.2432	0.486		61.3
k_A1 (d^{-1})	0.08029	0.02793	0.00242	0.02495	0.136	8.6	
f_A1_to_A2	1	0.4767	0.01909	0.05543	1.945		30.0
k_A2 (d^{-1})	0.07331	0.02962	0.00742	0.01462	0.132	9.5	

Compartment A2:



Only the visual fit for X11449757 is shown here. The parameters for parent and X11393729 were only slightly changed after addition of X11449757 to the model.

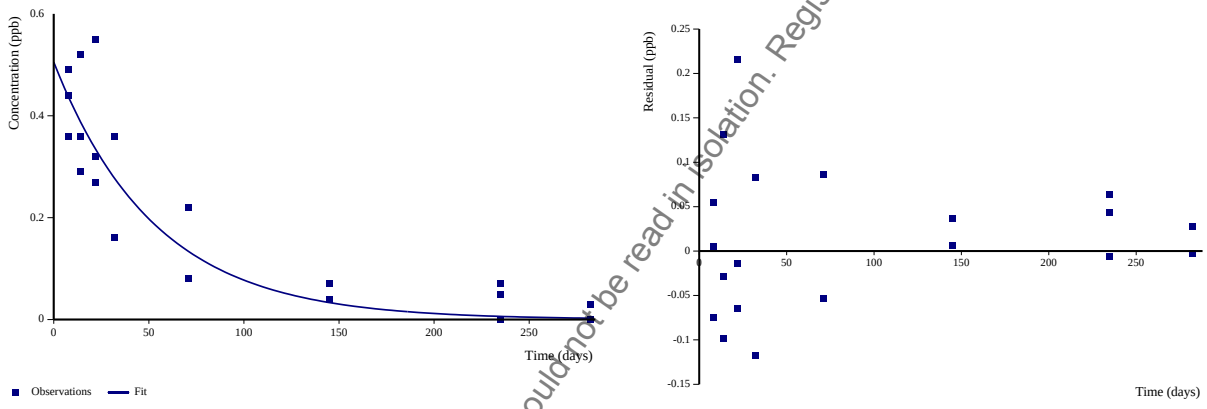
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The visual fit for X11449757 showed over-prediction of the decline rate at later time points and the χ^2 error was high for all compartments. The RMS agrees with the Applicant assessment in this case.

A top-down fit was attempted for the X11449757 metabolite. The maximum residue was seen at 8.0 DAT (31 DAT real time) which is after 10 mm rainfall. Therefore, the top-down fit was performed starting at 8.0 DAT. This gave 8 time points on the decline curve. Results are shown in the following table:

Figure B.8.172 Statistics for kinetic fitting of France, Autumn, X11449757, top down from peak (occurred after 10mm rainfall), SFO

Parameter	Value	σ	Prob > t	Lower CI	Upper CI	DT50 (d)	X^2 err (%)
k (d^{-1})	0.01877	0.00450	0.000198	0.00944	0.028	36.9	11.0



The χ^2 error was low and the visual fit was good despite the low residues.

The best fit for the X11449757 metabolite was obtained with the top-down SFO model and the DT50 value of 37 days can be proposed as a conservative estimate; the RMS can agree with this proposal. Although the sequential fit with the SFO model gave a poorer fit than top-down, a DT50 of 9.5 days and a formation fraction of 1 (from X11393729) together with the optimised parameters for parent and X11393729 described above can be proposed as inputs for modelling X11449757. The RMS is rather doubtful of the second proposal in this case given the poor fitting of parent and X11393729.

Non-linear Least Squares fitting vs Iteratively Reweighted Least Squares fitting

The Applicant provided visual examples of fitting of metabolite X11393729 at the Germany Spring and UK Autumn sites. In addition, tables of kinetic parameters and χ^2 error for all trial sites for parent and X11393729 with both IRLS and NLLS were submitted. A comparison of NLLS and IRLS fitting for X11449757 was not pursued. The tables of output are given below.

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Table B.8 107 Output of sequential fitting, XDE-729 methyl + X11393729, normalised field dissipation data, IRLS fitting.

			Parent		Acid		
Location	Season	Model	DT50 (d)	χ^2	DT50 (d)	FF	χ^2
Germany	Spring	DFOP/SFO	0.7[1]↓	28↑	23↑	0.12↓	34↓
Germany	Autumn	SFO/SFO	2.5↑	32	42↓	0.44↑	25
UK	Spring	SFO/SFO	27↓	28	35↑	0.66↓	33
UK	Autumn	SFO/SFO	1.1↓	40↑	51↑	0.36↓	14↓
Spain	Spring	SFO/SFO	6.4↓	17↑	34↑	0.33↓	49↓
Spain	Autumn	SFO/SFO	9.1↓	20	40↑	0.34↓	49↓
France	Spring	SFO/SFO	6.6↓	40↑	2.3↓	1.00	32↓
France	Autumn	SFO/SFO	0.7	27	11	0.34↑	61↑
		Geomean	**3.3**		**22**	0.38	
		Average	6.8	29	30	**0.45**	37
		SD	8.8		16	0.27	
		% CV	130		55	60	
		Median	4.5		35	0.35	

[1] DT50 calculated from DFOP fast phase rate constant

Table B.8 108 Output of sequential fitting, XDE-729 methyl + X11393729, normalised field dissipation data, NLLS fitting.

			Parent		Acid		
Location	Season	Model	DT50 (d)	χ^2	DT50 (d)	FF	χ^2
Germany	Spring	DFOP/SFO	4.6[1]	23	8.7	0.21	49
Germany	Autumn	SFO/SFO	2.3	32	44	0.42	25
UK	Spring	SFO/SFO	28	28	33	0.69	33
UK	Autumn	SFO/SFO	3.3	14	33	0.54	30
Spain	Spring	SFO/SFO	7.7	16	30	0.38	50
Spain	Autumn	SFO/SFO	9.5	20	38	0.35	50
France	Spring	SFO/SFO	8.4	39	2.8	1.00	37
France	Autumn	SFO/SFO	0.7	27	11	0.33	60
		Geomean	**5.0**		**19**	0.44	
		Average	8.1	25	25	**0.49**	42
		SD	8.6		15	0.25	
		% CV	107		61	51	
		Median	6.2		32	0.4	

[1] DT50 calculated from DFOP fast phase rate constant

For parent, using IRLS optimisation tends to overall result in a reduction in DT50 value. The difference is not that great, but it must be born in mind that overall the length of parent DT50 is quite short; in one or two cases, the magnitude in change is quite marked, e.g. Germany Spring and UK Autumn. There is also a trend for a slight increase in χ^2 error, and in only one case was the increase marked (UK Autumn)

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although it must be borne in mind that the χ^2 error is tending to related to data scatter rather than an inherent inability of the kinetic model to describe the overall trend of the data.

By contrast, using IRLS fitting tended to improve fitting for X11393729, sometimes marginally, but considerably in other instances (Germany Spring and UK Autumn). There was a trend for an increase in DT50, however, formation fraction tended to be reduced. The overall impact on risk assessment of IRLS fitting is difficult to judge with small changes in geometric mean/average parameters, and it may be that these would cancel each other out in a risk assessment.

The impact on fitting of X11393729 in the two trials most affected by the weighting method is shown below.

Figure B.8.173 Visual fitting for X11393729, Germany Spring, in sequence with parent, IRLS weighting

DE Spring Acid fit with DFOP/SFO using IRLS:

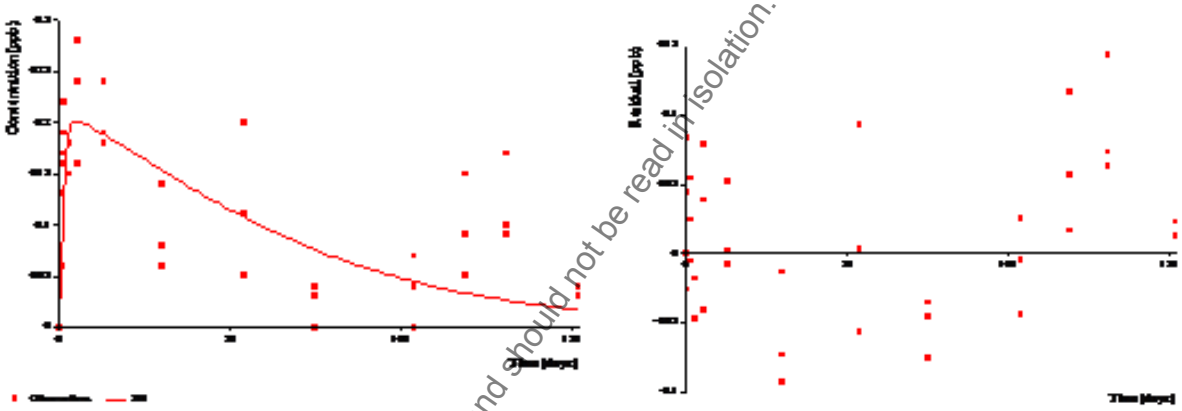
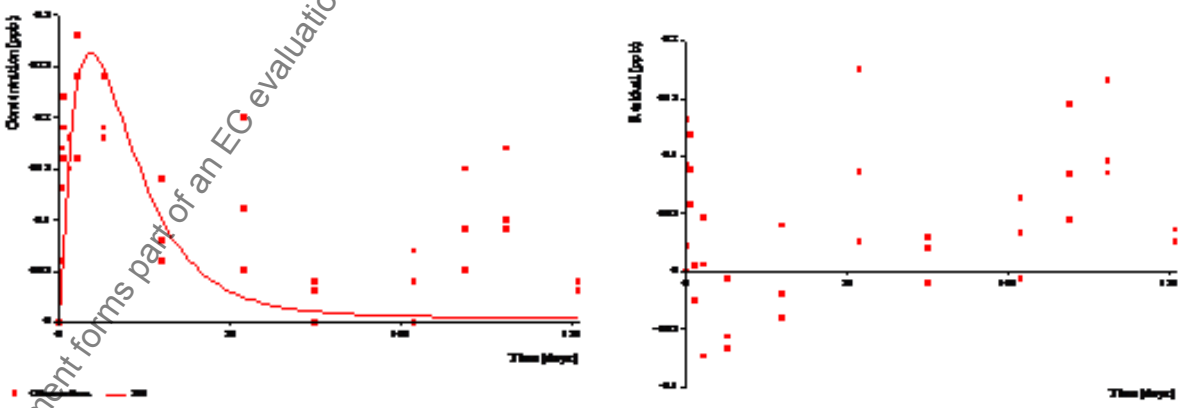


Figure B.8.? Visual fitting for X11393729, Germany Spring, in sequence with parent, NLLS weighting

DE Spring Acid fit with DFOP/SFO using OLS:



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Figure B.8.174 Visual fitting for X11393729, UK Autumn, in sequence with parent, IRLS weighting

UK Autumn Acid fit with SFO/SFO using IRLS:

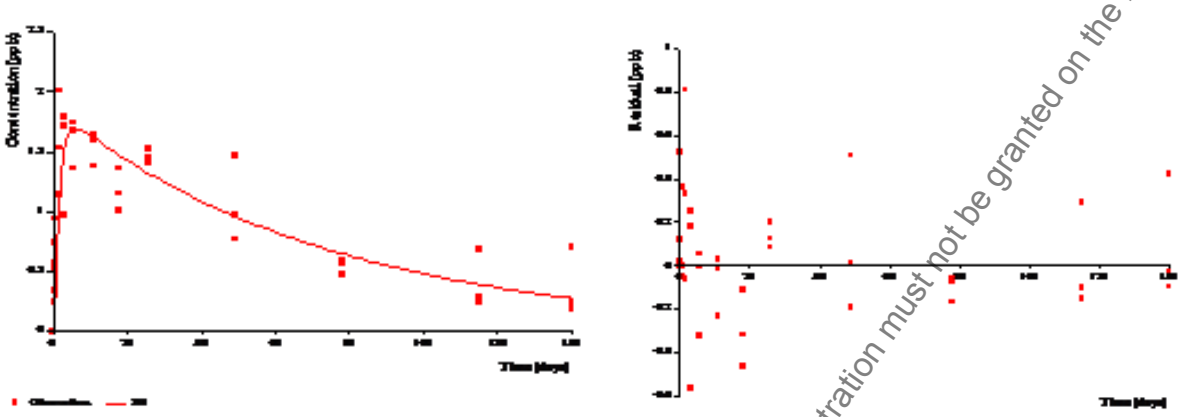
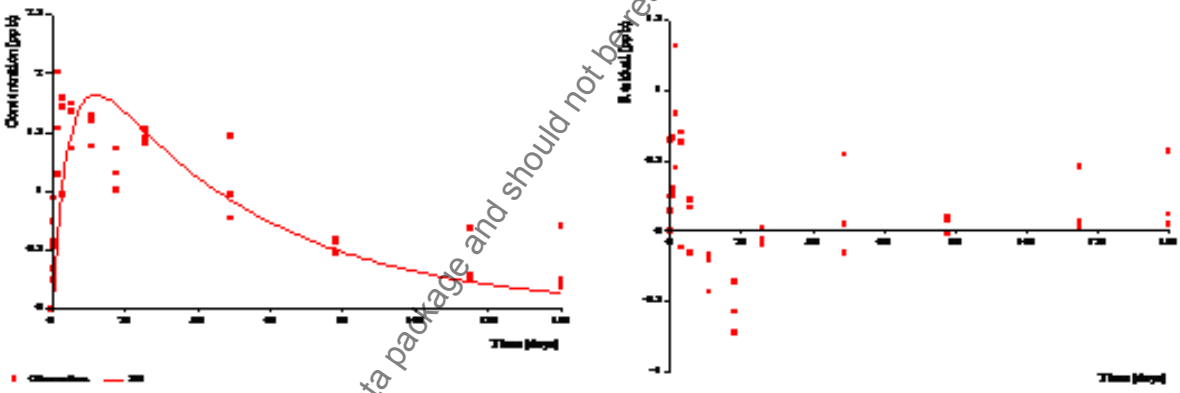


Figure B.8.175 Visual fitting for X11393729, UK Autumn, in sequence with parent, NLLS weighting

UK Autumn Acid fit with SFO/SFO using OLS:

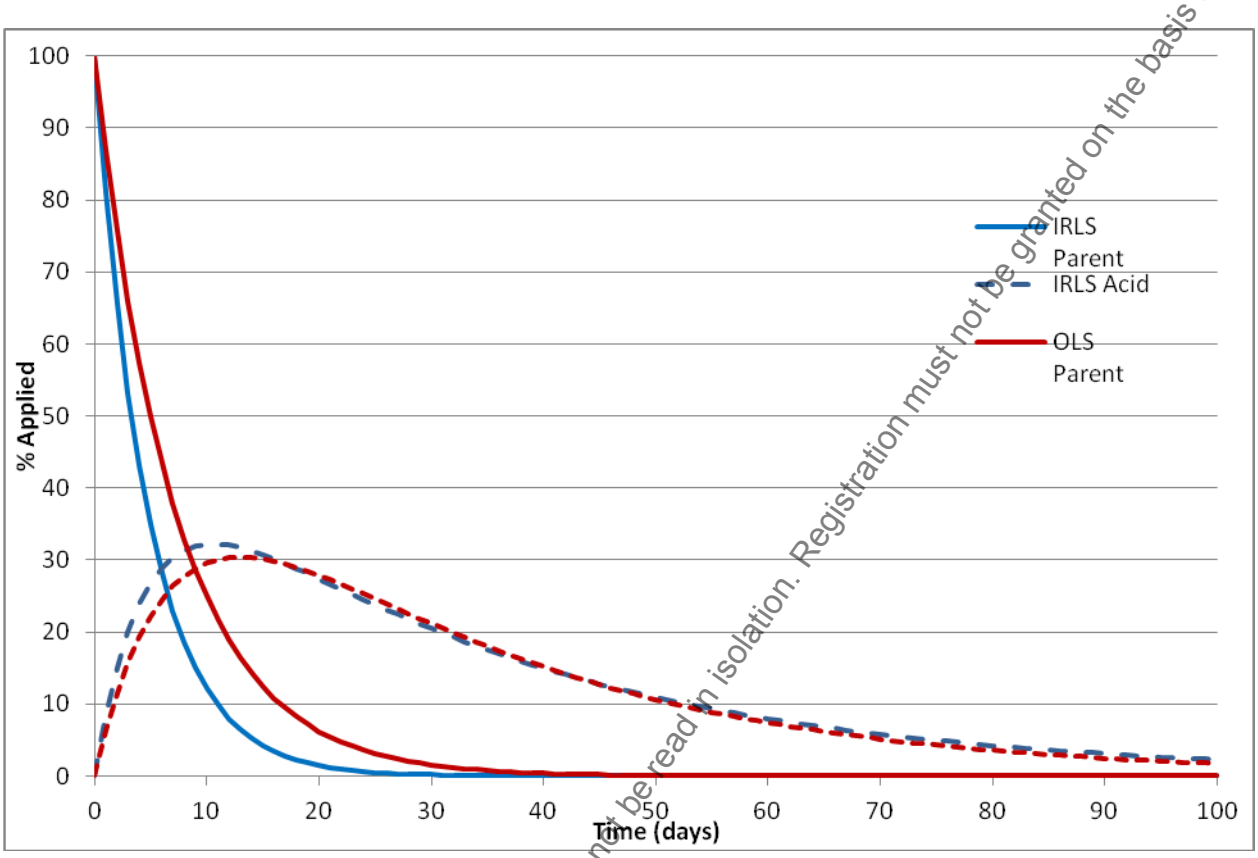


For Germany Spring site, the dataset is showing separate peaks of formation for the metabolite and none of the kinetic models are able to describe the behaviour well. However, the IRLS fitting is tending to give a better overall fit to the data. It is of interest that the IRLS fitting is potentially attempting to achieve a better fit to later time points whereas the emphasis of the NLLS appears to be on the earlier time points.

The Applicant illustrated the overall impact of using either NLLS or IRLS on parent decline and X11393729 formation and decline by generating metabolism profiles using the geometric mean parent and X11393729 degradation rates and arithmetic mean formation fractions.

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Figure B.8.176 Simulated XDE-729 methyl and X11393729 profiles using sequential parameters from NLLS (OLS) and IRLS weighting.



Overall, the RMS considers it is acceptable to allow the use of IRLS fitting in this case as there seems to be little impact on kinetic parameters for X11393729. This is with the proviso that separate exposure modelling is conducted for parent with more conservative kinetic parameters to represent the possibility of slower degradation in the bulk matrix of the soil. This modelling should be distinct from exposure modelling for the metabolites which could allow the use of less conservative kinetic parameters from the whole dataset. Theoretically, the use of faster parent degradation rates would result in greater formation of metabolite which theoretically would give a more conservative metabolite assessment.

Derivation of persistence parameters

Given that values from field dissipation studies are generally generated under more realistic conditions than those experienced in the laboratory, the RMS prefers to use field dissipation rates to describe persistence, and to give parameters for use in simplistic PECsoil calculations.

The following persistence endpoints have been collated by the RMS. In some cases for XDE-729 methyl. the RMS has disagreed with the Applicant as to the best choice of model. In these cases, the RMS has tended to consider visual and residual fits and χ^2 error as being the most important aspects of goodness of fit. In these cases, the Applicant has given greater weight to aspects such as t-test and lower confidence interval than the RMS has. In some cases, the Applicant has often accepted a worse fitting (as defined by the visual and χ^2 error, usually very closely linked to the visual

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and residual fits) SFO model above a better fitting biphasic model. The RMS accepts that in some cases, the differences in fit are slight but can lead to a longer DT90 where the biphasic model is used. Whilst the RMS accepts that a range of criteria are recommended in FOCUS Kinetics guidance for determining the best fitting model, the RMS takes the view that the most important aspects are visual and residual fit and the closely related χ^2 error statistic.

For metabolites, the RMS prefers to consider the top-down SFO parameters describing decline from peak formation to describe persistence as this is more reflective of what soil organisms are likely to experience, as opposed to a 'true degradation' parameter generated from sequential parent+metabolite modelling. A top down SFO value is also well suited to a simple PECsoil calculation.

Table B.8.109 Comparison of Applicant and RMS choice of persistence endpoints for XDE-729 methyl from field dissipation studies

Site	Season	Applicant choice			RMS choice		
		Best fit model	DT50 (days)	DT90 (days	Best fit model	DT50 (days)	DT90 (days
Germany	Spring Autumn	SFO SFO	18 6.0	60 20	SFO FOMC	18 5	60 78
UK	Spring Autumn	SFO SFO	43 21	144 68	SFO FOMC	43 15	144 106
Spain	Spring Autumn	SFO SFO	15 13	51 44	SFO FOMC	15 11	51 86
France	Spring Autumn	SFO FOMC	15 1.7 (8.1)*	49 27	SFO DFOP	15 2.1	49 51
Worst case					SFO	43	144

* pseudo SFO DT50 derived from FOMC DT90/3.322

Table B.8.110 Top down SFO persistence endpoints for X11393729 from field dissipation studies

Site	Season	Model	DT50 (days)	DT90 (days
Germany	Spring Autumn	SFO SFO	Not used 101.7	Not used 337.9
UK	Spring Autumn	SFO SFO	264.4 163.5	871.7 543.2
Spain	Spring Autumn	SFO SFO	62 108	207 359
France	Spring Autumn	SFO SFO	17 44	56 145
Worst case		SFO	264.4	871.7

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Table B.8.111 Top down SFO persistence endpoints for X11449757 from field dissipation studies

Site	Season	Model	DT50 (days)	DT90 (days)
Germany	Spring	SFO	Not used	Not used
	Autumn	SFO	197.0	654.4
UK	Spring	SFO	187.1	621.4
	Autumn	SFO	Not used	Not used
Spain	Spring	SFO	113.2	375.9
	Autumn	SFO	104.7	347.8
France	Spring	SFO	146.0	484.9
	Autumn	SFO	87.3	290.2
Worst case		SFO	197.0	654.4

Derivation of modelling parameters

XDE-729 methyl

In selecting kinetic parameters for use in exposure modelling for XDE-729 methyl, the Applicant considered that best fits in many cases were derived from SFO kinetics after elimination of data points before 10mm rainfall. The RMS notes that in many cases the datasets seem to be typically biphasic in nature, however, the rapid phase of degradation is tending to describe at least 85-90% of the degradation. Therefore this could be interpreted as SFO kinetic describing the decline well. In most cases, applying the DFOP and HS flow charts failed to deliver a completely 'acceptable' set of biphasic kinetic parameters. In most cases, one or both rate constants would fail a statistical test such as t-test (which tends to be closely linked to the error around the optimised parameter) or confidence intervals (i.e. lower confidence interval should not be negative). In addition, the RMS notes that the SFO DT50 after 10mm rainfall was often very similar to the slow phase DT50 of HS. This should be unsurprising, as if the HS breakpoint is close to the time of 10mm rainfall, the slow phase of HS should be very similar to free-fitting an SFO curve through data after 10mm rainfall.

The Applicant recognised that the DT50s calculated from this approach were often much longer than those from fitting using the whole database. Using the slower parent DT50 values in a simultaneous exposure assessment including metabolites might lead to a conservative assessment for parent but not necessarily for metabolites. Therefore, the Applicant proposed to derive a set of conservative degradation endpoints for use in modelling for parent only, and another set of less conservative parameters for parent that could be used in separate exposure modelling intended primarily to obtain a conservative estimate for metabolites. The RMS can agree with separating the exposure modelling approaches for parent and metabolites as this is more likely to give more conservative estimates for the parent and first metabolite. Therefore the RMS can agree with the following parameter choice for parent only exposure modelling.

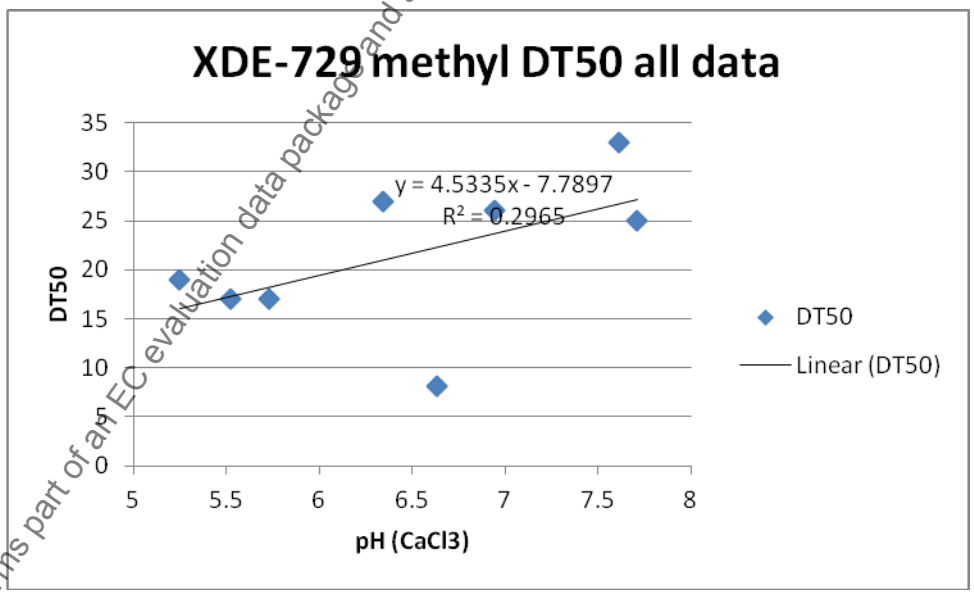
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Table B.8.112 Kinetic endpoints for XDE-729 methyl exposure modelling (i.e. should not be used in exposure modelling simulating formation of subsequent metabolites)

Location	Season	Model	DT50 (d)	*Chi² Error (%)*
Germany	Spring	SFO (after 10mm rain)	17	*24*
Germany	Autumn	SFO (after 10mm rain)	27	*24*
UK	Spring	SFO (after 10mm rain)	26	*19*
UK	Autumn	SFO (after 10mm rain)	8.2	*20*
Spain	Spring	SFO (after 10mm rain)	25	*32*
Spain	Autumn	SFO (after 10mm rain)	33	*11*
France	Spring	SFO (after 10mm rain)	17	*15*
France	Autumn	SFO (after 10mm rain)	19	*19*
		Geomean	**20**	-
		Average	22	-
		Median	22	-

The RMS investigated the potential for XDE-729 methyl to show pH dependency of degradation. The modelling endpoints were plotted against the pH of the soils as shown below. The RMS considers that there is no consistent trend and the difference in DT50s in this case is likely to be within the range of natural variation. This is generally in line with the conclusion made on the laboratory data. Therefore the RMS proposes that pH dependency of degradation does not need to be considered in exposure modelling of XDE-729 methyl.

Figure B.8.177 Relationship of XDE-729 methyl DT50 with pH, normalised field dissipation studies



Metabolite X11393729

Overall, the RMS considered that the Applicants proposals regarding sequential fitting of metabolites with the whole datasets from each trials sites seemed reasonable although there were some cases where the Applicants conclusions in terms of fitting

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seemed optimistic. However, the overall conclusion and context of the trials data sets needs to also be taken into consideration.

Following on from the conclusions on the parent substance, it was recognised that using the conservative DT50 values for the parent may not give a conservative assessment for metabolites. This is because the conservative parent DT50 values are associated more with the latter part of the parent decline curve whereas much of the formation and decline of X11393729 in the trials is associated with the former part of the curve, i.e. before or around 10mm of rainfall. The Applicant suggested that whilst the initial fast phase of degradation of the parent may have included additional dissipation process such as photolysis which should be disregarded when considering exposure modelling for parent only, including the initial parent phase might be conservative for the metabolite as it assumes that such processes lead to formation of this metabolite. The RMS can understand this logic and in this case accepts that this might lead to a more conservative metabolite assessment. The RMS also notes that the general profile of decline in laboratory and field studies is similar, suggesting that any surfaces processes in the field may have had a relatively small impact on decline of the parent. Therefore the Applicant proposed the following kinetic endpoints for sequential exposure modelling of XDE-729 methyl and X11393729. Top down parameters from the normalised datasets are shown for completeness but are not proposed for use in exposure assessment.

Table B.8.113 Kinetic endpoints for sequential exposure modelling of XDE-729 methyl and X11393729 (Acid)

		Parent + Acid (SFO+SFO)					Top-down SFO	
Location	**Season**	**Parent DT50 (d)**	***Chi² Err (%)***	**Acid DT50 (d)**	**FF**	***Chi² Err (%)***	**Acid DT50 (d)**	***Chi² Err (%)***
Germany	Spring	0.7*	*28*	23	0.12	*34*	59	*32*
Germany	Autumn	2.5	*32*	42	0.44	*25*	30	*13*
UK	Spring	27	*28*	35	0.66	*33*	88	*6.5*
UK	Autumn	1.1	*40*	51	0.36	*14*	59	*9.5*
Spain	Spring	6.4	*17*	34	0.33	*49*	62	*15*
Spain	Autumn	9.1	*20*	40	0.34	*49*	85	*16*
France	Spring	6.6	*40*	2.3	1.00	*32*	29	*25*
France	Autumn	0.7	*27*	11	0.34	*61*	28	*36*
	Geomean	**3.3**	-	**22**	0.38	**-**	**50**	-
	Average	6.8	-	30	**0.45**	-	55	-
	Median	4.5	-	35	0.35	-	59	-

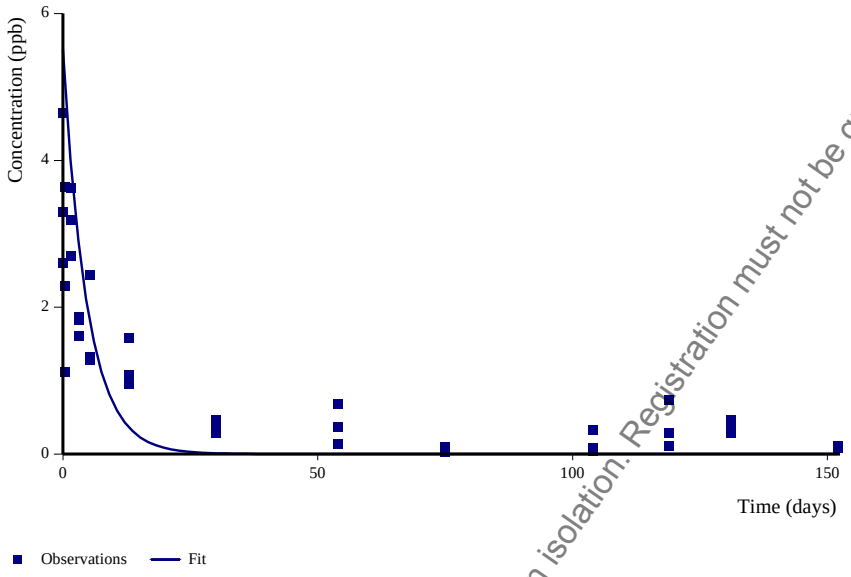
FF = formation fraction * DFOP/SFO model used

As indicated above, the RMS had some concerns over the quality of fitting and representation of X11393729. With this in mind, the Applicant plotted the geomean/average kinetic endpoints shown above against the data from the eight trials sites. Initial concentration was the calculated theoretical day 0 concentration taking into account any metabolite residues at day 0. In addition, the average concentrations from each sample time at each trial site were combined and plotted against the simulated curves for parent and metabolite to show the overall representation of the proposed parent and X11393729 endpoints. These are shown below.

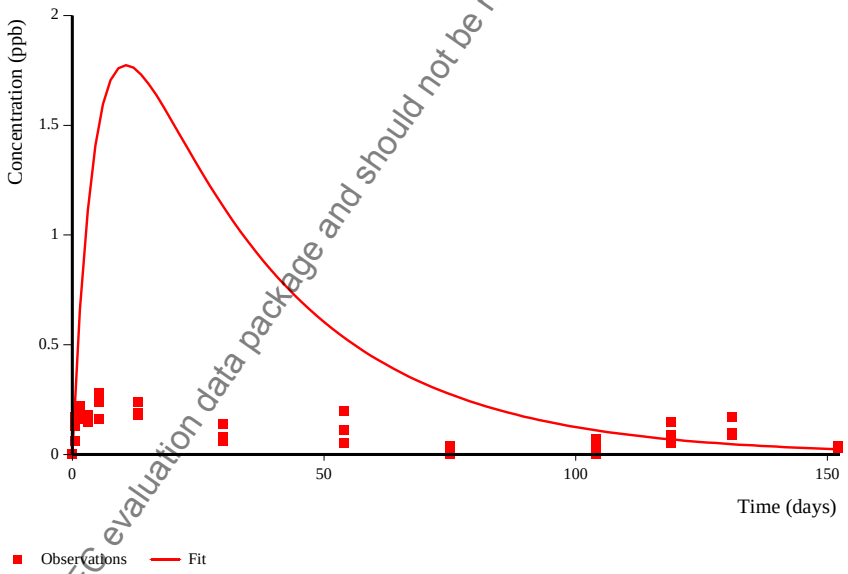
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Figure B.8.178 Theoretical vs measured residues of XDE-729 methyl and X11393729 in soil using mean SFO/SFO optimised parameters (Germany, Spring)

(a) Parent



(b) Acid

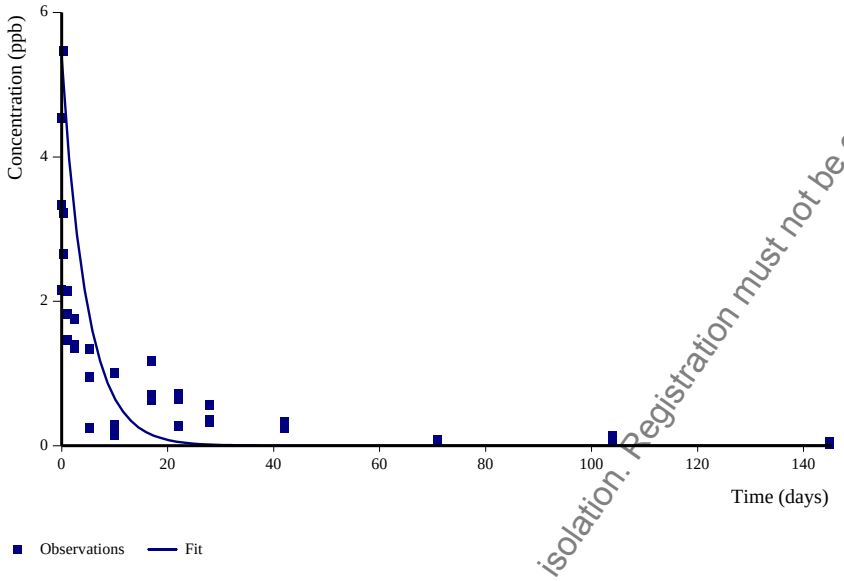


Parameter	Value
Parent_0	5.51
k_Parent	0.21
f_Parent_to_A1	0.45
k_A1	0.0315

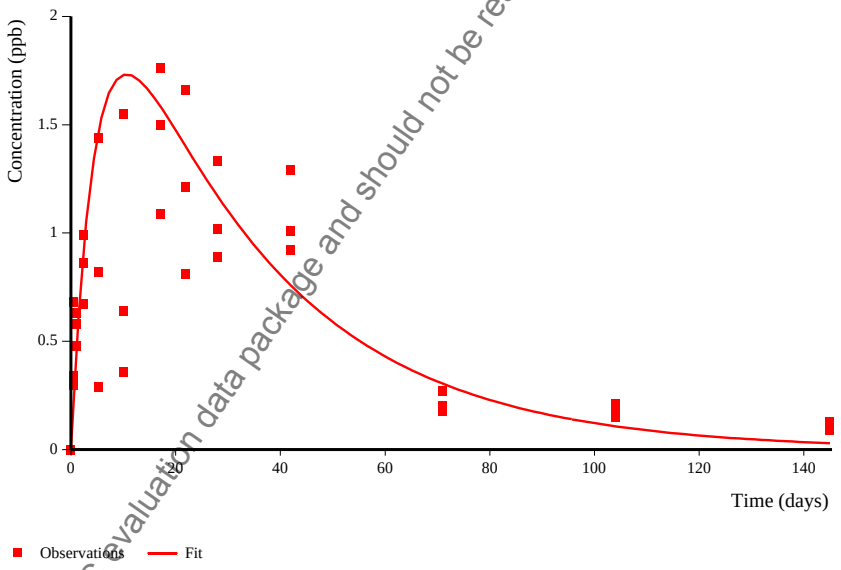
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Figure B.8.179 Theoretical vs measured residues of XDE-729 methyl and X11393729 in soil using mean SFO/SFO optimised parameters (Germany, Autumn)

(a) Parent



(b) Acid

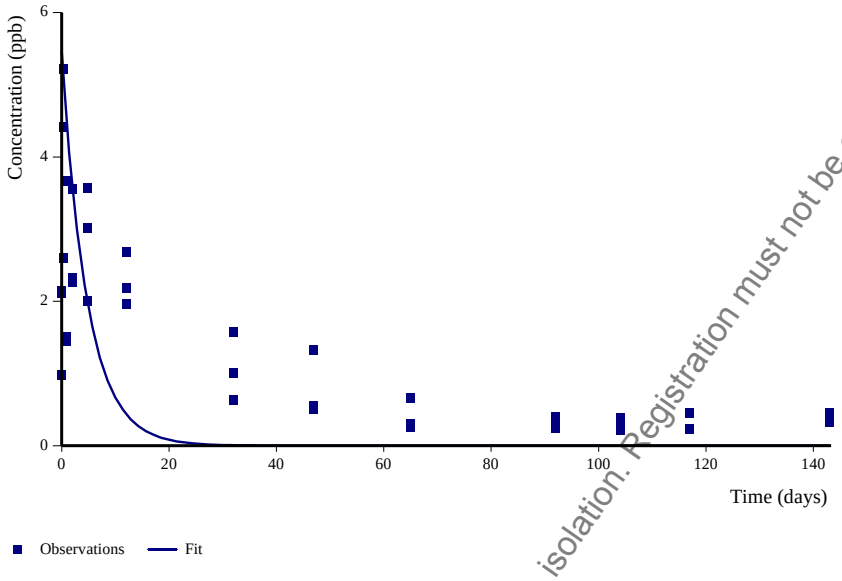


Parameter	Value
Parent_0	5.38
k_Parent	0.21
f_Parent_to_A1	0.45
k_A1	0.0315

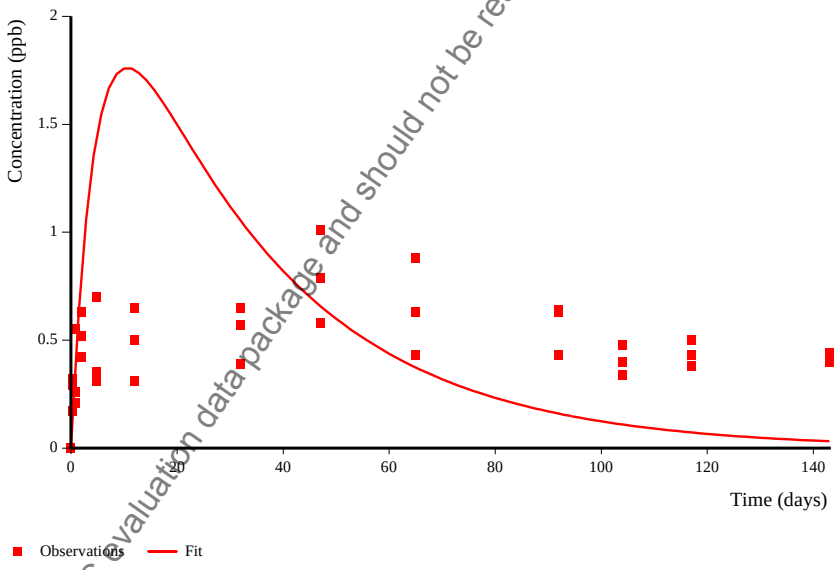
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Figure B.8.180 Theoretical vs measured residues of XDE-729 methyl and X11393729 in soil using mean SFO/SFO optimised parameters (UK, Spring)

(a) Parent



(b) Acid

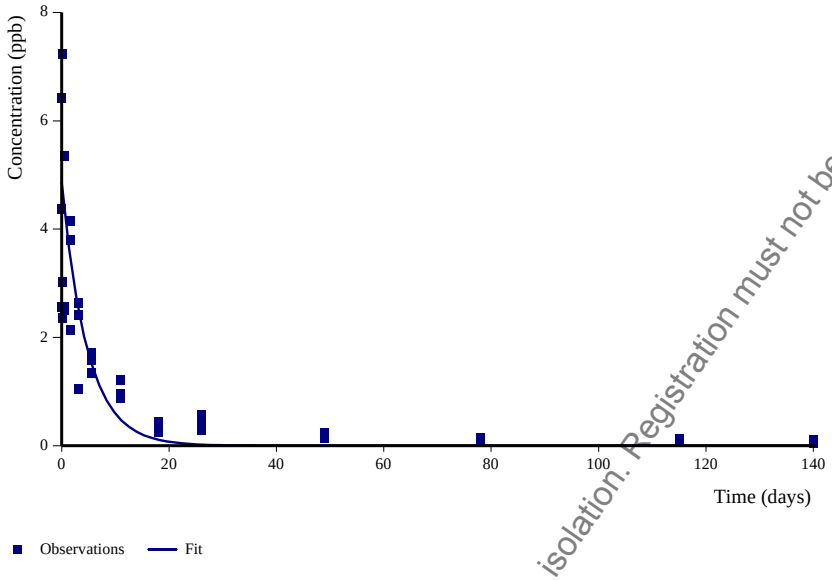


Parameter	Value
Parent_0	5.47
k_Parent	0.21
f_Parent_to_A1	0.45
k_A1	0.0315

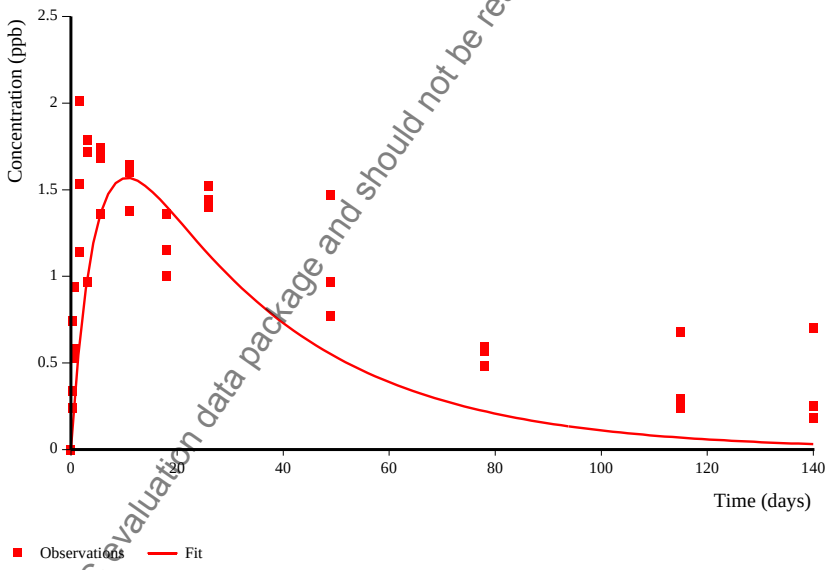
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Figure B.8.181 Theoretical vs measured residues of XDE-729 methyl and X11393729 in soil using mean SFO/SFO optimised parameters (UK, Autumn)

(a) Parent



(b) Acid

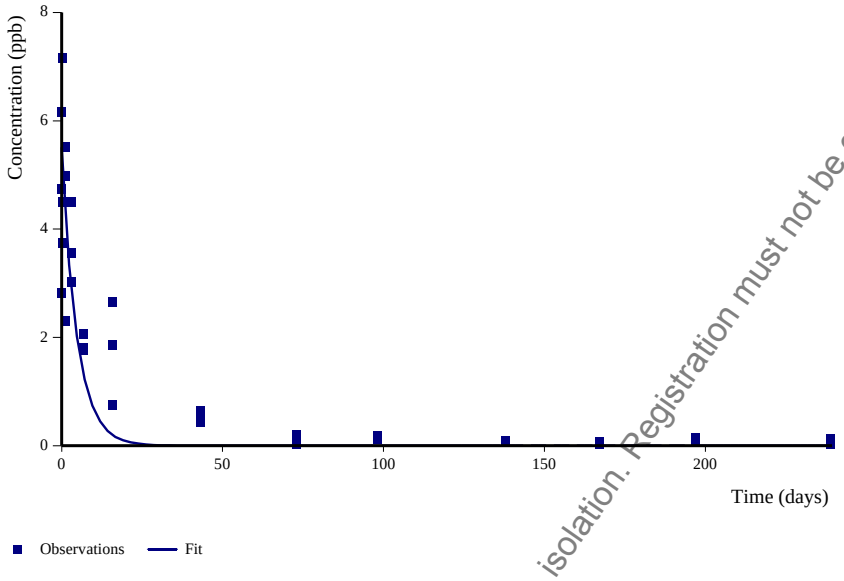


Parameter	Value
Parent_0	4.87
k_Parent	0.21
f_Parent_to_A1	0.45
k_A1	0.0315

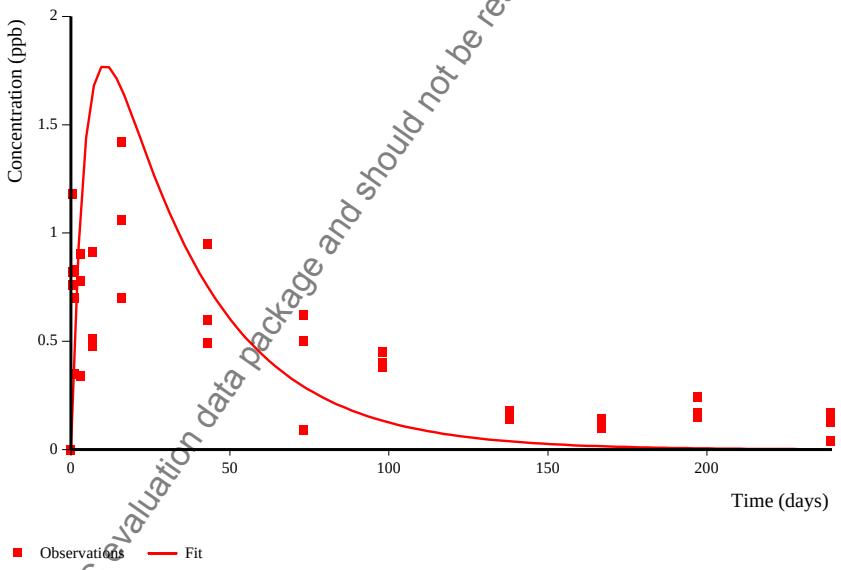
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Figure B.8.182 Theoretical vs measured residues of XDE-729 methyl and X11393729 in soil using mean SFO/SFO optimised parameters (Spain, Spring)

(a) Parent



(b) Acid

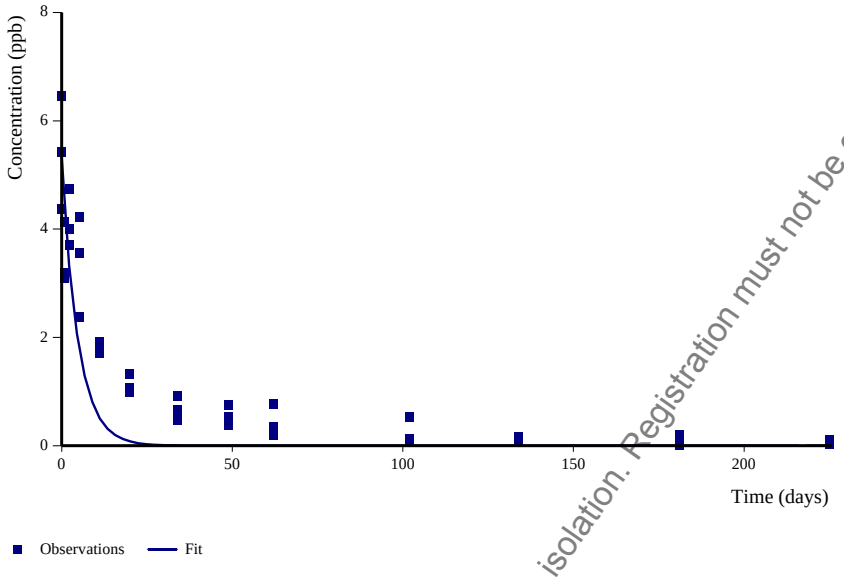


Parameter	Value
Parent_0	5.51
k_Parent	0.21
f_Parent_to_A1	0.45
k_A1	0.0315

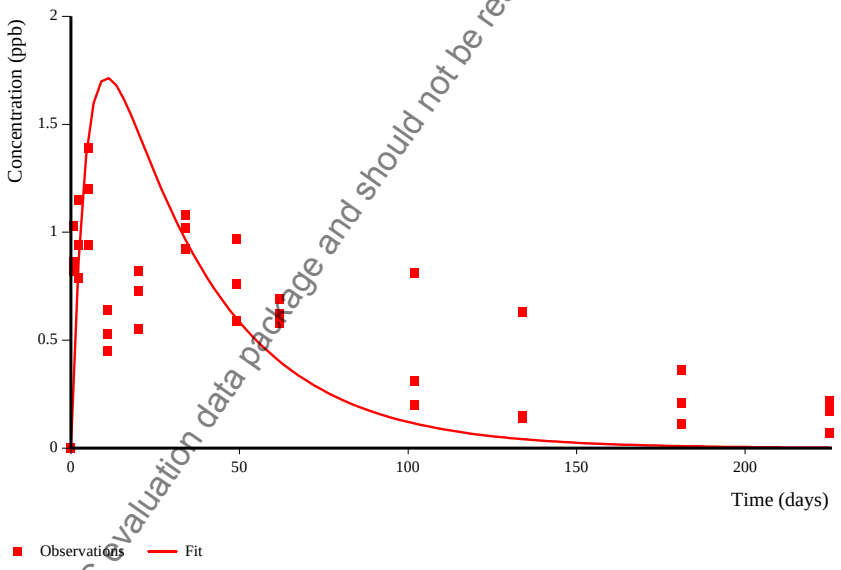
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Figure B.8.183 Theoretical vs measured residues of XDE-729 methyl and X11393729 in soil using mean SFO/SFO optimised parameters (Spain, Autumn)

(a) Parent



(b) Acid

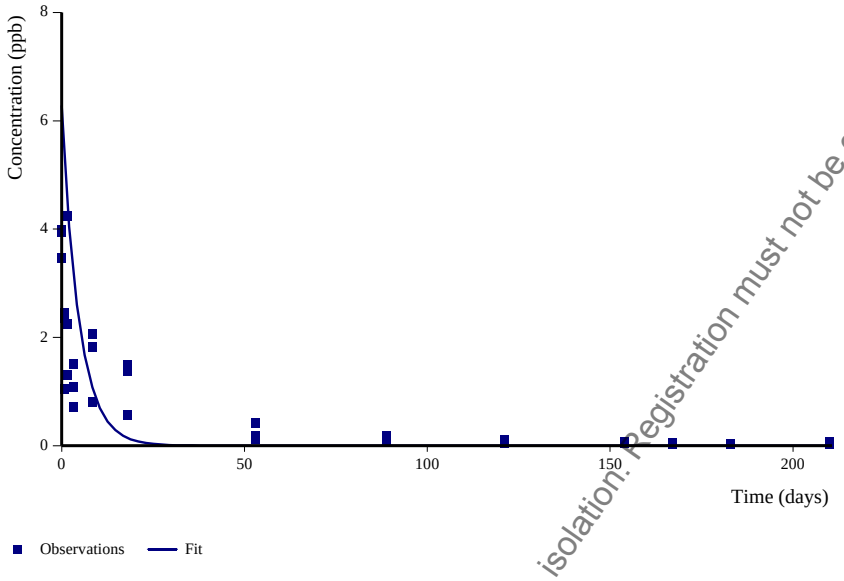


Parameter	Value
Parent_0	5.33
k_Parent	0.21
f_Parent_to_A1	0.45
k_A1	0.0315

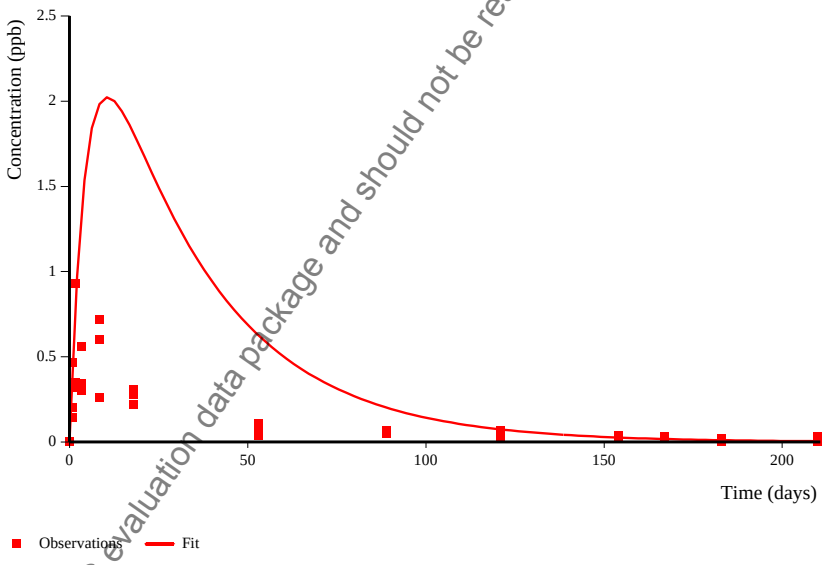
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Figure B.8.184 Theoretical vs measured residues of XDE-729 methyl and X11393729 in soil using mean SFO/SFO optimised parameters (France, Spring)

(a) Parent



(b) Acid

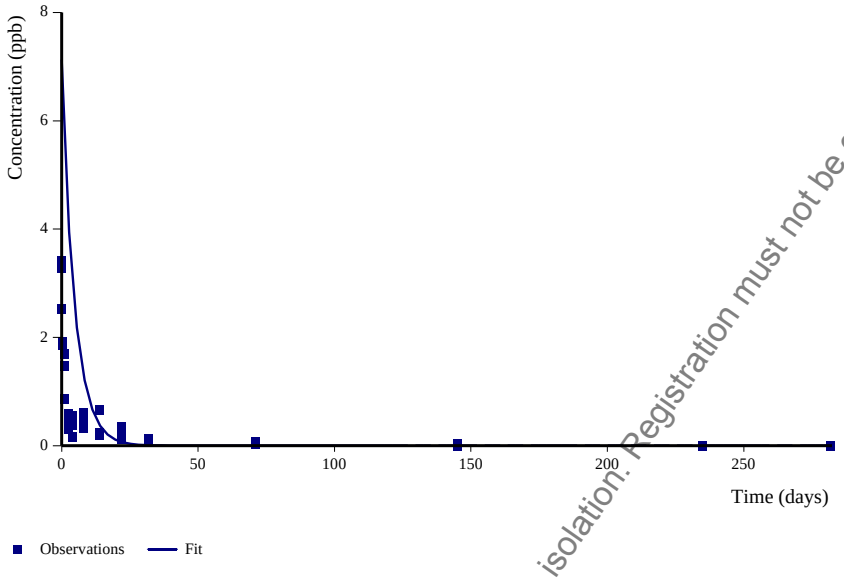


Parameter	Value
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f_Parent_to_A1	0.45
k_A1	0.0315

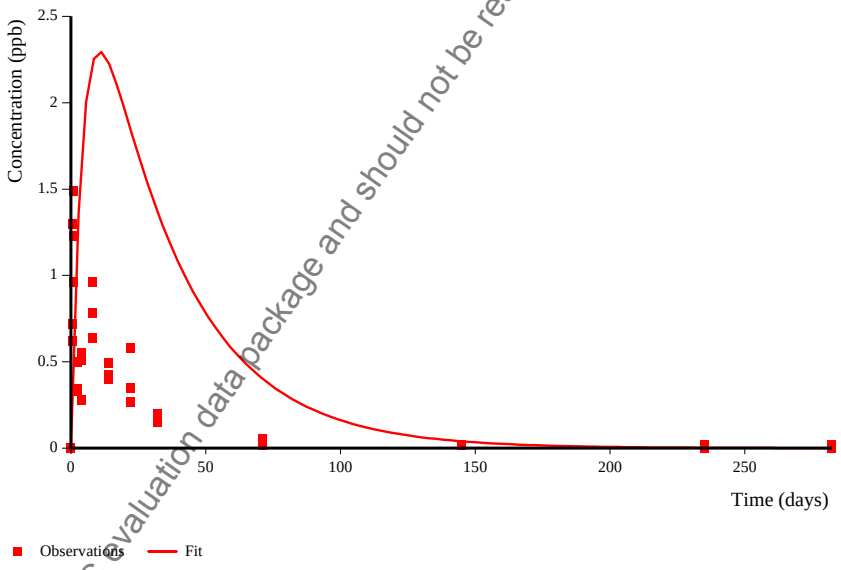
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Figure B.8.185 Theoretical vs measured residues of XDE-729 methyl and X11393729 in soil using mean SFO/SFO optimised parameters (France, Autumn)

(a) Parent



(b) Acid

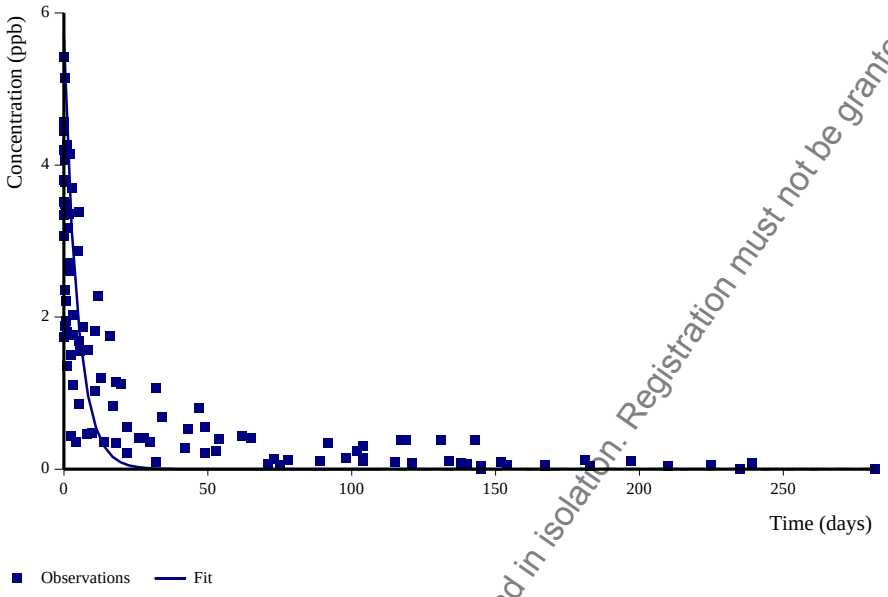


Parameter	Value
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f_Parent_to_A1	0.45
k_A1	0.0315

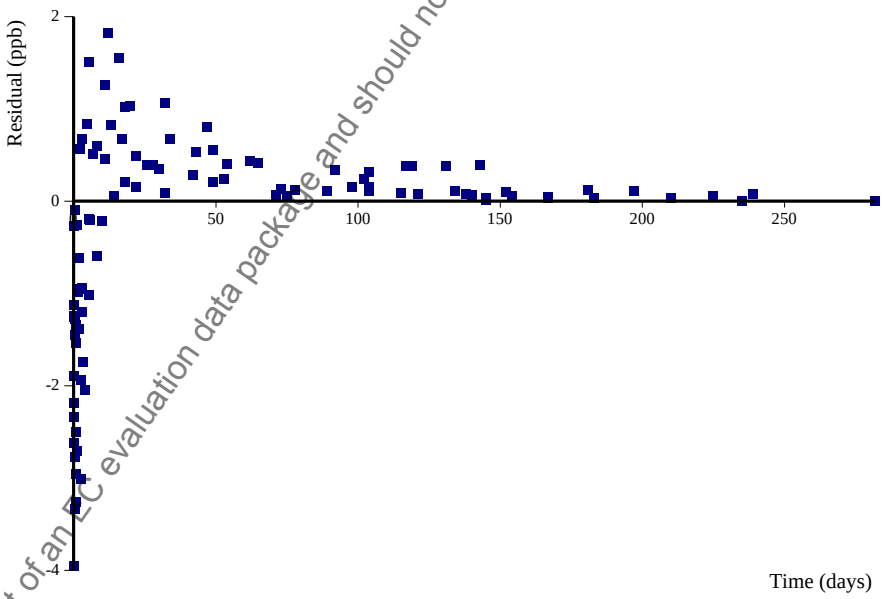
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Figure B.8.186 Theoretical vs measured residues of XDE-729 methyl and X11393729 in soil using mean SFO/SFO optimised parameters based on average residues for all eight trials data sets

(a) Parent Observed v Predicted



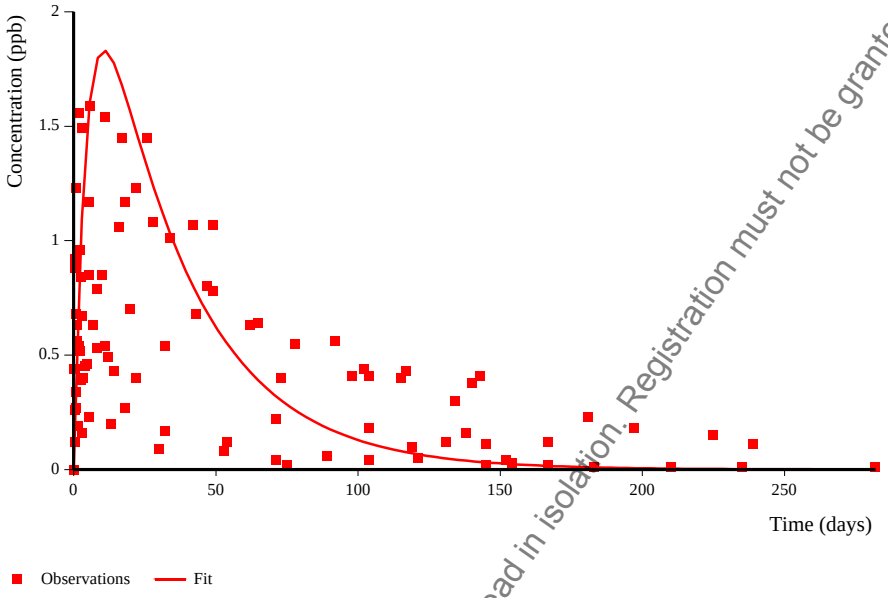
(b) Parent Residuals



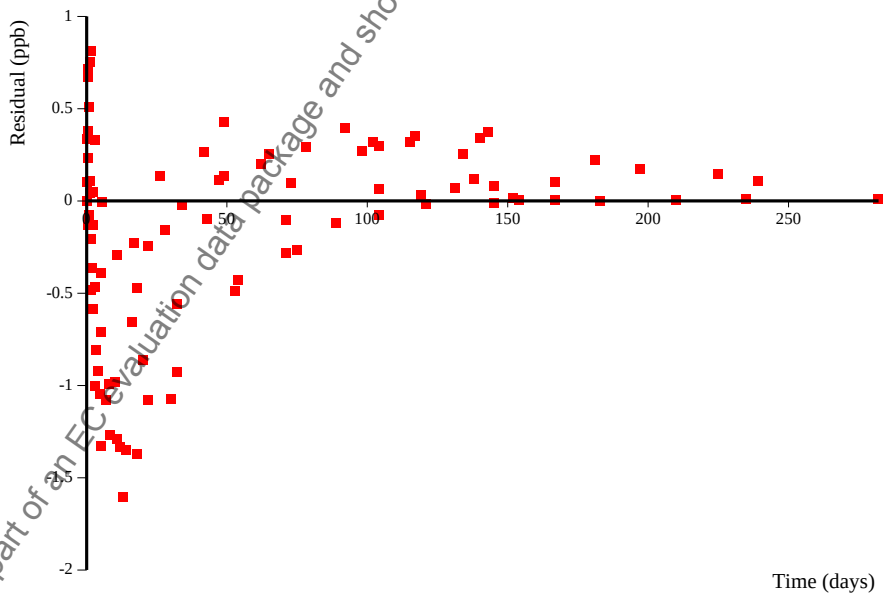
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Figure B.8.187 Theoretical vs measured residues of XDE-729 methyl and X11393729 in soil using mean SFO/SFO optimised parameters based on average residues for all eight trials data sets (continued)

(c) Acid Observed v Predicted



(d) Acid Residuals



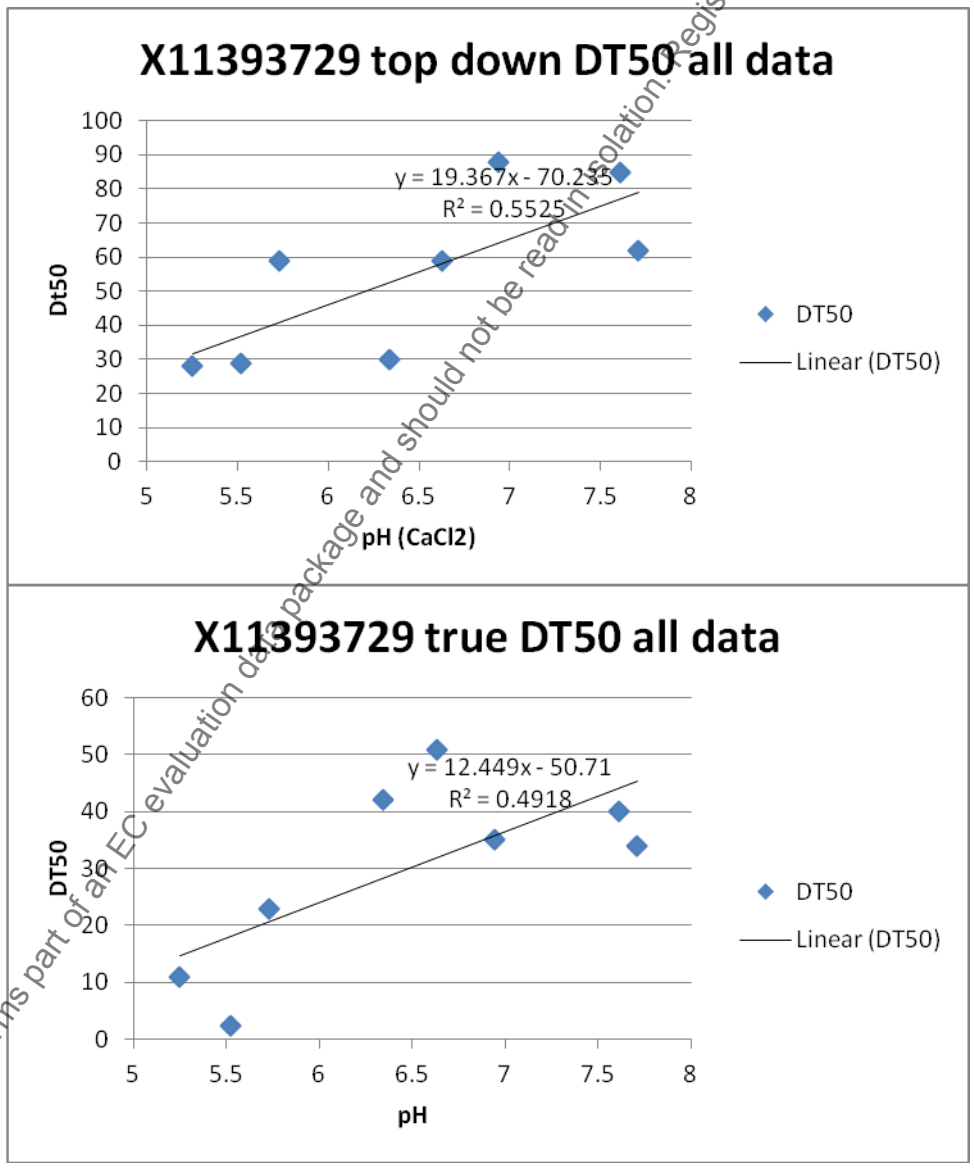
Overall, the RMS notes the consistent over-prediction of the parent degradation rate. This is to be expected from the fitting observed previously. For X11393729, in some individual cases the mean parameters clearly over predict the metabolite profile, in some they under-predict, and in some there is a tendency to over predict highest concentrations whilst under-predicting the later residues. The final figure above using

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average data from individual time points from all sites illustrates the overall pattern from using mean degradation parameters. This figure clearly shows that for X11393729 there is a reasonable over prediction of peak residues, and an under prediction from approximately 100 days onwards, the initial very rapid formation is missed, but not by a large number of days. The RMS notes that the extent of over predicting residues is much greater than the extent of under predicting residues.

For X11393729, top down DT50 varied from 28-88 days, true degradation DT50 varied from 2.3 – 51 days. There appeared to be a trend to slowing degradation rate with increasing pH with top down DT50 values, but this was not consistent across the eight trials. The shortest DT50 was at the lowest pH, but the longest DT50 was at just under pH7. The relationship is shown below.

Figure B.8.188 Relationship of X11393729 DT50 with pH, normalised field dissipation studies, (i)top down SFO DT50 and (ii) true degradation rate



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In light of the apparent trend for pH dependency of degradation in the laboratory incubations, it is considered that pH dependence of degradation should be taken into account. However, the RMS considers that it would be useful to consider by expert discussion whether this range of DT50 would be considered to fall within that expected by virtue of natural variation.

It is noted that the Applicant has submitted exposure modelling for ground- and surface water (see section B.8.6) which does not take potential pH dependency into account. Overall, the RMS considers that the mean parameters proposed by the Applicant for X11393729 are reasonable representation of the formation and decline of this metabolite, but further consideration of whether pH dependency for this metabolite needs to be taken into account is required. In the meantime, the Applicants exposure modelling ignoring any pH dependencies has been presented at section B.8.6.2.

Metabolite X11449757

In a similar manner to that described for X11393729, mean parameters were fitted to each individual dataset for X11449757 and also to the combined data sets. The RMS notes from the table below that the fitting for X11449757 was less successful, as reflected in the descriptions of individual datasets above. Top down parameters are proposed for simpler exposure calculation such as PECsoil.

Table B.8.114 Kinetic endpoints for sequential exposure modelling of XDE-729 methyl, X11393729 (Acid) and X11449757 (X-757).

		Parent + Acid + X-757 (SFO+SFO+ SFO)						Top-down SFO	
Location	**Season**	**Parent DT50**	**Acid DT50**	**Acid FF**	**X-757 DT50 (d)**	**X-757 FF**	***Chi² Err (%)***	**X-757 DT50 (d)**	***Chi² Err (%)***
Germany	Spring	NC	NC	NC	NC	NC	*NC*	NC	*NC*
Germany	Autumn	1.9	43	0.41	8.9	1.00	*16*	76	*4.6*
UK	Spring	NC	NC	NC	NC	NC	*NC*	60	*13*
UK	Autumn	1.0	54	0.35	22	0.22	*37*	NC	*NC*
Spain	Spring	NC	NC	NC	NC	NC	*NC*	84	*26*
Spain	Autumn	NC	NC	NC	NC	NC	*NC*	60	*12.6*
France	Spring	5.8	1.9	1.00	73	0.18	*36*	107	*21*
France	Autumn	0.7	8.6	0.36	9.5	1.00	*30*	37	*11*
	Geomean	**1.7**	**14**	0.48	**19**	0.45	-	**67**	-
	Average	2.4	27	**0.53**	28	**0.60**	-	71	-
	Median	1.5	26	0.39	16	0.61	-	68	-

FF = formation fraction NC = not calculated

Figures showing the predicted curves for X11449757 using the above mean parameters are shown below. The Applicant did not provide the graphs for the parent and X11393729 curves as they considered them to be similar to the curves obtained for parent and X11393729 without X11449757.

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Figure B.8.189 Theoretical vs measured residues of X11449757 in soil using mean SFO/SFO optimised parameters from sequential SFO model with XDE-729 methyl and X11393729 (Germany, Spring)

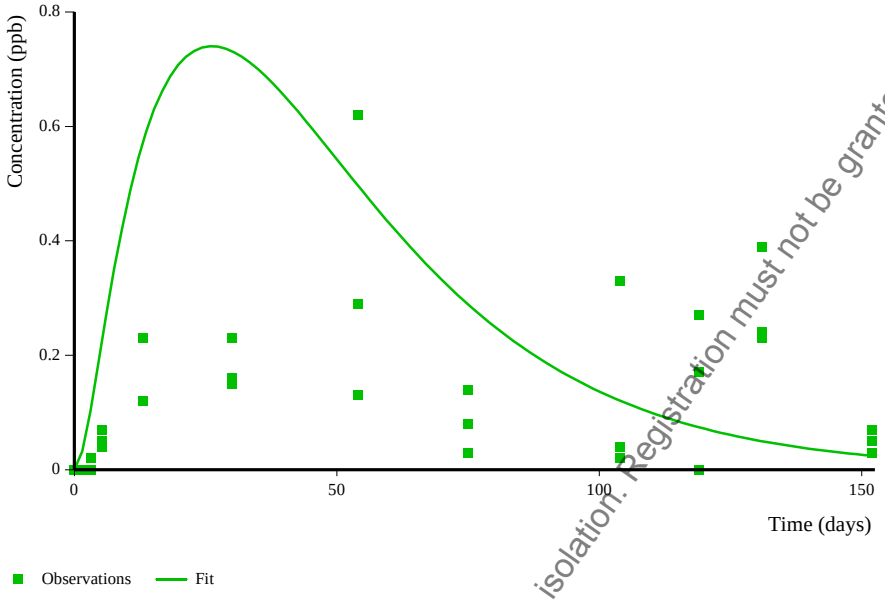
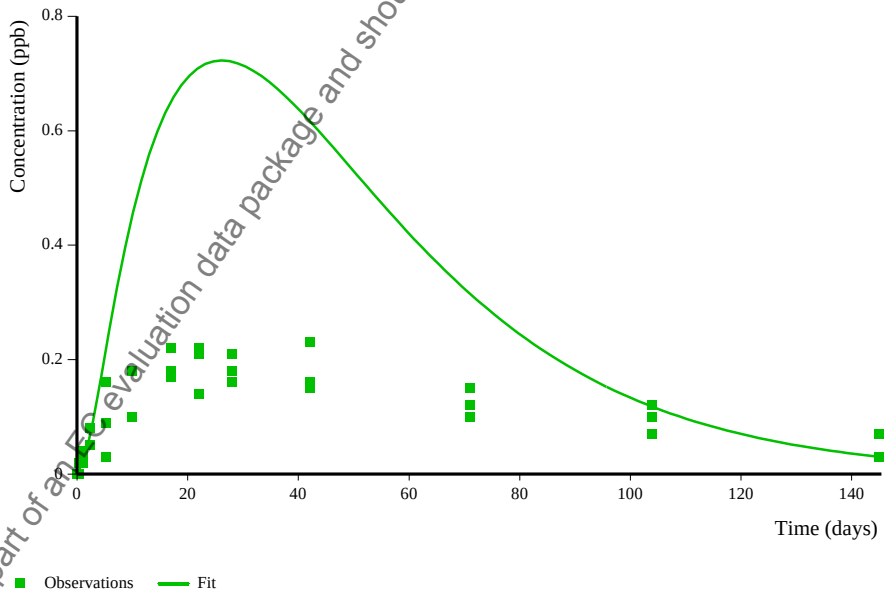
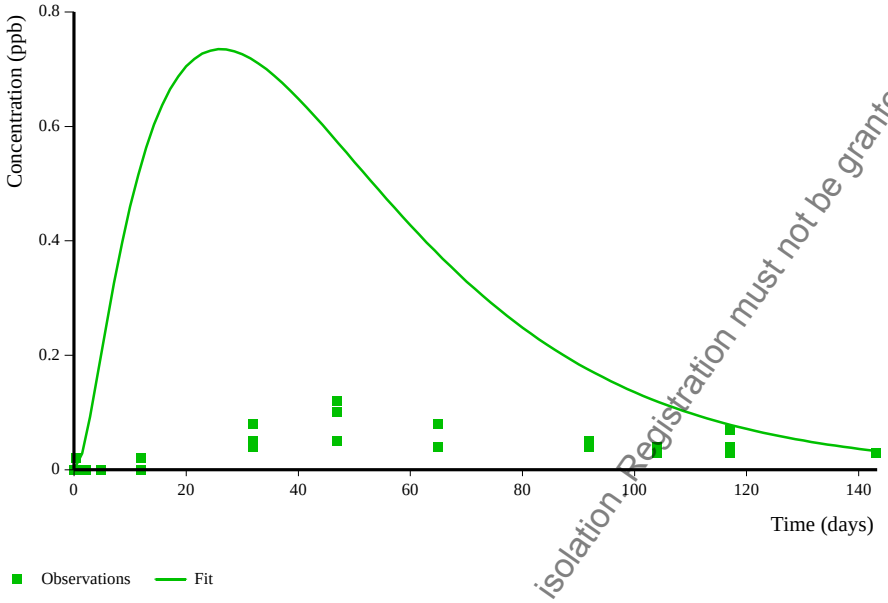


Figure B.8.190 Theoretical vs measured residues of X11449757 in soil using mean SFO/SFO optimised parameters from sequential SFO model with XDE-729 methyl and X11393729 (Germany, Autumn)



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Figure B.8.191 Theoretical vs measured residues of X11449757 in soil using mean SFO/SFO optimised parameters from sequential SFO model with XDE-729 methyl and X11393729 (UK, Spring)



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Figure B.8.192 Theoretical vs measured residues of X11449757 in soil using mean SFO/SFO optimised parameters from sequential SFO model with XDE-729 methyl and X11393729 (UK, Autumn)

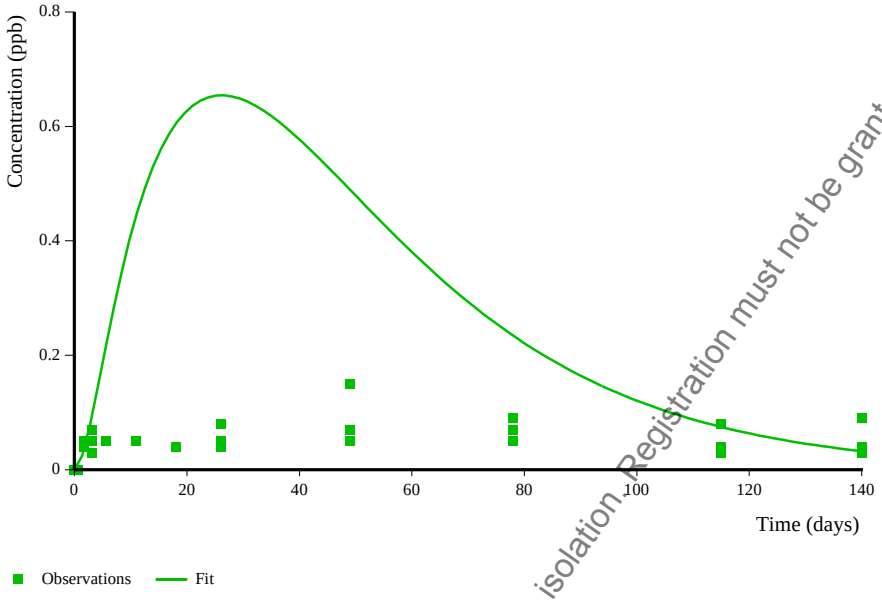
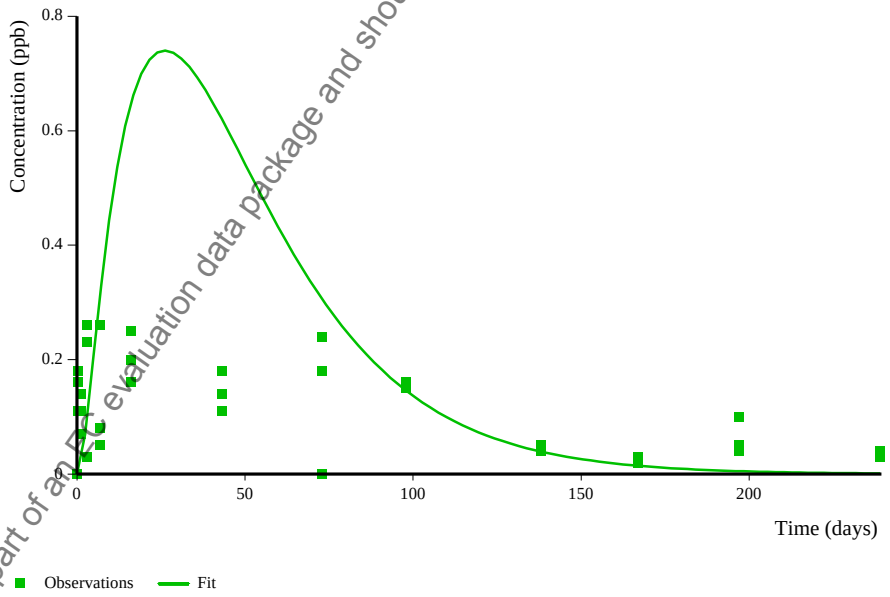


Figure B.8.193 Theoretical vs measured residues of X11449757 in soil using mean SFO/SFO optimised parameters from sequential SFO model with XDE-729 methyl and X11393729 (Spain, Spring)



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Figure B.8.194 Theoretical vs measured residues of X11449757 in soil using mean SFO/SFO optimised parameters from sequential SFO model with XDE-729 methyl and X11393729 (Spain, Autumn)

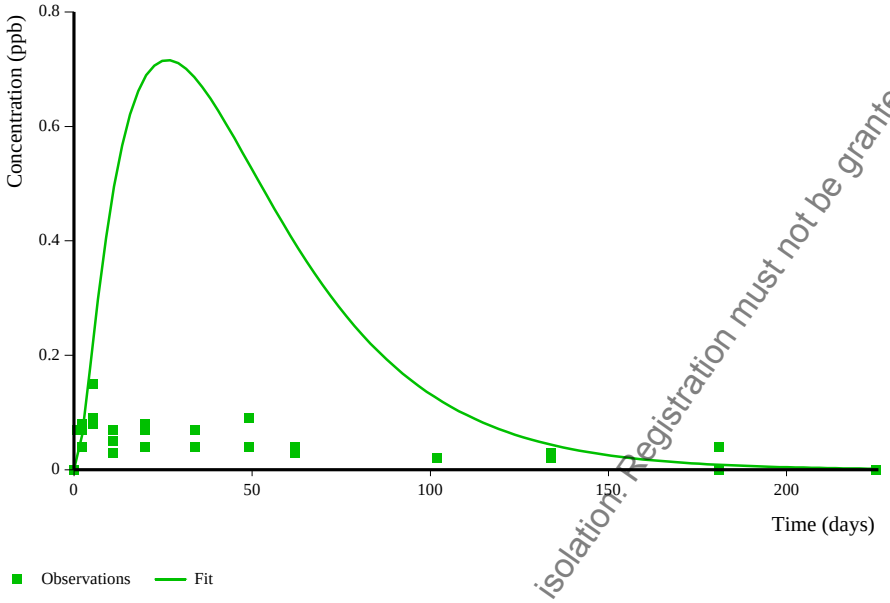
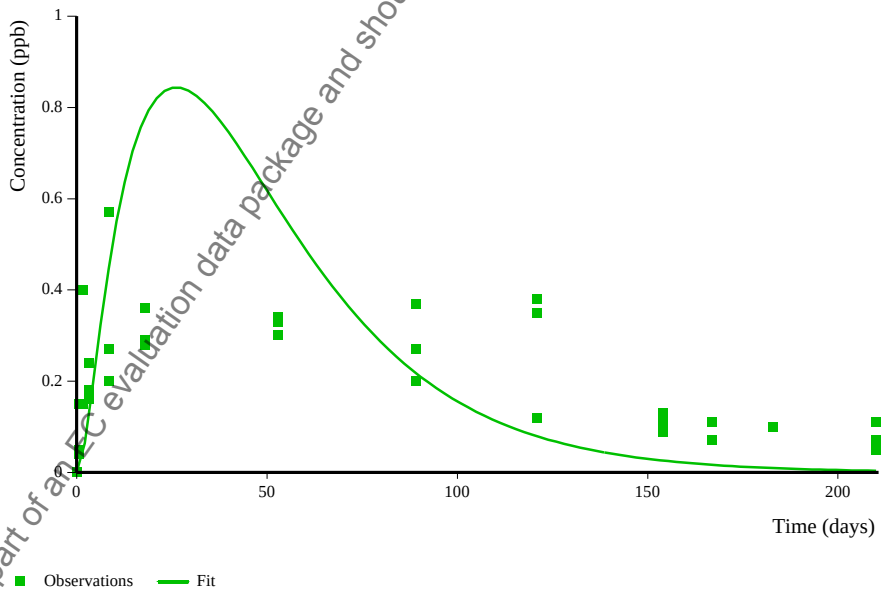
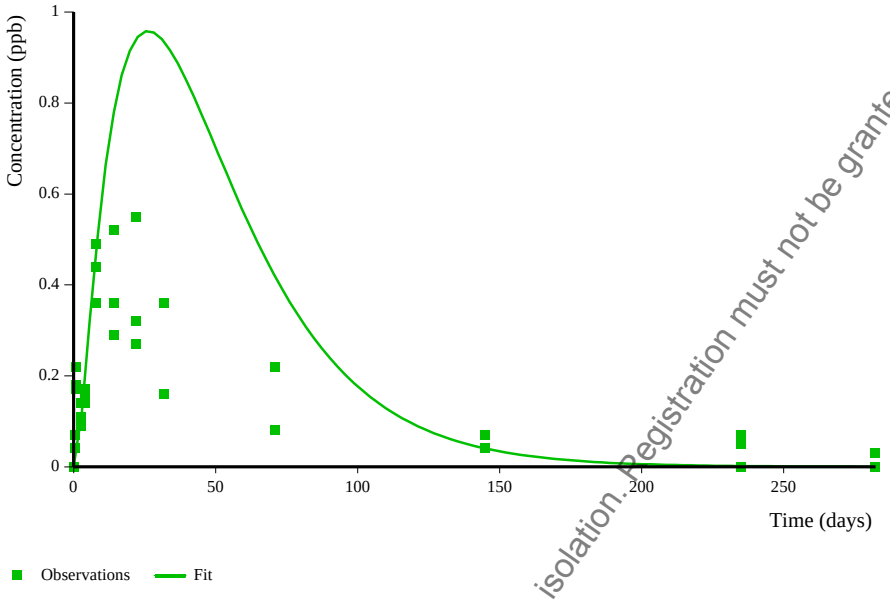


Figure B.8.195 Theoretical vs measured residues of X11449757 in soil using mean SFO/SFO optimised parameters from sequential SFO model with XDE-729 methyl and X11393729 (France, Spring)



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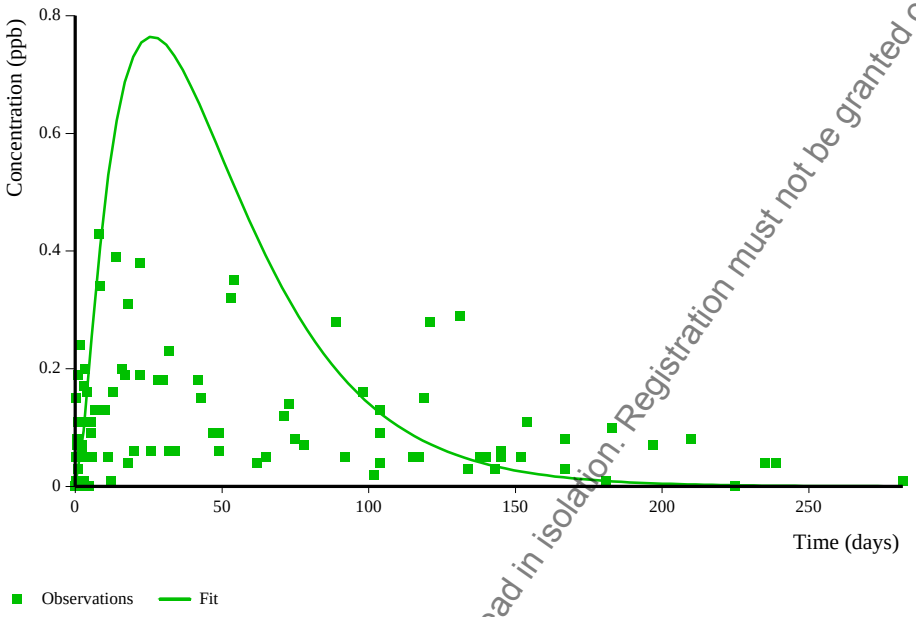
Figure B.8.196 Theoretical vs measured residues of X11449757 in soil using mean SFO/SFO optimised parameters from sequential SFO model with XDE-729 methyl and X11393729 (France, Autumn)



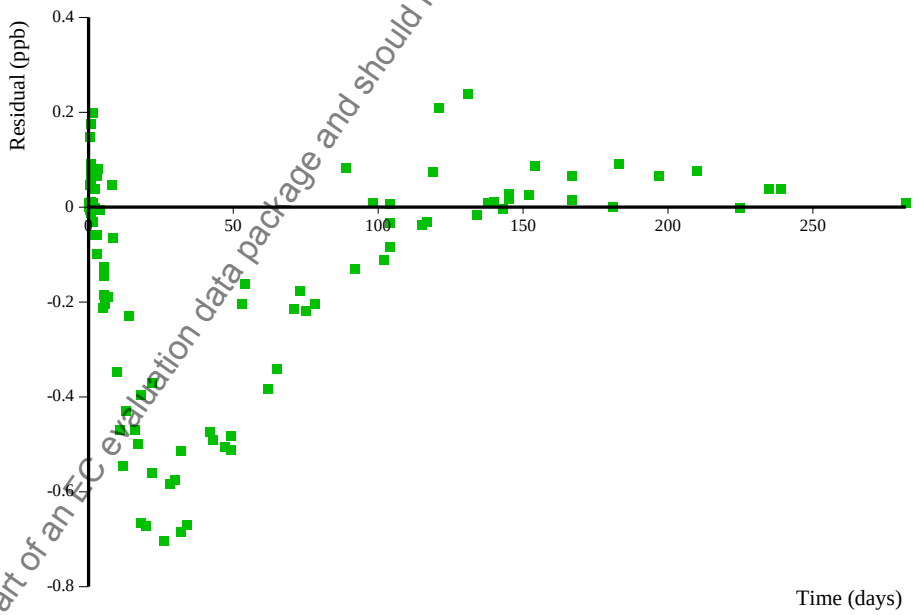
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Figure B.8.197 Theoretical vs measured residues of X11449757 in soil using mean SFO/SFO optimised parameters from sequential SFO model with XDE-729 methyl and X11393729 based on average residues for all eight trials data sets

(a) X-757 Observed v Predicted



(b) X-757 Residuals

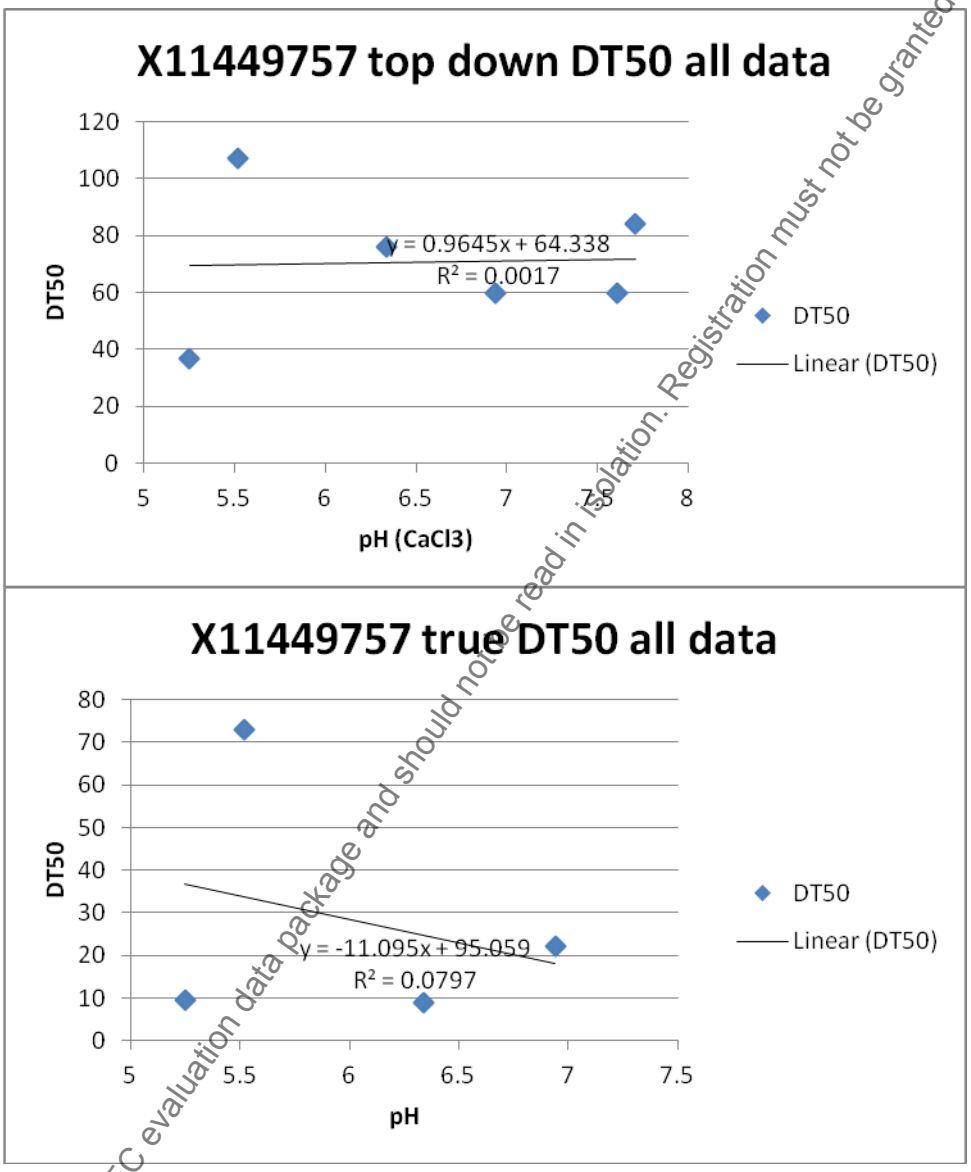


The mean parameters tend to provide an even greater relative over-estimate of X11449757. The extent of under predicting residues towards the end of the time period is smaller than for X11393729. The RMS considers that the proposed mean parameters are appropriate for separate sequential exposure modelling of X11449757.

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The RMS assessed the top down DT50 values for X11449757 from the field dissipation studies and found that there was no clearly observable trend for any relationship with pH, as shown below.

Figure B.8.198 Relationship of X11449757 DT50 with pH, normalised field dissipation studies, (i) top down SFO DT50, (ii) true SFO DT50



The proposed kinetic endpoints for exposure modelling are shown below. The RMS can agree to these albeit with some reservations regarding potential pH dependence of degradation of X11393729.

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Table B.8.115 Summary of recommended kinetics parameters for XDE-729 methyl and its metabolites for inputs to models

Component to be Modelled	Parameter	Value	Comment
Parent only	DT50(Parent) k (Parent)	20 d 0.0347 d^{-1}	Geomean from SFO fit after 10 mm rain (n = 8)
X11393729	DT50(Parent) k (Parent)	3.3 d 0.210 d^{-1}	Geomean from sequential SFO/SFO* fit with Parent + Acid (n = 8)
	DT50(Acid) k (Acid)	22 d 0.0315 d^{-1}	
	FF (Parent→Acid)	0.45	Average from sequential SFO* fit (n = 8)
X11449757	DT50(Parent) k (Parent)	1.7 d 0.408 d^{-1}	Geomean from sequential SFO/SFO/SFO fit with Parent + Acid + X-757 (n = 4)
	DT50(Acid) k (Acid)	14 d 0.0495 d^{-1}	
	DT50(X-757) k (X-757)	19 d 0.0365 d^{-1}	
	FF (Parent→Acid)	0.53	Average from sequential SFO fit (n = 4)
	FF (Acid→X-757)	0.60	

* DFOP/SFO fit for Germany/Spring data set

(Jackson 2012? & 2013)

B.8.1.6 Summary & assessment – Soil studies

Route of degradation – aerobic soil

A study was conducted to investigate aerobic route of degradation of XDE-729 methyl on four soils. A similar study was also conducted on sterile samples of the same soils. In general the soils were considered to represent an appropriate range of soil properties, possessing a range of pH from moderately acid to weakly basic. Initial microbial content in three of the four soils appeared to be less than 1% of the organic carbon content, but the RMS does not consider this to be an unacceptable deviation from the OECD 307 study guideline. Whilst three of the four soils had a lower microbial biomass than the 1% of total organic carbon recommended by the OECD 307 guideline, the acceptability of the microbial viability of these soils could also be partially inferred from the different behaviour observed in the truly sterile soils, particularly in relation to the degradation of the metabolite X11393729. Study temperature and moisture conditions were 20ºC and 50% of MHC. The study was conducted in the dark. Acceptable mass balances were obtained in all four soils.

Extraction procedures appear to have been designed to extract as much radioactivity as possible without adversely altering the identity of the substances extracted. Given the instability of the parent under moderately acid and alkaline conditions, the Applicant found that more commonly used extraction strategies resulted in hydrolysis of extracted substances and/or loss of radioactivity. This explains the use of the accelerated solvent extraction, and this is considered to be reasonable. However, in spite of the efforts to obtain a method capable of extracting the residue without changing its nature, XDE-729 methyl still formed high levels of unextracted residues, even with exhaustive extraction techniques. In practice, the Uniform Principles criteria

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of '*no authorisation where.....during laboratory tests, form non-extractable residues in amounts exceeding 70% of the initial dose after 100 days with a mineralisation rate of less than 5% in 100 days.....*' are met in the RefSol 03-G soil where the incubation with pyridine-labelled XDE-729 methyl reached 73.8% AR unextracted residue with 3.3% mineralisation. Two of the other soils also exceeded 70% unextracted residues during the study but also had greater than 5% mineralisation and thus do not officially meet the strict Uniform Principles criteria. Nevertheless, the RMS considers that the effects of possible accumulation of unextracted residue must be addressed as specified by the Uniform Principles.

With this in mind, the applicant conducted a kinetic assessment to obtain degradation parameters for unextracted residues formed in the aerobic route and rate of degradation study. The modelling generally appeared to be acceptable although it must be borne in mind that formation and turn-over of soil organic matter generally tends to be a long-term process. The maximum duration of the study was 153 days. Thus there may be significant uncertainty over the accuracy of the predictions as the unextracted residue levels at study end were either still increasing or only experiencing a small decline; optimised parameters often showed relatively high standard deviation and at times confidence intervals including zero and resulting DT50 parameters were extrapolated well beyond the study duration. However in most cases the total extractable residue had fallen below 10% AR by study end. With these caveats in mind, the modelling predicted the extractable residue to decline biphasically and there was reasonable visual simulation of the unextracted residue using FOMC kinetics for the extractable residue followed in sequence by SFO kinetics for the unextracted residue. Applying the predicted formation and decline of unextracted residues to a simulation of annual applications of XDE-729 methyl, the maximum accumulation was predicted to be 0.87 - 3.83 times the initial parent residue (on a molar basis). The PY label predicted greater accumulation than the PH label. Maximum accumulation was predicted within 10-15 years for the PY label and 5-10 years for the PH label. Given that there is much uncertainty over the extent of accumulation, the RMS considers that the maximum accumulation factor of 3.83x the initial parent dose should be used for risk assessment purposes. However, it must be borne in mind that even using the highest accumulation factor may not necessarily reflect highest levels of accumulation and the extent of. It should be noted that the Applicant also conducted a separate study investigating formation of unextracted residues in two soils to support a study to test the effect of unextracted residues on earthworms. This generally noted lower levels of unextracted residues than seen in the standard route and rate of degradation studies, however, reasonable levels of unextracted residues had developed by approximately 30 days after treatment, i.e. the time at which earthworms were introduced into the effects study. An assessment of possible accumulation of unextracted residues is presented in section B.8.3.

As stated above, XDE-729 methyl gave rise to relatively high levels of unextracted residue in microbially active soils. Generally, the pyridine ring-labelled material tended to give higher levels of unextracted residues, with 62.5 – 82.5% AR at 104 DAT; the phenyl ring-labelled material gave 59.5 – 64.4% AR as unextracted at 104 DAT. However, mineralisation was moderate with 1.8 – 17.3% AR as CO_2 at 104 DAT with the phenyl ring-labelled material and 3.3 – 21.0% AR at 104 days with the pyridine ring-labelled material. Mineralisation would suggest that the molecule is undergoing significant degradation, as would the presence of polar and 'other'

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material. In particular, the RefSol 03-G soil which met the Uniform Principles unextracted residue/mineralisation criteria, showed up to 4.4% polar material and up to 7.2% of 'other' comprising a number of unidentified components, none of which exceeded 5% AR. Again, this suggests that significant degradation is occurring to the a.s. and its primary metabolites in microbially active soils rather than unchanged or relatively unchanged substance being incorporated into soil as unextracted residue. In the sterile soils, much lower levels of mineralisation and formation of unextracted residues were seen at equivalent sample times, suggesting that microbial activity is responsible for degradation of the active substance and metabolites and incorporation of the radiolabelled residue into unextracted residues. Results of the sterile incubations also suggest that there was a slowing of the degradation of XDE-729 methyl, although it was still relatively rapid (non-sterile soil DT50 values in the range of 1 – 2 days and DT90 values in the range 4 – 16 days; sterile soil DT50 in the range 7-12 days and DT90 values in the range 22-75 days. This suggests that microbial activity is involved in degradation of XDE-729 methyl, but abiotic processes are also likely to be involved. The magnitude of degradation rates seen in the hydrolysis study (section B.8.4.1) suggests that simple hydrolysis may not be the dominant abiotic process, but that there may be some form of catalysed process occurring to maintain the relatively rapid degradation of the a.s. in the absence of an active microbial population. In addition, the sterile incubations demonstrate that degradation of X11393729 is clearly microbially mediated, with an accumulation of residues of this metabolite at high levels at the end of the study in sterile incubations, as opposed to rapid formation followed by relatively fast decline under non-sterile conditions. This would further support the theory that the formation of unextracted residues following application of XDE-729 methyl is due to microbial degradation processes.

The Applicant also conducted a further study on two soils to explore formation of unextracted residues. This was to support Ecotoxicological testing intended to assess the effects of accumulated unextracted residues on earthworms. Both soils, similar to two soils used in the standards route and rate of degradation study, were dosed with three different concentrations of Py-labelled XDE-729 methyl. The study lasted for 89 days. At this time, levels of unextracted residues had increased to 67.8 – 81.7% AR

Three metabolites were positively identified. The primary metabolite, X11393729, is the demethylated carboxylic acid metabolite and can be thought of as the acid formed by hydrolysis of the ester bond; the methyl group is lost from the pyridine ring. High levels were formed relatively quickly, maximum levels being 38.2 – 72.7 % AR at 3 - 7 DAT. The subsequent study in sterile samples of the same soils demonstrated slower transformation of XDE-729 methyl to the acid suggesting that although an abiotic process was capable of forming the acid, microbial degradation is still likely to be significant in the formation of the acid. The sterile incubations also demonstrated that microbial degradation is also likely to be responsible for degradation of X11393729 as its concentrations had not apparently peaked during the 62 day sterile incubation in all four soils, whereas concentrations had markedly declined by this point in the microbially active incubations.

The secondary metabolite in terms of concentration was X11449757 which reached 2.7 – 17.4 % AR at 3 - 14 DAT. Generally the peak of formation of X11449757 was one sample time after the peak of X11393729 formation suggesting relatively rapid formation of X11449757 from X11393729. X11449757 appears to be formed from

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X11393729 by loss of the methyl group associated with the phenyl ring, forming a hydroxyl group.

A further metabolite, X11406790, was also identified, but the maximum amount seen was 1.4% AR at 3 DAT. It is considered by the RMS that this metabolite does not need any further consideration in environmental exposure assessment for soil or groundwater. However, both X11393729 and X11449757 must be included in environmental exposure assessment for soil and groundwater. X11406790 appears to be formed from XDE-729 methyl by loss of the methyl group associated with the phenyl ring, forming a hydroxyl group.

Relatively low levels of polar material (presumably eluting very quickly from the HPLC column at the solvent front) and 'others' (unidentified components, none of which individually formed 5% AR at any one time) were formed during the incubations.

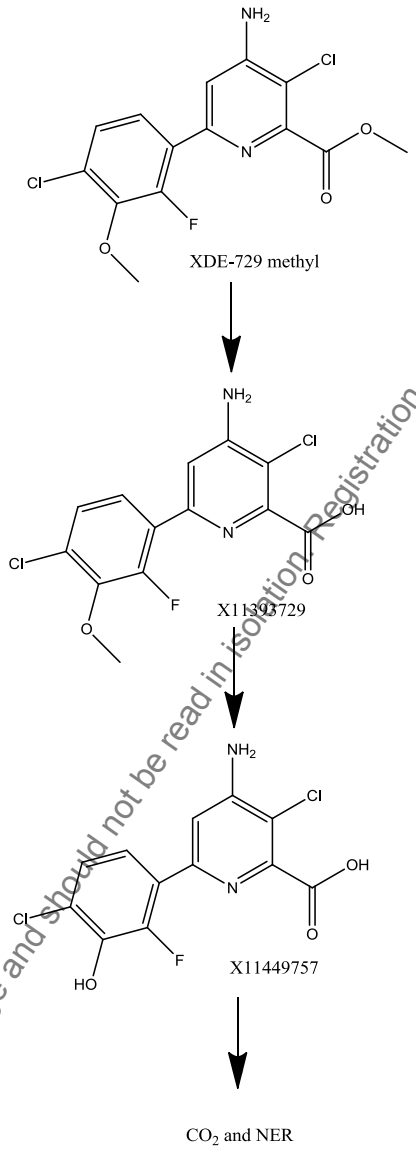
An incubation at 10ºC was also conducted in a single soil. The same pattern of metabolite formation was seen at the lower temperature compared to the 20ºC incubation, but degradation and formation processes appeared to be slowed down as might be expected. Parent degradation rate appeared to be 2x that at 20ºC; the top down DisT50 for X11393729 was approx 2.8x longer than at 20ºC.

The proposed metabolic pathway of XDE-729 methyl under dark, aerobic soil conditions is presented below.

The RMS considers that the metabolites X11393729 and X11449757 should be included in environmental exposure assessment for soil, groundwater and surface water/sediment (as soil metabolites potentially reaching surface water).

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Figure B.8.199 Proposed metabolic pathway of XDE-729 methyl under dark, aerobic soil conditions



Route of degradation – anaerobic soil

A study investigating the anaerobic route of degradation of XDE-729 methyl in four soils was conducted. Study conduct was generally appropriate and was of a similar design to the aerobic studies described above. The study was conducted with a two day aerobic period, corresponding to approximately one half-life, before flooding and purging with nitrogen to initiate anaerobic conditions. This is in-line with the OECD 307 study guideline and is thus appropriate. Reference to redox potential and dissolved oxygen content in the incubations suggest that anaerobic conditions developed over time post-flooding of the soils.

The use of the same four soils as in the aerobic study allows a good comparison of behaviour under anaerobic and aerobic conditions. The extent of both mineralisation and formation of unextracted residues were significantly reduced under anaerobic conditions, and there was relatively little difference between radiolabels. The

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maximum mineralisation and unextracted residues under anaerobic conditions were 0.8% AR and 48.6% AR respectively after 100 days. This compares to maxima of 21% mineralisation and 82.5% AR unextracted residue at 100 DAT in the aerobic study.

The profile of degradation was very similar for XDE-729 methyl, and it is possible that the majority of degradation had taken place before the establishment of truly anaerobic conditions had taken place. However, it still appears that degradation of XDE-729 methyl to form X11393729 was largely unaffected by imposition of anaerobic conditions; degradation rates calculated from the day of flooding ranged from DT50s of 0.9 – 2.8 days with DT90s of 3.1 – 29 days. The first degradation product appears to be X11393729 which apparently underwent slower degradation under anaerobic conditions but was still degraded to an appreciable extent; SFO top down DT50s range from 21 – 100 days. However, there were clear indications that metabolite X11449757 exhibited much slower degradation with accumulation to levels of up to 54.3% at or close to the end of the study (120 days); it was not possible to calculate top down degradation rates for this metabolite due to no or insufficient decline by the end of the study suggesting potential persistence under anaerobic conditions. However, the RMS considers that under the majority of agricultural conditions, the imposition of anaerobic conditions so soon after treatment and for such an extended time is unlikely and that in practice, accumulation of X11449757 to such high levels is unlikely. A further metabolite, X11406790, was only seen at levels <3% AR with these highest levels occurring at or soon after flooding and were probably associated with formation under aerobic conditions. The route of degradation of XDE-729 methyl under anaerobic conditions is essentially the same as that proposed under aerobic conditions. It was also noted that over the course of the study, there was significant partitioning of radioactivity out of the soil and into the water, such that the maximum amount of radioactivity in the water ranged from 29 – 54% AR.

Route of degradation – soil photolysis

A soil photolysis study was performed on a single soil; this soil had also been used in the aerobic and anaerobic soil studies. Moist soils were incubated for 15 days at 28ºC with continuous exposure to a xenon lamp, equivalent to 28 days summer sunlight at 40ºN. The lamp was appropriately filtered to exclude wavelength <290nm. In this study, it was apparent that both XDE-729 methyl and X11393729 degraded more slowly under irradiated conditions than under the dark control conditions, particularly from 4 DAT onwards. The wording of the study suggests that the dark control samples were supplied with moistened air, but this was not stated to be the case with the irradiated samples. It is possible that under the bright artificial light conditions in the irradiated samples that the soil may have been subject to drying and this may have resulted in the differences in a.s. concentration from 4 DAT. Given the apparent influence of both microbial and abiotic factors in the degradation of the a.s., drier conditions could have inhibited these processes. Thus, under the conditions of the study, there was a very limited influence of photolytic processes on degradation compared to aerobic processes. However, this finding is in sharp contrast to the potential influence of photolysis in aquatic systems (see section B.8.4.2).

The identified metabolites were those found in both aerobic and anaerobic studies, and there was no indication of any photolysis specific metabolites being formed.

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Metabolite formation was greater in the dark control compared to the illuminated and this is most likely to be related to the same conditions which limited degradation of the parent in the irradiated samples. The route of soil photolytic degradation is postulated to be the same as that under aerobic soil conditions.

Rate of degradation – aerobic soil

An additional report was submitted calculating degradation rates of XDE-729 methyl and its two main soil metabolites requiring environmental exposure assessment from the aerobic soil route and rate of degradation study. The study was conducted to obtain modelling endpoints according to FOCUS Degradation Kinetics guidance, but was also considered appropriate to obtain persistence endpoints for these substances.

XDE-729 methyl was found to degrade very rapidly at 20ºC and optimum moisture content with DT50 values in the range of 1 – 2 days and DT90 values in the range 4 – 16 days. The first metabolite to be formed, X11393729, was also generally rapidly degraded, with decline DT50 from the peak observed concentrations ranging from 3 – 36 days and DT90s of 11 – 119 days. The other metabolite, X11449757, appeared to decline more slowly, with decline DT50 from peak observed in the range 25 – 77 days with DT90s of 106 – 255 days.

The longest decline rates for all three substances were observed on one soil (Yolo). There appeared to be no particularly extreme characteristics of this soil that would suggest any reason why degradation may have been slower on this soil, and this may just reflect natural variation in capability of soils to degrade these substances.

Following consideration of the physical/chemical properties of the parent and two main aerobic metabolites, particularly the pKa values and solubilities, and investigating potential correlations between DT50 and soil properties, the RMS considers that pH dependent degradation should be taken into account for X11393729 and X11449757 in environmental exposure modelling but not for XDE-729 methyl. For FOCUS modelling, short DT50 values should be used for acid pH and long DT50 should be used for alkaline pH. A further description of how the long pH has been taken into account in groundwater modelling is given in section B.8.6.2.

The magnitude of the DT50 and DT90 values for XDE-729 methyl do not trigger field dissipation studies. One DT50 value for X11449757 exceeds the DT50 of 60 days which triggers field dissipation studies for parent substances. However, the Applicant has submitted European field dissipation studies anyway.

Persistence and modelling endpoints from laboratory incubations are reproduced below.

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Table B.8.116 Laboratory soil persistence endpoints for XDE-729 methyl and its soil metabolites (values in parentheses for RefSol 03-G soil are moisture corrected)

	XDE-729 methyl	**X11393729**	**X11449757**
Yolo			
Kinetics	FOMC	Top down SFO	Top down SFO
DT50	1.8 d	35.9 d	76.7 d
DT90	16.3 d	119 d	255 d
χ^2	3.3	6.0	5.2
RefSol 03-G			
Kinetics	SFO	Top down SFO	Top down SFO
DT50	1.3 d (1.1 d)	3.3 d (2.7 d)	25.1 d (20.4 d)
DT90	4.5 d (3.7 d)	11 d (9.0 d)	84 d (68.4 d)
χ^2	8.4	20.1	17.0
Site E			
Kinetics	FOMC	Top down SFO	Top down SFO
DT50	1.1 d	7.6 d	31.8 d
DT90	6.1 d	25.4 d	106 d
χ^2	4.4	13.1	13.8
Site I2			
Kinetics	FOMC	Top down SFO	Top down SFO
DT50	0.9 d	13.6 d	47.7 d
DT90	3.8 d	45.2 d	158.5 d
χ^2	7.0	11.3	12.3
Worst case			
DT50	1.8 d	35.9 d	76.7 d
DT90	16.3 d	119 d	255 d

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Table B.8.117 Soil modelling endpoints for XDE-729 methyl and its soil metabolites (values in parentheses for RefSol 03-G soil are moisture corrected)

	XDE-729 methyl	**X11393729**	**X11449757**
Yolo			
Kinetics	SFO	SFO (in series)	Top down SFO
DT50	2.4 d (2.0 d)	28.7 d	76.7
DT90	8.1 d (6.7 d)	95 d	255
Formation fraction	-	0.6372	1**
χ^2	12.5 (18.3)	16.4	5.2
RefSol 03-G			
Kinetics	SFO	SFO (in series)	Top down SFO
DT50	1.3 d (1.1 d)	2.0 d (1.6 d)	25.1 (20.4 d)
DT90	4.5 d (3.7 d)	6.8 d (5.5 d)	84 (68.4 d)
Formation fraction	-	0.8548	1**
χ^2	8.4	14.4	17.0
Site E			
Kinetics	SFO	SFO (in series)	Top down SFO
DT50	1.3 d (1.2 d)	4.7 d	31.8
DT90	4.2 d (4.0 d)	15.8 d	106
Formation fraction	-	0.7733	1**
χ^2	13.3 (10.9)	14.4	13.8
Site I2			
Kinetics	SFO	SFO (in series)	Top down SFO
DT50	1.0 d (0.9 d)	11.7 d	47.7
DT90	3.3 d (3.0 d)	38.9 d	158.5
Formation fraction	-	0.7753	1**
χ^2	8.0 (9.3)	14.7	12.3
Geometric mean			
DT50	1.4 d (1.3 d)	7.5 d	41.3 d (39.4 d***)
Formation fraction*	-	0.7602	1

*Arithmetic mean **Worst case assumption using top down DT50 values
***omitting Site I2 value from geometric mean

Field dissipation studies

It is noted that whilst the results of the aerobic soil degradation studies in soil indicate XDE-729 methyl does not trigger field studies under data requirements for Directive 91/414/EEC, the Applicant chose to provide field dissipation studies. The studies were all conducted at the same sites (Germany, UK, Spain and France) but with spring and autumn applications investigated separately, presumably as the intended GAP may recommend either autumn or spring applications. In general the studies were considered to be acceptable with appropriate sampling numbers and sampling depth, on-site weather recording as well as measurement of soil temperature and moisture. The studies were on bare soil plots and were of approximately one year duration. Analysis was made for XDE-729 methyl, X11393729 and X11449757. The method of analysis was virtually identical to that employed in the laboratory soil studies. Given

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the low application dose (up to 8 g a.s./ha), the method had a suitably low LOQ of 0.05 µg/kg which was able to quantify well below 10% of the parent; in relation to the lowest peak average residue across the three replicate plots recorded at the France Autumn applied study, the LOQ equated to 1.6% of the parent dose, but at other sites was usually around or below 1% of the parent dose. Procedural recovery information suggested that recoveries could vary quite widely, particularly for metabolites. However, in general, the ranges appeared reasonable in comparison with EU guidance on methods of analysis for pre-registration studies. There were some instances of very high or very low procedural recoveries, but the RMS does not consider that these are sufficient to invalidate the studies.

Residues were generally detected down to a maximum depth of 30cm, thus there was no regular sampling below this depth. The RMS considers this to be acceptable and a scrutiny of the residues in the lowest analysed layers suggests that residues were generally less than 1% of the average peak residue of the parent at each specific trial site. This suggests to the RMS that there were no significant leaching losses below the lowest depth of sampling.

Generally, XDE-729 methyl was observed to dissipate at a slower rate compared to that seen in the laboratory. With the exception of the Spanish site, dissipation appeared to be faster when applications were made in the autumn. A biphasic pattern was often apparent with a pronounced 'tail' often occurring around 90% dissipation of the parent. However, it was also apparent that at every site, by the time the first sample after treatment was taken, there had been appreciable degradation of the parent given the marked residues of X11393729 and sometime X11449757 at 0 DAA. In calculating the true time 0 residue for the purposes of calculating dissipation rates under ambient conditions, the metabolite residues were added to the parent residues but not corrected for molecular weight difference. The RMS considers that this is acceptable in this case as both metabolites are not that different in molecular weight to the parent. In any case, molecular weight correct would lead to slightly higher initial parent residues which tends to have the effect of shortening the parent dissipation rate. The RMS interpretation of the kinetic fitting for the parent under ambient weather conditions suggests a range of DT50 values from 2.1 – 43 days with DT90 values 49 – 144 days; these values are from a SFO, FOMC and DFOP kinetics. The longest DT50/DT90 combination was 43 days/144 days with SFO kinetics at the UK Spring site. This combination is proposed for use in simple PECsoil calculation procedures.

As noted above, metabolites X11393729 and X11449757 were frequently observed. Using the mean replicate residues and correcting for molecular weight, X11393729 was seen at maximum observed molar formation of 6.5 – 40.1%. The time of occurrence of these residues was variable, occurring at 0 – 89 DAT. These levels of formation were typically lower than seen in laboratory aerobic soil tests. For X11449757, maximum observed molar formation was 1.8 – 13.8% at 0 – 180 DAT. Observed formation was typically within the range of that seen in laboratory aerobic soils.

Whilst sequential parent/metabolite modelling of kinetic parameters was challenging in terms of obtaining robust parameters, both metabolites typically showed decline phases. Based on calculation of top down SFO kinetics, X11393729 had dissipation

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DT50 ranging from 17 – 264 days, with two of the DT90s being longer than 1 year. Thus a consideration of potential accumulation of X11393729 should be undertaken.

Also based on calculation of top down SFO kinetics, X11449757 had dissipation DT50 ranging from 87 – 197 days, with four of the DT90s being longer than 1 year. Thus a consideration of potential accumulation of X11449757 should also be undertaken.

In terms of generating modelling parameters from the field dissipation studies, the Applicant undertook a temperature and moisture timestep normalisation procedure. The Applicant considered that the studies were suitable for normalising as they considered that there the data described degradation rather than encompassing other dissipation processes such as volatilisation, plant uptake or leaching. The RMS evaluated the cases presented and agrees with this assessment for XDE-729 methyl, X11393729 and X11449757.

In undertaking the assessment for parent XDE-729 methyl, following discussions with the RMS, the Applicant attempted to take into account the EFSA PPR Opinion from 2010 on obtaining DegT50 values from field dissipation studies. In particular, this took into account the date by which 10mm rainfall had occurred following application. this is principally to eliminate the influence of surface processes such as soil photolysis or volatilisation. With hindsight, it is possible that the principles of the Opinion may not be that applicable to a substance such as this that tends to show relatively rapid degradation to an initial metabolite. Overall, the reasons for the apparently slower degradation seen in the field compared to laboratory conditions have not been elucidated. It is possible that the rapid decline phase seen in the field is consistent with hydrolysis to the acid metabolite, but it is possible that there may also have been an influence of photolysis as well. In addition, whilst the rapid degradation phase accounted for most of the disappearance of the parent, the presence of a distinct tail in the data at residues which tended to be greater than those seen in laboratory studies is not known. Therefore the RMS considers that it was still a reasonable request to make of the Applicant to conduct such an assessment.

SFO kinetics for parent were generated on complete datasets and following elimination of data before 10mm rainfall. In addition, flowcharts for application of DFOP and HS kinetics to the complete datasets were applied. In general, the DFOP and/or HS flowcharts tended to fail for one reason or another. The RMS observed that for the DFOP kinetic, the ‘g’ parameter was typically greater than 0.75 indicating that most of the residue was simulated to be in the fast phase compartment and with rapid degradation tending to dominate most of the residue decline. It is possible that this may have been due to relatively rapid hydrolysis of the parent methyl ester to the acid metabolite. Soil photolysis may have contributed to this, but given that degradation in the field was slower than in the laboratory, the RMS concludes that soil photolysis probably had only a minor role. Overall, the RMS can agree to the use of these parameters calculated after 10mm rainfall as they ought to represent ‘bulk soil matrix degradation’. The applicant eventually proposed to use SFO parameters for parent generated following elimination of data before 10mm rainfall. With this in mind, the recommended geometric mean SFO DT50 for use on exposure modelling using FOCUS groundwater and FOCUS surface water methodology is 20 days.

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For the metabolites, it was noted that peak concentrations, particularly of X11393729, occurred relatively early after treatment. As noted above, applying DFOP kinetics to the parent generally resulted in high 'g' values as the fast phase of degradation tended to dominate the overall decline. If a process such as soil photolysis hastened the degradation of the parent, it is likely that the observed formation of metabolites may have been enhanced, and the Applicant proposed that it may be precautionary to use kinetic parameters from sequential modelling of parent and metabolites in exposure modelling provided that the rapid parent degradation was taken into account. Whilst the EFSA guidance of 2010 does not expressly detail how metabolites can be taken into account, the RMS can understand the Applicant's logic, particularly as there is a view that faster degradation of a precursor tends to lead to conservative formation of subsequent metabolites in exposure models. With this in mind, the Applicant derived separate endpoints for exposure modelling of parent alone, parent + X11393729 (for exposure concentrations of X11393729), and parent + X11393729 + X11449757 (for exposure concentrations of X11449757). It will be noted that in each step of modelling the calculated DegT50 values of precursors gets shorter, potentially increasing metabolite. This may be partly as the result of the use of IRLS weighting in the kinetic model which tends to result in better fitting of precursor substances than the more typical OLS weighting method. Thus the following parameters are proposed for FOCUS exposure modelling.

Table B.8.118 Kinetic endpoints for XDE-729 methyl exposure modelling (i.e. should not be used in exposure modelling simulating formation of subsequent metabolites)

Location	**Season**	**Model**	**DT50 (d)**	***Chi*^{2} *Error (%)***
Germany	Spring	SFO (after 10mm rain)	17	*24*
Germany	Autumn	SFO (after 10mm rain)	27	*24*
UK	Spring	SFO (after 10mm rain)	26	*19*
UK	Autumn	SFO (after 10mm rain)	8.2	*20*
Spain	Spring	SFO (after 10mm rain)	25	*32*
Spain	Autumn	SFO (after 10mm rain)	33	*11*
France	Spring	SFO (after 10mm rain)	17	*15*
France	Autumn	SFO (after 10mm rain)	19	*19*
		Geomean	**20**	-
		Average	22	-
		Median	22	-

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Table B.8.119 Kinetic endpoints for sequential exposure modelling of XDE-729 methyl and X11393729 (Acid), derivation of X11393729 PEC values only

Location	Season	Parent + Acid (SFO+SFO)					Top-down SFO	
		Parent DT50 (d)	*Chi² Err (%)*	Acid DT50 (d)	FF	*Chi² Err (%)*	Acid DT50 (d)	*Chi² Err (%)*
Germany	Spring	0.7*	*28*	23	0.12	*34*	59	*32*
Germany	Autumn	2.5	*32*	42	0.44	*25*	30	*13*
UK	Spring	27	*28*	35	0.66	*33*	88	*6.5*
UK	Autumn	1.1	*40*	51	0.36	*14*	59	*9.5*
Spain	Spring	6.4	*17*	34	0.33	*49*	62	*15*
Spain	Autumn	9.1	*20*	40	0.34	*49*	85	*16*
France	Spring	6.6	*40*	2.3	1.00	*32*	29	*25*
France	Autumn	0.7	*27*	11	0.34	*61*	28	*36*
	Geomean	**3.3**	-	**22**	0.38	-	**50**	-
	Average	6.8	-	30	**0.45**	-	55	-
	Median	4.5	-	35	0.35	-	59	-

FF = formation fraction * DFOP/SFO model used

Table B.8.120 Kinetic endpoints for sequential exposure modelling of XDE-729 methyl, X11393729 (Acid) and X11449757 (X-757), derivation of X11449757 PEC values only

Location	Season	Parent + Acid + X-757 (SFO+SFO+ SFO)						Top-down SFO	
		Parent DT50	Acid DT50	Acid FF	X-757 DT50 (d)	X-757 FF	*Chi² Err (%)*	X-757 DT50 (d)	*Chi² Err (%)*
Germany	Spring	NC	NC	NC	NC	NC	*NC*	NC	*NC*
Germany	Autumn	1.9	43	0.41	8.9	1.00	*16*	76	*4.6*
UK	Spring	NC	NC	NC	NC	NC	*NC*	60	*13*
UK	Autumn	1.0	54	0.35	22	0.22	*37*	NC	*NC*
Spain	Spring	NC	NC	NC	NC	NC	*NC*	84	*26*
Spain	Autumn	NC	NC	NC	NC	NC	*NC*	60	*12.6*
France	Spring	5.8	1.9	1.00	73	0.18	*36*	107	*21*
France	Autumn	0.7	8.6	0.36	9.5	1.00	*30*	37	*11*
	Geomean	**1.7**	**14**	0.48	**19**	0.45	-	**67**	-
	Average	2.4	27	**0.53**	28	**0.60**	-	71	-
	Median	1.5	26	0.39	16	0.61	-	68	-

FF = formation fraction NC = not calculated

The RMS notes that only three locations are represented for X11449757, which is acceptable for a metabolite. However, the RMS considers that the conduct of the studies under autumn and spring conditions and slightly different soil properties means that each site constitutes two separate results, i.e. there are four separate results for X11449757.

The RMS revisited the question of potential pH dependence of degradation. In the laboratory studies, the RMS considered that there appeared to be a trend towards increasing DT50 with increasing pH for both X11393729 and X11449757. In order to

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do this, the RMS considered the normalised SFO DT50 values in order to remove potential temperature and moisture interferences. The RMS considered both the top down and true metabolite degradation DT50 values. Making the assumption that normalisation should remove any differences from conducting studies in spring or autumn, the full data set of DT50s for each substance was used.

For parent, there was no consistent trend across the eight trials and the variation might be expected to be within natural variation. Therefore pH dependence is not taken into consideration.

For X11393729, there appeared to be a trend to increasing degradation rate with increasing pH with both top down and true degradation DT50 values, but this was not consistent across the eight trials. The lowest DT50 was at the lowest pH, but the highest DT50 was at just under pH7. In light of the apparent trend for pH dependency of degradation in the laboratory incubations, it is considered that pH dependence of degradation should be taken into account. However, whether this range would be considered to fall within that expected by virtue of natural variation could be the subject of an expert discussion.

For X11449757, top down DT50 varied from 37 – 107 days in the six sites it was calculated for. The maximum and minimum values in this range were at the Spain site with autumn and spring applications respectively, i.e. at very similar pH. There was no consistent trend in the top down or true degradation DT50s from the field studies for pH dependent degradation. The RMS does not consider that pH dependence of degradation should be taken into consideration for this metabolite given results under more realistic environmental conditions. However, the apparent discrepancy between the laboratory and field databases could be the subject of expert discussion as to whether pH dependence should be considered.

Thus, the RMS can accept the proposed geomean normalised field DT50 for exposure modelling purposes for XDE-729 methyl and X11449757, but proposes to use high and low DT50 values in each scenario for X11393729 to illustrate the influence of pH.

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Route of degradation (aerobic) in soil (Annex IIA, point 7.1.1.1.1)

Mineralization after 100 days ‡	Non-sterile conditions: 14.8 – 17.3 % after 104 d, [^{14}C-Phenyl]-label (n[1]= 3) 3.3 – 21.0 % after 104 d, [^{14}C-Pyridine]-label (n= 4) Sterile conditions: 0.3 – 0.7 % after 62 d, [^{14}C-Phenyl]-label (n= 4) 0.6 – 1.0 % after 62 d, [^{14}C-Pyridine]-label (n= 4)
Non-extractable residues after 100 days ‡	Non-sterile conditions: 59.5 – 64.4 % after 104 d, [^{14}C-Phenyl]-label (n= 3) 62.5 – 82.5 % after 104 d, [^{14}C-Pyridine]-label (n= 4) Note: one soil met regulatory trigger of >70% unextracted residue and <5% mineralisation at 104 days with Pyridine label. Sterile conditions: 0.0 – 6.7 % after 62 d, [^{14}C-Phenyl]-label (n= 4) 0.0 – 11.9 % after 62 d, [^{14}C-Pyridine]-label (n= 4)
Metabolites requiring further consideration ‡ - name and/or code, % of applied (range and maximum)	X11393729 – 38.2 – 72.7 % at 3 - 7 d (n= 4) X11449757 – 2.7 – 17.4 % at 3 - 14 d (n= 4) [^{14}C-phenyl] & [^{14}C-pyridine] labels

Route of degradation in soil - Supplemental studies (Annex IIA, point 7.1.1.1.2)

Anaerobic degradation ‡

Mineralization after 100 days	0.3 – 0.8 % after 100 d, [^{14}C-Phenyl]-label (n= 4) 0.3 – 0.7 % after 100 d, [^{14}C-Pyridine]-label (n= 4)

[1] n corresponds to the number of soils.

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Non-extractable residues after 100 days	21.9 – 48.6 % after 100 d, [^{14}C-Phenyl]-label (n= 4) 19.1 - 47.4% after 100 d, [^{14}C-Pyridine]-label (n= 4)
Metabolites that may require further consideration for risk assessment - name and/or code, % of applied (range and maximum)	X11393729 – 47.4 – 79.6 % at 0 - 14 days post flooding (n= 4) X11449757 – 25.7 – 54.3 % at 100 - 121 days post flooding (n= 4) [^{14}C-phenyl] & [^{14}C-pyridine] labels

Soil photolysis ‡

Metabolites that may require further consideration for risk assessment - name and/or code, % of applied (range and maximum)	X11393729 – 49.1 % at 15 d (n= 1) X11449757 – 6.8 % at 15 d (n= 1) [^{14}C-phenyl] & [^{14}C-pyridine] labels

Rate of degradation in soil (Annex IIA, point 7.1.1.2, Annex IIIA, point 9.1.1)

Laboratory studies ‡

Parent	Aerobic conditions						
Soil type	X[2]	pH	t. °C / % MWHC	DT_{50} /DT_{90} (d)	DT_{50} (d) 20°C pF2/10kPa	St. (χ^2)	Method of calculation
Clay loam		7.1	20 °C / 50 %	1.8 / 16.3 2.0 / 6.7	1.8 / 16.3 2.0 / 6.7	3.3 18.3	FOMC - P SFO - M
Loam		5.0	20 °C / 50 %	1.3 / 4.5 1.3 / 4.5	1.1 / 3.7 1.1 / 3.7	8.4 8.4	SFO – P SFO - M
Silt loam		5.9	20 °C / 50 %	1.1 / 6.1 1.2 / 4.0	1.1 / 6.1 1.2 / 4.0	4.4 110.9	FOMC – P SFO - M
Sandy loam		7.5	20 °C / 50 %	0.9 / 3.8 0.9 / 3.0	0.9 / 3.8 0.9 / 3.0	7.0 9.3	SFO – P SFO – M
Silt loam		5.9	10 °C / 50%	2.2 / 12.2	-	4.9	FOMC - P
Geometric mean (SFO DT50 for modelling)					1.3		

P = persistence endpoint M = modelling endpoint

[2] X This column is reserved for any other property that is considered to have a particular impact on the degradation rate.

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X11393729	Aerobic conditions							
Soil type	X[1]	pH	t. °C / % MWHC	DT_{50}/ DT_{90} (d)	f. f. k_{dp}/ k_f	DT_{50} (d) 20°C pF2/10kPa	St. (χ^2)	Method of calculation
Clay loam		7.1	20 °C / 50 %	35.9 / 119 28.7 / 95	0.6372	35.9 / 119 28.7 / 95	6.0 16.4	TD SFO – P SFO IS - M
Loam		5.0	20 °C / 50 %	3.3 / 11 2.0 / 6.8	0.8548	2.7 / 9 1.6 / 5.5	20.1 14.4	TD SFO – P SFO IS - M
Silt loam		5.9	20 °C / 50 %	7.6 / 25.4 4.7 / 15.8	0.7733	7.6 / 25.4 4.7 / 15.8	13.1 14.4	TD SFO – P SFO IS - M
Sandy loam		7.5	20 °C / 50 %	13.6 / 45.2 11.7 / 38.9	0.7753	13.6 / 45.2 11.7 / 38.9	11.3 14.7	TD SFO – P SFO IS - M
Silt loam		5.9	10 °C / 50%	21.0 / 69.6		-	10.0	TD SFO - P
Geometric mean (SFO DT50 for modelling)					0.7602*	7.5		

P = persistence endpoint M = modelling endpoint TD = top down IS = in series *arithmetic mean

X11449757	Aerobic conditions							
Soil type	X[1]	pH	t. °C / % MWHC	DT_{50}/ DT_{90} (d)	f. f. k_{dp}/ k_f	DT_{50} (d) 20°C pF2/10kPa	St. (χ^2)	Method of calculation
Clay loam		7.1	20 °C / 50 %	76.7 / 255	1	76.7 / 255	5.2	TD SFO – P & M
Loam		5.0	20 °C / 50 %	25.1 / 84	1	20.4 / 68.4	17.0	TD SFO – P & M
Silt loam		5.9	20 °C / 50 %	31.8 / 106	1	31.8 / 106	13.8	TD SFO – P & M
Sandy loam		7.5	20 °C / 50 %	47.7 / 158	1	47.7 / 158	12.3	TD SFO – P & M
Geometric mean (SFO DT50 for modelling)					1	41.3		

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Field studies - Persistence endpoints

Parent				
Site	Season	Best fit model	DT50 (days)	DT90 (days
Germany	Spring Autumn	SFO FOMC	18 5	60 78
UK	Spring Autumn	SFO FOMC	43 15	144 106
Spain	Spring Autumn	SFO FOMC	15 11	51 86
France	Spring Autumn	SFO DFOP	15 2.1	49 51
Worst case		SFO	43	144

X11393729 – top down				
Site	Season	Model	DT50 (days)	DT90 (days
Germany	Spring Autumn	SFO SFO	Not used 101.7	Not used 337.9
UK	Spring Autumn	SFO SFO	264.4 163.5	871.7 543.2
Spain	Spring Autumn	SFO SFO	62 108	207 359
France	Spring Autumn	SFO SFO	17 44	56 145
Worst case		SFO	264.4	871.7

X11449757 – top down				
Site	Season	Model	DT50 (days)	DT90 (days
Germany	Spring Autumn	SFO SFO	Not used 197.0	Not used 654.4
UK	Spring Autumn	SFO SFO	187.1 Not used	621.4 Not used
Spain	Spring Autumn	SFO SFO	113.2 104.7	375.9 347.8
France	Spring Autumn	SFO SFO	146.0 87.3	484.9 290.2
Worst case		SFO	197.0	654.4

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Site	Peak concentration of parent (DAT)	Molar observed formation of X11393729 (%, DAT)	Molar observed formation of X11449757 (%, DAT)
Germany Spring	3.51 µg/kg (0 DAT)	6.5% (13 DAT)	9.9% (91 DAT)
UK Spring	4.34 µg/kg (1 DAT)	18.3% (89 DAT)	2.0% (89 DAT)
Spain Spring	6.21 µg/kg (1 DAT)	37.1% (0 DAT); 17.1% (27 DAT)	12.6% (0 DAT); 3.3% (27 DAT)
France Spring	3.79 µg/kg (0 DAT)	14.0% (3 & 15 DAT)	9.2% (15 DAT)
Germany Autumn	4.23 µg/kg (1 DAT)	34.3% (62 DAT)	4.6% (62 DAT)
UK Autumn	4.97 µg/kg (7 DAT)	32.1% (29 DAT)	1.8% (180 DAT)
Spain Autumn	5.42 µg/kg (0 DAT)	21.7% (7 DAT)	2.0% (7 DAT)
France Autumn	3.07 µg/kg (0 DAT)	40.1% (3 DAT)	13.8% (31 DAT)

Field studies - Modelling endpoints

Modelling to derive XDE-729 methyl concentrations only				
Location	**Season**	**Model**	**DT50 (d)**	***Chi^2 Error (%)***
Germany	Spring	SFO (after 10mm rain)	17	*24*
Germany	Autumn	SFO (after 10mm rain)	27	*24*
UK	Spring	SFO (after 10mm rain)	26	*19*
UK	Autumn	SFO (after 10mm rain)	8.2	*20*
Spain	Spring	SFO (after 10mm rain)	25	*32*
Spain	Autumn	SFO (after 10mm rain)	33	*11*
France	Spring	SFO (after 10mm rain)	17	*15*
France	Autumn	SFO (after 10mm rain)	19	*19*
		Geomean	**20**	-
		Average	22	-
		Median	22	-

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Modelling to derive X11393729 ('Acid') concentrations only pH dependence to be accounted for in exposure assessment								
		Parent + Acid (SFO+SFO)					Top-down SFO	
Location	Season	Parent DT50 (d)	*Chi² Err (%)*	Acid DT50 (d)	FF	*Chi² Err (%)*	Acid DT50 (d)	*Chi² Err (%)*
Germany	Spring	0.7*	*28*	23	0.12	*34*	59	*32*
Germany	Autumn	2.5	*32*	42	0.44	*25*	30	*13*
UK	Spring	27	*28*	35	0.66	*33*	88	*6.5*
UK	Autumn	1.1	*40*	51	0.36	*14*	59	*9.5*
Spain	Spring	6.4	*17*	34	0.33	*49*	62	*15*
Spain	Autumn	9.1	*20*	40	0.34	*49*	85	*16*
France	Spring	6.6	*40*	2.3	1.00	*32*	29	*25*
France	Autumn	0.7	*27*	11	0.34	*61*	28	*36*
	Geomean	**3.3**	-	**22**	0.38	-	**50**	-
	Average	6.8	-	30	**0.45**	-	55	-
	Median	4.5	-	35	0.35	-	59	-

FF = formation fraction * DFOP/SFO model used

Modelling to derive X11449757 ('X-757') concentrations only									
		Parent + Acid + X-757 (SFO+SFO+ SFO)						Top-down SFO	
Location	Season	Parent DT50	Acid DT50	Acid FF	X-757 DT50 (d)	X-757 FF	*Chi² Err (%)*	X-757 DT50 (d)	*Chi² Err (%)*
Germany	Spring	NC	NC	NC	NC	NC	*NC*	NC	*NC*
Germany	Autumn	1.9	43	0.41	8.9	1.00	*16*	76	*4.6*
UK	Spring	NC	NC	NC	NC	NC	*NC*	60	*13*
UK	Autumn	1.0	54	0.35	22	0.22	*37*	NC	*NC*
Spain	Spring	NC	NC	NC	NC	NC	*NC*	84	*26*
Spain	Autumn	NC	NC	NC	NC	NC	*NC*	60	*12.6*
France	Spring	5.8	1.9	1.00	73	0.18	*36*	107	*21*
France	Autumn	0.7	8.6	0.36	9.5	1.00	*30*	37	*11*
	Geomean	**1.7**	**14**	0.48	**19**	0.45	-	**67**	-
	Average	2.4	27	**0.53**	28	**0.60**	-	71	-
	Median	1.5	26	0.39	16	0.61	-	68	-

FF = formation fraction NC = not calculated

pH dependence ‡ (yes / no) (if yes type of dependence)	XDE-729 methyl – no X11393729 – yes, increasing DT50 with increasing pH X11449757 - no,(in lab, increasing DT50 with increasing pH; no trend apparent in field)

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Laboratory studies ‡

Parent	Anaerobic conditions						
Soil type	X[3]	pH	t. °C / % MWHC	DT_{50} /DT_{90} (d)	DT_{50} (d) 20°C pF2/10k Pa	St. (χ^2)	Method of calculation
Clay loam		7.1	20 °C / 50 % for 1 day, flooded there-after	2.8 / 29	-	4.9	DFOP from day of flooding
Loam		5.0	20 °C / 50 %% for 1 day, flooded there-after	1.6 / 5.5	-	10.3	SFO from day of flooding
Silt loam		5.9	20 °C / 50 %% for 1 day, flooded there-after	0.9 / 3.1	-	9.3	SFO from day of flooding
Sandy loam		7.5	20 °C / 50 %% for 1 day, flooded there-after	1.9 / 6.5	-	6.5	SFO from day of flooding
Geometric mean/median							

[3] X This column is reserved for any other property that is considered to have a particular impact on the degradation rate.

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X11393729	Anaerobic conditions							
Soil type	X[1]	pH	t. °C / % MWHC	DT_{50}/ DT_{90} (d)	f. f. k_{dp}/k_f	DT_{50} (d) 20°C pF2/10k Pa	St. (χ^2)	Method of calculation
Clay loam		7.1	20 °C / 50 % for 1 day, flooded there-after	77 / 257 90 / 299	0.9784	-	4.7 6.3	DFOP/SFO SFO TD
Loam		5.0	20 °C / 50 %% for 1 day, flooded there-after	21 / 70 21 / 70	$2.3x10^{-14}$*	-	4.3 4.6	SFO/SFO SFO TD
Silt loam		5.9	20 °C / 50 %% for 1 day, flooded there-after	14 / 46 21 / 69	0.8213	-	6.6 27.2	SFO/SFO SFO TD
Sandy loam		7.5	20 °C / 50 %% for 1 day, flooded there-after	106 / 352 109 / 334	1.0000	-	3.4 3.8	SFO/SFO SFO TD
Geometric mean/median								

*unrealistic optimised ff as peak on day of flooding TD = top down

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X11449757	Anaerobic conditions							
Soil type	X[1]	pH	t. °C / % MWHC	DT_{50}/ DT_{90} (d)	f. f. k_{dp}/k_f	DT_{50} (d) 20°C pF2/10k Pa	St. (χ^2)	Method of calculation
Clay loam		7.1	20 °C / 50 % for 1 day, flooded there-after	92 / 304	0.6416	-	6.0	DFOP/SFO/ SFO
Loam		5.0	20 °C / 50 %% for 1 day, flooded there-after	165 / 549	0.9505	-	13.4	SFO/SFO/S FO
Silt loam		5.9	20 °C / 50 %% for 1 day, flooded there-after	127 / 421	0.7011	-	10.1	SFO/SFO/S FO
Sandy loam		7.5	20 °C / 50 %% for 1 day, flooded there-after	>1000 / >1000	0.7366	-	20.3	SFO/SFO/S FO
Geometric mean/median								

Top down kinetics not possible due to insufficient time points after peak, or peak not reached at study end.

Soil photolysis – degradation of XDE-729 methyl and X11393729 slower under illuminated conditions than under dark control conditions.

B.8.2 Adsorption, desorption and mobility in soil (IIA 7.1.2, 7.1.3, IIIA 9.1.2)

B.8.2.1 Adsorption and desorption

a) A batch equilibrium adsorption/desorption study was conducted for XDE-729 methyl and its soil metabolites X11393729 and X11449757 according to OECD 106 and US EPA guidelines (OPPTS 835.1230) and GLP.

It should be noted at the outset that due to certain issues with the conduct of this study for the soil adsorption values for XDE-729 methyl in this study are not used for in exposure assessment. A replacement study from which XDE-729 methyl adsorption parameters are derived is at B.8.2.1 b).

The procedure used in this study was essentially the same for XDE-729 methyl, X11393729 and X11449757 with the exception that the metabolites were not subject to

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the desorption step at Tier 3 of the study (i.e. where adsorption and desorption isotherms are established).

Samples of XDE-729 methyl, X11393729 and X11449757, all radiolabelled in the phenyl ring were used. Seven different soils were selected for the study, four of which had been used in the aerobic route and rate of degradation studies. The soil properties are detailed below. The soils were all sterilised using gamma irradiation before use, apparently in an effort to give a greater level of stability to XDE-729 methyl.

Preliminary studies were undertaken to determine soil:solution ratios, equilibrium time, stability of test substances and adsorption to experimental equipment.

XDE-729 methyl was found to be unstable under the conditions of the study with significant formation of X11393729. Both X11393729 and X11449757 were found to be stable under the conditions of the study. In tests to determine equilibrium time with XDE-729 methyl, peak of adsorption had occurred or was decreasing by 24 hours in 5 of the seven soils. The decrease in adsorption was attributed to degradation to X11393729 as shown by analysis of the solutions. The study authors chose an equilibrium time of 24 hours in an attempt to maximise opportunity for adsorption whilst limiting degradation. For the two metabolites, only limited additional adsorption was seen beyond 24 hours in most soils, thus a 24 hour equilibrium time was also chosen for these soils. No adsorption to test equipment was detected.

The following soil:solution ratios were used.

XDE-729 methyl: Yolo, RefSol 01-A and Site M2 - 1:30; RefSol 03-G, Site E and Site I2 - 1:15; Site K - 1:5

X11393729: Yolo, RefSol 01-A, RefSol 03-G, Site E and Site K - 1:5; Site I2 - 1:2; Site M2 - 1:10

X11449757: Yolo, RefSol 03-G, Site E and Site K and Site M2 - 1:10; RefSol 01-A - 1:5; Site I2 - 1:2

For the establishment of soil adsorption isotherms, duplicate samples of five different concentrations (nominally ranging from 0.01 – 1.0 mg/l) for each soil were continuously shaken for the determined equilibrium period. The aqueous phase was separated by centrifugation and decanted and analysed by HPLC. The soil pellet was extracted by the ASE procedure described for the soil route and rate of degradation studies in Section B.8.1.

As a result of instability issues with XDE-729 methyl in the test system, the following procedure was used to determine the adsorption isotherm for each soil. Two replicates were available for each dosing concentration. Following shaking for the required equilibrium period and centrifugation, the aqueous phase was separated from the soil phase. One of the two replicates was analysed for total radioactivity and XDE-729 methyl using HPLC. The other replicate was only analysed for gross radioactivity using LSC and the amount of parent material extrapolated from the replicate that had had been subject to HPLC analysis. The initial $CaCl_2$ extract was subject to the same regime where by the amount of parent material in one replicate was extrapolated from

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the results of the HPLC analysis in the other. It should be noted that at the very lowest dosing concentration of 0.01 mg/l, there were insufficient parent residues to be accurately quantified with the analytical method, therefore the amount of parent in solution was extrapolated from the results obtained at the immediately higher concentration. The study authors indicated in the study that the LOD and LOQ were 10 dpm and 40 dpm above background counts. For the lowest dosing concentration of 0.01 mg/l, the LOD was stated to be equivalent to 0.01% AR. For the soil extract resulting from the ASE procedure, a similar method of extrapolation from one replicate to the other at each dosing concentration was followed. However, at the lowest two dosing concentrations of 0.05 and 0.01 mg/l, there were similar issues with ability to quantify the lowest parent residue using HPLC analysis of the extract, and thus the amount of parent at these two lower doses were extrapolated from the results at the next highest dose. The Applicant considered that the extrapolation approach taken for the lowest concentrations was reasonable given the relatively low water solubility dictating the maximum concentration and the guideline requirement to span two orders of magnitude in the test. The extrapolation approach from one replicate to another was considered by the Applicant to be reasonable in light of what they considered to be the relatively low variability in % of parent substance between replicates and the large number of analyses required. The Applicant clarified that this was on the basis of the LSC quantification of radioactive residues in the water and the soil phases. It was argued by the Applicant that whilst the residues were not identified in both replicates at each dose, good agreement in LSC counts between water and soil phases in each replicate was seen. The Applicant suggested that this signifies similar amounts of hydrolysis of the parent ester (XDE-729 methyl) and the acid metabolite (X11393729). The RMS generally concurs with the view that similar LSC results were seen in duplicate samples, although within individual datasets there were some examples where, for example, greater than 10% difference in the LSC results between replicates at individual doses were seen. However, this was a relatively low frequency and there did not appear to be a consistent pattern to the occurrence. The Applicant stated that the LSC results could be used to justify extrapolation of XDE-729 methyl results from one replicate to the other because the different water solubilities of the ester and acid (approx. 1.7 mg/L at pH 5 – 9 for XDE-729 methyl and 102 mg/L at pH 5, 3070 mg/L at pH 7 and 46100 mg/L at pH 9 for X11393729) would be expected to give different distributions of radioactivity between water and soil if the relative proportions of ester and acid were different. Overall, the RMS considers that the argument about extrapolation from one replicate to another is acceptable *in this case* as the relative differences in solubility might be expected to give rise to differing adsorption properties and therefore an overall different distribution in radioactivity between soil and water phases. However the RMS considers it is preferable that both replicates for each dose are analysed, given that the OECD 106 guideline states that batch sorption studies ought to have at least duplicate samples at each dose, and that analytical methodology to address the possibility of unstable substances is given by the guideline. Therefore the RMS considers that the approach used by the applicant cannot be generally advocated. In the case of extrapolating from higher to lower concentrations, the RMS considers that this may be reasonable given the experimental constraints imposed by the guideline requirements to cover two orders of magnitude in dosing concentrations, the water solubility of the substance and analytical limits of quantification.

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It was noted that the above procedure does not apply to the metabolites X11393729 and X11449757 as these were determined to be stable under study conditions and thus no correction for hydrolysis was required. However, the study report indicates that representative samples of aqueous layers and organic extracts were analysed to prove stability. Given that stability was shown, the LSC determinations are considered acceptable in providing appropriate data for the determination of adsorption isotherms.

For XDE-729 methyl, the desorption isotherm was also established. Following removal of the aqueous phase from the adsorption isotherm test, fresh $CaCl_2$ solution was added to the original soil:solution ratio and shaken for 24 hours. The aqueous and soil layers were separated by centrifugation and analysed as before. The desorption isotherm test was not conducted for X11393729 and X11449757. As the results of the desorption isotherm test on XDE-729 methyl are not used in the risk assessment, the detailed results of aqueous and soil concentrations from the desorption test have not been presented, but the results of the isotherm calculations have been presented.

Mass balances were generally within the expected range of 90 – 110% AR, although some results for XDE-729 methyl failed to achieve 90% AR recovery. The Applicant applied thresholds of less than 85% AR and greater than 111% AR for exclusion of results. this results in seven out of 70 replicates for XDE-729 methyl being excluded. Results of the soil adsorption isotherm determinations are shown below; where results have been excluded on the grounds of either too high or too low mass balance, these are shown as 'N/A'. OECD 106 indicates that where mass balance less than 90% is encountered, the substance has to be considered unstable. However, the study guideline then states that studies on substances with mass balance <90% can still be continued taking into account the instability, with both phases being analysed. As will be noted from the above description, analysis of both phases was performed on one of two replicates per dose. The RMS reiterates that this is not ideal but can accept the approach taken.

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Table B.8.121 Properties of soils used in soil adsorption determinations of XDE-729 methyl, X11393729 and X11449757

Parameter	Results			
Study Designation	M800*	M801	M802*	M803*
Soil Series	Yolo	RefSol 01-A	RefSol 03-G	Site E
Geographic Location	Yolo County, CA, USA	Hagen, Lower Saxony, Germany	Ebbinghof, Northrhine, Westphalia, Germany	Farditch Farm, Chelmorton, Derbyshire, UK
Latitude and Longitude	38°32'N 121°52'W	52°34'N 09°26'E	51°10'N 08°17'E	53°13'N 1°50'W
USDA Texture Class	Clay Loam	Loamy Sand	Loam	Silt Loam
% Sand	33	81	33	27
% Silt	34	14	46	58
% Clay	33	5	21	15
International Texture Class	Light Clay	Loamy Sand	Clay Loam	Loam
% Sand	47	87	51	57
% Silt	20	8	28	28
% Clay	33	5	21	15
pH ($CaCl_2$, 1:2 ratio)	7.1	5.2	5.0	5.9
% Organic Carbon	1.3	1.1	2.5	3.6
CEC (meq/100g)	21.2	4.7	14.8	20.2
Moisture Capacity at 1/3 bar	22.4	6.5	24.9	25.3
Moisture Holding Capacity	65.6	30.7	57.3	62.9
Bulk Density (g/cm3)	1.11	1.47	1.07	1.03

* Soil previously used in XDE-729 methyl aerobic soil metabolism study

Parameter	Results		
Study Designation	M804*	M822	M823
Soil Series	Site I2	Site K	Site M2
Geographic Location	Longwoods Quarry, Lincolnshire, UK	Woodside Farm, Empingham, Rutland, UK	Lindholme, South Yorkshire, UK
Latitude and Longitude	53°7' N 0°25' W	52º39' N 0º35' W	53°32' N 57°45' W
USDA Texture Class	Sandy Loam	Clay Loam	Organic (Peat or Muck)
% Sand	75	32	92
% Silt	12	37	7
% Clay	13	31	1
International Texture Class	Sandy Loam	Light Clay	Organic (Peat or Muck)
% Sand	78	48	96
% Silt	8	21	3
% Clay	13	31	1
pH ($CaCl_2$, 1:2 ratio)	7.5	7.2	4.1
% Organic Carbon	1.4	4.4	33.1
CEC (meq/100g)	9.0	32.7	84.9
Moisture Capacity at 1/3 bar	9.3	30.7	42.0
Moisture Holding Capacity	48.5	76.0	136.7
Bulk Density (g/cm3)	1.28	1.02	0.64

* Soil previously used in XDE-729 methyl aerobic soil metabolism study

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Table B.8.122 Concentrations of XDE-729 methyl in liquid and soil phases in adsorption isotherm tests

		Yolo Light Clay (M800)			RefSol 01-A Loamy Sand (M801)		
conc (µg/ml)	Rep	sorbed µg/g	in soln µg/ml	% sorbed	sorbed µg/g	in soln µg/ml	% sorbed
1	1	13.5200	0.4430	43.5	12.0500	0.5589	39
1	2	13.5100	0.4428	43.4	11.6000	0.5478	37.5
0.5	1	7.1620	0.1821	48.5	N/A	N/A	N/A
0.5	2	7.1680	0.1828	48.5	N/A	N/A	N/A
0.1	1	1.5860	0.0300	53	1.3690	0.0414	46
0.1	2	1.6000	0.0305	53.4	1.4100	0.0399	47.4
0.05	1	0.8659	0.0145	56.4	0.7209	0.0198	47.2
0.05	2	0.8483	0.0143	55.2	0.7308	0.0199	47.9
0.01	1	0.1832	0.0027	65.6	0.1606	0.0037	57.9
0.01	2	0.1929	0.0026	69.1	0.1416	0.0040	51
		RefSol 03-G Clay Loam (M802)			Site E Silt Loam (M803)		
1	1	6.7800	0.1953	43.5	4.6280	0.1444	30.2
1	2	6.7340	0.1912	43.3	4.4820	0.1435	29.2
0.5	1	3.2960	0.0878	44.6	2.2400	0.0663	30.8
0.5	2	N/A	N/A	N/A	2.2750	0.0669	31.2
0.1	1	0.7444	0.0153	49.7	N/A	N/A	N/A
0.1	2	0.7402	0.0155	49.4	0.4740	0.0116	32.1
0.05	1	0.3193	0.0103	41.6	0.2710	0.0058	35.8
0.05	2	0.4057	0.0073	52.8	0.2595	0.0060	34.3
0.01	1	0.0815	0.0014	58.3	0.0613	0.0011	44.6
0.01	2	0.0846	0.0014	60.5	0.0469	0.0015	34.1
		Site I2 Sandy Loam (M804)			Site K Light Clay (M822)		
conc (µg/ml)	Rep	sorbed µg/g	in soln µg/ml	% sorbed	sorbed µg/g	in soln µg/ml	% sorbed
1	1	6.0580	0.4733	39.3	0.4807	0.0293	9.2
1	2	6.0870	0.4726	39.5	0.4683	0.0297	9
0.5	1	3.2190	0.1956	43.9	0.2469	0.0131	10
0.5	2	2.5890	0.2427	35.3	0.2508	0.0132	10.2
0.1	1	0.6968	0.0329	47	0.0633	0.0024	12.6
0.1	2	0.6852	0.0340	46.2	0.0609	0.0025	12.1
0.05	1	0.3655	0.0163	48	0.0412	0.0011	16
0.05	2	0.4019	0.0169	52.8	0.0436	0.0010	17
0.01	1	0.0823	0.0031	59.5	N/A	N/A	N/A
0.01	2	0.0839	0.0030	60.6	N/A	N/A	N/A
		Site M2 Organic (Peat or Muck) (M823)					
1	1	25.5800	0.0282	83			
1	2	25.4600	0.0306	82.6			
0.5	1	12.1400	0.0130	82.9			
0.5	2	11.2500	0.0117	76.8			
0.1	1	2.6000	0.0023	87.6			
0.1	2	2.5930	0.0023	87.4			
0.05	1	1.3230	0.0012	87			
0.05	2	1.3430	0.0012	88.3			
0.01	1	0.2747	0.0002	99.3			
0.01	2	N/A	N/A	N/A			

N/A = not available. Sample mass balance was unacceptable

Note that Rep 1 was measured for XDE-729 methyl content, Rep 2 was extrapolated. Lowest concentration results for both Reps extrapolated from next highest concentration.

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Table B.8.123 Concentrations of X11393729 in liquid and soil phases in adsorption isotherm tests

		Yolo Light Clay (M800)			RefSol 01-A Loamy Sand (M801)		
conc (µg/ml)	Rep	sorbed µg/g	in soln µg/ml	% sorbed	sorbed µg/g	in soln µg/ml	% sorbed
1	1	1.189E+00	6.882E-01	25.2	1.661E+00	6.035E-01	35.3
1	2	8.687E-01	7.486E-01	18.4	1.237E+00	6.954E-01	26.3
0.5	1	6.792E-01	3.596E-01	26.9	5.173E-01	4.066E-01	20.5
0.5	2	6.371E-01	3.680E-01	25.2	5.378E-01	3.944E-01	21.3
0.1	1	1.686E-01	6.620E-02	32.9	1.426E-01	7.414E-02	27.8
0.1	2	1.852E-01	6.283E-02	36.1	1.444E-01	7.184E-02	28.2
0.05	1	8.201E-02	3.210E-02	33.3	N/A	N/A	N/A
0.05	2	8.127E-02	3.223E-02	33.0	6.964E-02	3.504E-02	28.3
0.01	1	N/A	N/A	N/A	1.490E-02	6.902E-03	30.2
0.01	2	1.829E-02	6.055E-03	37.0	1.549E-02	6.710E-03	31.4
		RefSol 03-G Clay Loam (M802)			Site E Sit Loam (M803)		
1	1	N/A	N/A	N/A	1.408E+00	6.289E-01	29.9
1	2	1.480E+00	6.206E-01	31.4	1.601E+00	5.956E-01	34.0
0.5	1	9.105E-01	3.114E-01	36.1	9.032E-01	3.073E-01	35.8
0.5	2	8.818E-01	3.146E-01	35.0	9.120E-01	3.074E-01	36.1
0.1	1	2.354E-01	5.227E-02	45.9	2.192E-01	5.477E-02	42.7
0.1	2	2.387E-01	5.170E-02	46.6	2.308E-01	5.265E-02	45.0
0.05	1	1.082E-01	2.645E-02	44.0	1.087E-01	2.612E-02	44.1
0.05	2	1.114E-01	2.610E-02	45.3	1.053E-01	2.671E-02	42.7
0.01	1	2.523E-02	4.717E-03	51.1	N/A	N/A	N/A
0.01	2	N/A	N/A	N/A	2.477E-02	4.668E-03	50.2
		Site I2 Sandy Loam (M804)			Site K Light Clay (M822)		
conc (µg/ml)	Rep	sorbed µg/g	in soln µg/ml	% sorbed	sorbed µg/g	in soln µg/ml	% sorbed
1	1	N/A	N/A	N/A	9.732E-01	7.109E-01	20.7
1	2	3.352E-01	7.249E-01	17.8	8.467E-01	7.370E-01	18.0
0.5	1	1.370E-01	4.028E-01	13.6	4.332E-01	3.982E-01	17.2
0.5	2	1.631E-01	3.934E-01	16.2	4.365E-01	3.965E-01	17.3
0.1	1	4.983E-02	7.340E-02	24.3	1.289E-01	7.173E-02	25.1
0.1	2	5.085E-02	7.257E-02	24.8	1.310E-01	7.124E-02	25.6
0.05	1	2.228E-02	3.513E-02	22.6	5.538E-02	3.626E-02	22.5
0.05	2	2.445E-02	3.507E-02	24.8	6.161E-02	3.517E-02	25.0
0.01	1	4.463E-03	7.123E-03	22.5	N/A	N/A	N/A
0.01	2	4.693E-03	7.004E-03	23.6	1.282E-02	6.943E-03	26.0
		Site M2 Organic (Peat or Muck) (M823)					
1	1	8.753E+00	6.436E-02	92.9			
1	2	8.759E+00	6.362E-02	93.0			
0.5	1	4.721E+00	3.107E-02	93.6			
0.5	2	4.725E+00	3.086E-02	93.6			
0.1	1	9.738E-01	4.855E-03	95.0			
0.1	2	9.750E-01	4.720E-03	95.1			
0.05	1	4.674E-01	2.393E-03	94.9			
0.05	2	4.659E-01	2.541E-03	94.6			
0.01	1	9.401E-02	4.498E-04	95.2			
0.01	2	9.405E-02	4.433E-04	95.3			

N/A = not available. Sample mass balance was unacceptable

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Table B.8.124 Concentrations of X11449757 in liquid and soil phases in adsorption isotherm tests

		Yolo Light Clay (M800)			RefSol 01-A Loamy Sand (M801)		
conc (µg/ml)	Rep	sorbed µg/g	in soln µg/ml	% sorbed	sorbed µg/g	in soln µg/ml	% sorbed
1	1	1.395E+00	8.714E-01	13.8	1.391E+00	7.349E-01	27.5
1	2	1.752E+00	8.324E-01	17.3	1.404E+00	7.308E-01	27.7
0.5	1	8.470E-01	4.143E-01	16.9	7.562E-01	3.488E-01	30.2
0.5	2	8.855E-01	4.136E-01	17.7	7.695E-01	3.456E-01	30.7
0.1	1	2.016E-01	7.460E-02	21.1	1.655E-01	6.286E-02	34.6
0.1	2	2.018E-01	7.439E-02	21.1	1.647E-01	6.182E-02	34.4
0.05	1	1.097E-01	3.846E-02	22.0	1.004E-01	3.015E-02	40.2
0.05	2	1.074E-01	3.878E-02	21.5	9.232E-02	3.115E-02	37.0
0.01	1	2.428E-02	7.207E-03	25.0	2.128E-02	5.716E-03	43.8
0.01	2	2.578E-02	7.072E-03	26.6	2.074E-02	5.562E-03	42.7
		RefSol 03-G Clay Loam (M802)			Site E Silt Loam (M803)		
1	1	2.619E+00	7.409E-01	25.9	3.537E+00	6.481E-01	34.9
1	2	2.337E+00	7.668E-01	23.1	3.677E+00	6.390E-01	36.3
0.5	1	1.446E+00	3.568E-01	28.8	1.909E+00	3.051E-01	38.0
0.5	2	1.409E+00	3.548E-01	28.1	1.836E+00	3.118E-01	36.5
0.1	1	N/A	N/A	N/A	4.072E-01	5.340E-02	42.5
0.1	2	3.319E-01	6.106E-02	34.6	4.057E-01	5.428E-02	42.3
0.05	1	1.955E-01	2.982E-02	39.2	2.321E-01	2.619E-02	46.4
0.05	2	1.858E-01	3.079E-02	37.2	2.347E-01	2.615E-02	47.0
0.01	1	4.051E-02	5.602E-03	41.7	4.673E-02	4.935E-03	48.1
0.01	2	N/A	N/A	N/A	4.946E-02	4.658E-03	50.9
		Site I2 Sandy Loam (M804)			Site K Light Clay (M822)		
conc (µg/ml)	Rep	sorbed µg/g	in soln µg/ml	% sorbed	sorbed µg/g	in soln µg/ml	% sorbed
1	1	1.802E-01	8.656E-01	8.9	N/A	N/A	N/A
1	2	2.494E-01	8.269E-01	12.3	6.278E-01	9.331E-01	6.2
0.5	1	1.034E-01	4.162E-01	10.3	3.147E-01	4.606E-01	6.3
0.5	2	1.284E-01	4.050E-01	12.8	3.021E-01	4.605E-01	6.0
0.1	1	3.605E-02	7.323E-02	18.8	5.692E-02	8.746E-02	5.9
0.1	2	2.480E-02	7.874E-02	12.9	6.706E-02	8.660E-02	7.0
0.05	1	1.514E-02	3.960E-02	15.1	3.190E-02	4.581E-02	6.4
0.05	2	1.487E-02	3.977E-02	14.8	4.765E-02	4.491E-02	9.5
0.01	1	2.868E-03	7.750E-03	14.7	8.567E-03	8.688E-03	8.8
0.01	2	3.055E-03	7.845E-03	15.6	5.665E-03	8.994E-03	5.8
		Site M2 Organic (Peat or Muck) (M823)					
1	1	9.510E+00	5.986E-02	93.8			
1	2	9.516E+00	5.903E-02	93.9			
0.5	1	4.731E+00	2.751E-02	94.3			
0.5	2	4.727E+00	2.778E-02	94.2			
0.1	1	9.113E-01	4.465E-03	95.1			
0.1	2	9.131E-01	4.313E-03	95.3			
0.05	1	4.761E-01	2.238E-03	95.3			
0.05	2	4.766E-01	2.193E-03	95.4			
0.01	1	9.258E-02	4.329E-04	95.3			
0.01	2	9.291E-02	4.016E-04	95.7			

N/A = not available. Sample mass balance was unacceptable

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Table B.8.125 Adsorption and desorption constants for XDE-729 methyl

XDE-729 methyl												
	adsorption						desorption					
Soil	Kf	Kfoc	1/n	r^2	Kd	Koc	Kf	Kfoc	1/n	r^2	Kd	Koc
Yolo	29	2197	0.84	0.999	51	3887	52	3969	0.86	0.999	94	7221
RefSol 01-A	21	1902	0.87	0.997	33	2998	33	2975	0.90	0.998	52	4715
RefSol 03-G	29	1155	0.90	0.991	46	1821	77	3061	0.91	0.998	126	5056
Site E	28	778	0.93	0.990	39	1082	74	2063	0.89	0.998	137	3798
Site I2	11	794	0.84	0.995	19	1391	16	1164	0.84	0.991	32	2273
Site K	6	141	0.74	0.990	25	576	30	671	0.79	0.989	127	2897
Site M2	671	2026	0.92	0.999	1052	3178	957	2892	0.90	0.999	1726	5214
average	113	1285	0.86	0.994	178	2136	177	2399	0.87	0.996	324	4459
std dev	228	716	0.06	0.004	360	1298	319	1076	0.04	0.004	582	1875
median	28	1155	0.87	0.995	39	1821	52	2892	0.89	0.998	126	4715
max	671	2197	0.93	0.999	1052	3887	957	3969	0.91	0.999	1726	7221
min	6	141	0.74	0.990	19	576	16	671	0.79	0.989	32	2273

K_F units: $\mu g^{1-1/n} mL^{1/n} g^{-1}$

K_d and K_{oc} values reported as averages of all concentrations

Table B.8.126 Adsorption constants for X11393729

X11393729 adsorption						
Soil	Kf	Kfoc	1/n	r2	Kd	Koc
Yolo	1.48	113	0.83	0.988	2.23	172
RefSol 01-A	1.66	151	0.96	0.981	1.90	172
RefSol 03-G	2.40	96	0.83	0.995	3.87	155
Site E	2.40	67	0.84	0.997	3.63	101
Site I2	0.41	29	0.88	0.986	0.58	41
Site K	1.14	26	0.88	0.992	1.50	34
Site M2	113	341	0.91	0.998	179	539
average	17	118	0.88	0.991	27	179
std dev	42	108	0.05	0.006	65	171
median	1.66	96	0.88	0.992	2.23	155
max	113	341	0.96	0.998	179	539
min	0.41	26	0.83	0.981	0.58	34

K_F units: $\mu g^{1-1/n} mL^{1/n} g^{-1}$

K_d and K_{oc} values reported as averages of all concentrations

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Table B.8.127 Adsorption constants for X11449757

X11449757 adsorption						
Soil	Kf	Kfoc	1/n	r^2	Kd	Koc
Yolo	1.84	142	0.87	0.998	2.59	200
RefSol 01-A	1.86	169	0.86	0.999	2.73	248
RefSol 03-G	3.28	131	0.83	0.998	4.98	199
Site E	3.73	104	0.84	0.998	6.01	167
Site I2	0.26	19	0.90	0.988	0.34	24
Site K	0.66	15	0.95	0.988	0.76	17
Site M2	134	405	0.93	0.999	195	590
average	21	141	0.88	0.996	30	209
std dev	50	131	0.05	0.005	69	186
median	1.86	131	0.87	0.998	2.73	199
max	134	405	0.95	0.999	195	590
min	0.26	15	0.83	0.988	0.340	17

K_F units: $\mu g^{1-1/n} mL^{1/n} g^{-1}$
K_d and K_{oc} values reported as averages of all concentrations

(Yoder, Adusumilli and Smith 2011, amended 2012)

b) Given the instability of XDE-729 methyl in the initial adsorption/desorption study, a further study was conducted on this substance on the same seven soils but with shortened equilibrium time. The study was performed according to OECD 106 and US EPA guidelines (OPPTS 835.1230) and GLP.

Study design in respect of measurement of soil adsorption was essentially the same as described in B.8.2.1a) above, including gamma irradiation to sterilise the soils; the soil properties were essentially the same as those in the first adsorption study in B.8.2.1a). Soil:solution ratios were determined on Yolo and RefSol 01-A soils and a 1:25 soil:solution ratio was determined as being most appropriate (in contrast to the previous study where soil:solution ratios of 1:5, 1:15 and 1:30 were used). No significant adsorption to test equipment was determined, but as in the previous study, significant degradation took place. Therefore equilibrium times of two hours for soils Site E, Site K and Site M2, and six hours for the remaining four soils (Yolo, RefSol 01-A, RefSol 03-G and Site I2) were chosen. Whilst not explicitly stated, it appears that the aim was to try to retain 90% of undegraded parent material in the test system.

It is noted that mass balance was often less than 90% in individual replicates. The study authors chose to exclude results from replicates with mass balance <84%. It is noted that in the previous study, higher mass balances were seen and that replicates with <85% recovery were excluded and that there were a number of instances of mass balance between 85 and 90% AR. However, the number of instances of recovery lower than 90% in the new study was greater. The reasons for low mass balance were not specified in the study, but the Applicant attempted to explain the reduced mass balances in correspondence with the RMS, and the text of the reply is given below. If results with mass balance <90% were excluded, this would exclude the majority of results for some soils. The numbers of replicates with mass balance >90% in the old and new study are shown below. The study authors decided to use a 'cut-off' of 84% AR in order to be able to include sufficient soils to obtain a Freundlich isotherm.

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Table B.8.128 Numbers of replicates (out of 10) where mass balance was >90% AR

Soil	No replicates (out of 10) with mass balance >90% AR	
	New study	Old study
Yolo	3	10
RefSol 01-A	1	5
RefSol 03-G	8	9
Site E	5	9
Site I2	0	7
Site K	6	8
Site M2	7	8

"It is agreed that the mass balances in the new study are lower than in the original study. However, I can confirm that essentially the same acceptance criteria for mass balance have been used in both studies. In the old study, samples with mass balance < 85% were rejected. In the new study, the limit was set at 84%. However, there are only two values with recoveries between 84% and 85% (84.7% and 84.9% - see Table 8 of the study) so all other samples were > 85%, and so the acceptance/rejection criteria used are essentially the same. In the first study, 7 samples out of a total of 70 samples (i.e. 10%) were rejected due to mass balance <85% or >110%; in the second study, 11 samples (16%) were rejected for the same reason (not including the 2 samples just under 85% mentioned above, which were accepted). In the first study, 56 samples (80%) achieved a mass balance of 90-110%, compared to 30 samples (43%) in the second study.

The reasons for the lower recoveries in the second study are not obvious. The main objective of the second study was to minimise degradation of XDE-729 methyl so that more reliable data could be obtained. Therefore, in the second study, the adsorption and desorption measurements were performed as separate tests, whereas in the original study, the desorption phase was performed sequentially after the adsorption phase. The reason for this changed procedure was to minimise the degradation of XDE-729 Methyl by keeping the adsorption test as short as possible. This meant that, in the second study, the soil pellet following the adsorption phase contained higher levels of test substance prior to ASE extraction so that any losses that occurred during the transfer of soil to the ASE cell would be higher.

Also, a different soil:solution ratio was used in the two studies. The original study was conducted using three different soil: solution ratios. 1:5 (4 g soil plus 20 ml solution), 1:15 (2 g soil plus 30 ml solution) and 1:30 (1 g soil plus 30 ml solution). In an effort to reduce variability in the sampling procedure and to minimise degradation, the second study utilized a soil: solution ratio of 1:25 only (1 g soil plus 25 ml solution). The soil samples from the original study were freeze dried prior to mixing with diatomaceous earth (DE) and transferred to an ASE cell for extraction. Due to the small sample size (1 g dry weight) the wet soil pellet from the second study was mixed with DE before transfer to an ASE cell, in order to aid the transfer of the wet pellet. The loss of radioactivity in the second study could be due to incomplete transfer of the entire soil pellet and DE mass to the ASE cell due to the difficulty in quantitatively transferring such a small amount of soil. Since roughly half the radioactivity was recovered by extraction of the soil pellet, any such loss could result in lower mass balance. If radioactivity was lost during the soil extraction procedure, actual sorption

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coefficients may be considered more conservative as the measured coefficients will be lower because the amount of material sorbed to soil would be underestimated."

It was also noted from the previous study that whilst separate analysis of both aqueous and soil phases was conducted, this was only conducted on a single replicate per dose. The Applicant confirmed in separate correspondence that both replicates per dose were analysed (where replicates met the mass balance acceptance criteria), as shown below by text from their correspondence:

"Regarding the question about HPLC analysis, I confirm that all samples — including duplicate samples of all adsorption aqueous, desorption aqueous (when applicable) and ASE extracts—were analyzed by HPLC. All ASE extracts were concentrated prior to HPLC analysis. When direct injection was not possible due to low levels of radioactivity, aqueous samples were concentrated prior to HPLC analysis. All samples from the adsorption test were successfully analysed. Only for the lowest concentration desorption samples for the M823 organic (peat or muck) soil was it not possible to obtain reliable HPLC data. HPLC data are reported in Table 6 and Table7 of report 120834."

On the basis of the responses received, the RMS considers that the study can be accepted.

Results from the revised test are given below.

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Table B.8.129 Concentrations of XDE-729 methyl in liquid and soil phases in revised adsorption isotherm tests with shortened equilibrium time

		Yolo Light Clay (M800)			RefSol 01-A Loamy Sand (M801)		
conc (µg/ml)	Rep	sorbed µg/g	in soln µg/ml	% sorbed	sorbed µg/g	in soln µg/ml	% sorbed
1	1	9.8800	0.3995	41.43	8.7900	0.4519	38.33
1	2	9.2800	0.3997	41.25	8.4940	0.4503	38.11
0.5	1	6.3390	0.2159	48.93	4.6230	0.2230	37.2
0.5	2	5.3380	0.1780	46.02	N/A	N/A	N/A
0.1	1	1.3710	0.0369	50.63	1.0660	0.0444	43.38
0.1	2	N/A	N/A	N/A	N/A	N/A	N/A
0.05	1	0.6791	0.0168	48.76	0.5510	0.0228	40.35
0.05	2	0.6717	0.0152	50.15	N/A	N/A	N/A
0.01	1	0.1474	0.0040	60.74	0.1133	0.0035	45.33
0.01	2	0.1317	0.0029	54.85	0.1230	0.0033	54.73
		RefSol 03-G Clay Loam (M802)			Site E Sit Loam (M803)		
1	1	10.9400	0.3618	43.13	9.2140	0.3492	38.63
1	2	10.0700	0.3463	44.35	8.7620	0.3686	35.63
0.5	1	5.4250	0.1733	43.21	N/A	N/A	N/A
0.5	2	6.0720	0.1684	48.86	4.8250	0.1589	38.83
0.1	1	1.3550	0.0344	50.05	1.3540	0.0321	48.98
0.1	2	1.3420	0.0311	50.08	1.2480	0.0323	45.15
0.05	1	0.7219	0.0170	51.83	0.5655	0.0152	42.22
0.05	2	0.6949	0.0163	50.39	N/A	N/A	N/A
0.01	1	0.1299	0.0027	50.88	0.1226	0.0028	47.05
0.01	2	0.1304	0.0025	55.88	0.1124	0.0024	49.06
		Site I2 Sandy Loam (M804)			Site K Light Clay (M822)		
conc (µg/ml)	Rep	sorbed µg/g	in soln µg/ml	% sorbed	sorbed µg/g	in soln µg/ml	% sorbed
1	1	5.5220	0.5622	23.15	N/A	N/A	N/A
1	2	5.2720	0.5732	21.89	5.2090	0.3623	21.62
0.5	1	3.1110	0.2824	26.05	1.9380	0.2037	16.08
0.5	2	2.9280	0.2744	24.53	1.6280	0.1934	13.37
0.1	1	N/A	N/A	N/A	0.7842	0.0341	29.56
0.1	2	N/A	N/A	N/A	0.7722	0.0336	29.4
0.05	1	N/A	N/A	N/A	0.4324	0.0180	31.66
0.05	2	0.4092	0.0301	29.38	0.4473	0.0191	32.43
0.01	1	0.0776	0.0047	31.97	0.0886	0.0030	36.16
0.01	2	0.0810	0.0049	33.39	0.0855	0.0027	35.23
		Site M2 Organic (Peat or Muck) (M823)					
1	1	19.0400	0.0584	79.84			
1	2	17.8300	0.0570	76.99			
0.5	1	9.7640	0.0287	82.58			
0.5	2	9.8970	0.0286	82.08			
0.1	1	2.0090	0.0054	78.75			
0.1	2	2.0660	0.0060	79.41			
0.05	1	1.1380	0.0031	83.33			
0.05	2	1.0700	0.0035	76.81			
0.01	1	N/A	N/A	N/A			
0.01	2	0.2037	0.0006	81.48			

N/A = not available. Sample mass balance was unacceptable

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Table B.8.130 Revised soil adsorption parameters for XDE-729-methyl using shortened equilibrium times

	XDE-729 methyl											
	adsorption						desorption					
Soil	K_F	K_{FOC}	1/n	r^2	K_d	K_{oc}	K_F	K_{FOC}	1/n	r^2	K_d	K_{oc}
Yolo	24	1812	0.89	0.996	35	2659	29	2253	0.80	0.988	79	6070
RefSol 01-A	17	1553	0.88	0.999	25	2294	22	2012	0.89	0.977	38	3410
RefSol 03-G	28	1104	0.90	0.999	39	1576	26	1033	0.91	0.993	38	1524
Site E	24	660	0.88	0.997	36	1007	34	955	0.97	0.994	40	1098
Site I2	9	652	0.89	1.000	13	893	10	697	0.83	0.949	22	1593
Site K	8	190	0.76	0.972	21	473	15	343	0.88	0.974	26	582
Site M2	310	936	0.98	0.997	340	1026	606	1830	1.02	0.986	526	1589
average	60	987	0.88	0.994	73	1418	106	1303	0.90	0.980	110	2267
std dev	102	517	0.06	0.009	118	798	204	672	0.07	0.015	184	1891
median	24	936	0.89	0.997	35	1026	26	1033	0.89	0.986	38	1589
max	310	1812	0.98	1.000	340	2659	606	2253	1.02	0.994	526	6070
min	8	190	0.76	0.972	13	473	10	343	0.80	0.949	22	578

(Yoder, Brackman and Jonas, 2012)

B.8.2.2 Summary & assessment - Adsorption, desorption and mobility in soil

A single study was performed to determine the soil adsorption characteristics of XDE-729 methyl and its soil metabolites X11393729 and X11449757. The study was generally performed appropriately to OECD 106 guidelines. Seven soils were selected with an appropriate range of soil properties including clay content and pH. It was noted that one of the seven soils tested was an organic soil ('Site M2') with a high organic carbon content (33.1%) which also possessed the lowest pH of the tested soils (pH 4.1). This inevitably led to high measured values of adsorption on this soil for each of the three tested substances. Whilst the OECD 106 guideline recommends use of a soil with >10% oc, it is considered that a soil with 33% oc cannot be considered to be typical of EU agricultural soils; the Jokioinen FOCUSgw scenario, considered to have a relatively high organic carbon content, has a maximum %oc content of 4%. It is thus considered that the choice of soil adsorption parameters for use in FOCUS modelling should exclude results from this soil.

It must be borne in mind that XDE-729 methyl was unstable in the adsorption test, and whilst efforts were made to take this into account, this may have still impacted on the adsorption isotherms and increased uncertainty over their reliability relative to a more stable substance. The methodology used by the study authors of only analysing a single replicate for each dose and extrapolating the results to the other replicate is not ideal but the RMS can accept the specific case made by the Applicant as to the acceptability of this approach for XDE-729 methyl. In addition, the extrapolation of results at higher doses to those at lower doses is also not ideal, but is a consequence of the need to cover a concentration range of two orders of magnitude, the water solubility and the LOQ of the analytical method.

Given the uncertainty issues arising from degradation of XDE-729 methyl seen over the equilibrium time, the Applicant repeated the soil adsorption study for the parent

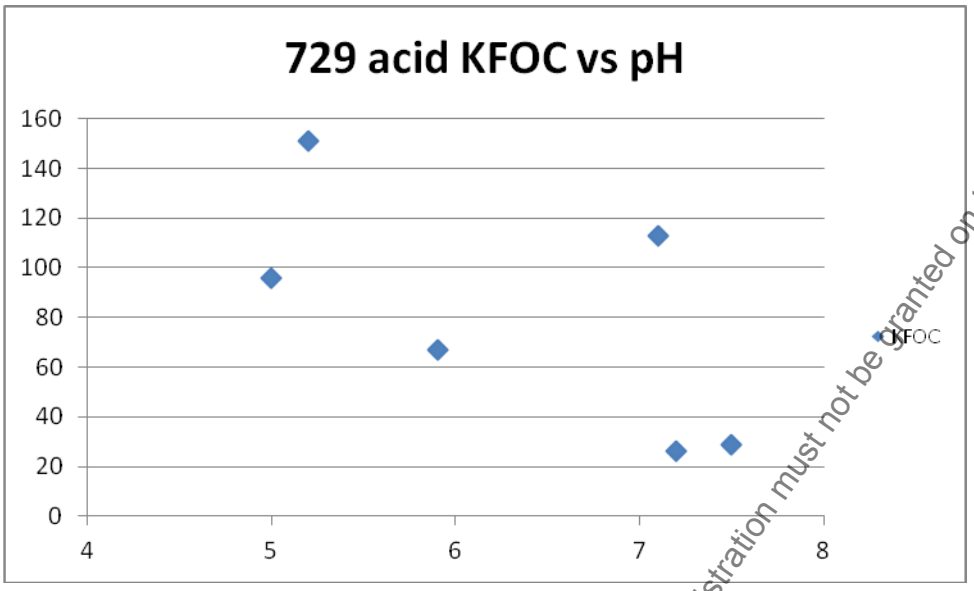
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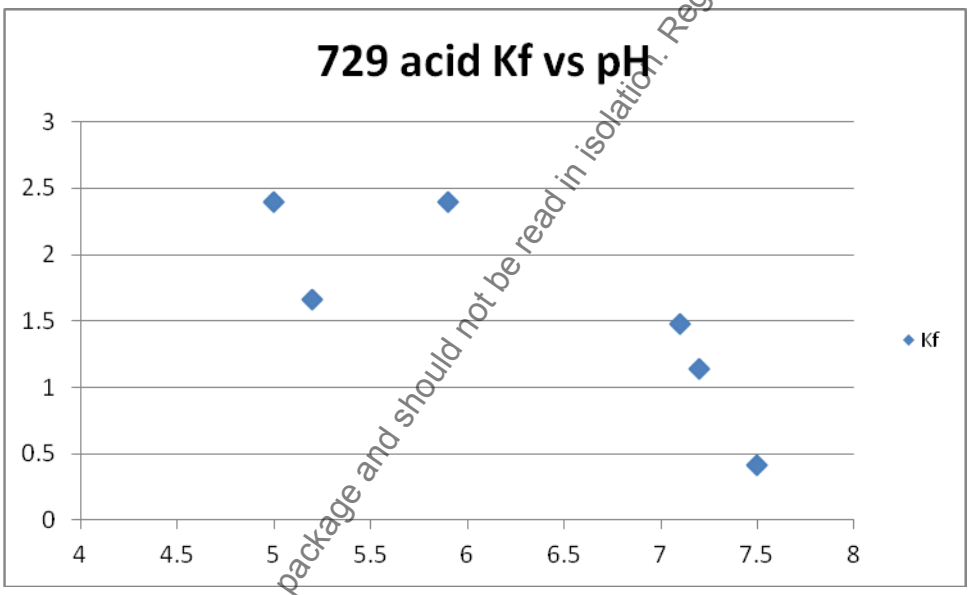
with shorter equilibrium time of 2 – 6 hours. The same seven soils used in the first study were tested. The shortened equilibrium time was used in an attempt to retain as much undegraded parent in the test system as possible whilst allowing some opportunity for adsorption. Whilst not specifically stated, it appears that from the results of the preliminary test that there was an aim for 90% unchanged parent to remain in the system at the end of the equilibrium time. However, it is noted that during the incubations to establish Freundlich adsorption isotherms, total mass balance often fell below 90%; measurements of mineralisation or adsorption to experimental equipment were excluded from the mass balance assessment. A threshold mass balance of 84% was applied to the results and whether they could be used in the calculation of the Freundlich isotherm. The Applicant clarified that analysis of both replicates per dose in the adsorption isotherm test had been conducted as appropriate, i.e. where mass balance criteria for acceptance were met. Given that this meets the requirements of OECD 106, the RMS considers that the study can be accepted and that there is less uncertainty over the results given that both replicates were analysed and the extrapolation procedure between replicates employed in the first study was not practiced in this second study. Given that the reservations of the RMS over the first of the two soil adsorption studies on XDE-729 methyl in relation to the analysis procedure used, the RMS considers it better to use the results of the second study rather than the first as the definitive soil adsorption endpoints. This coincidentally leads to slightly more conservative adsorption values.

Considering the results of the second study and excluding the results of the Site M2 organic soil, the Kfoc values of XDE-729 methyl in the repeated study range from 190 – 1812 ml/g and 1/n of 0.76 – 0.90. These Kfoc values from the new study are slightly lower than from the original study and may simply reflect the reduced opportunity for undegraded parent to adsorb to soil particles as a result of the shortened equilibrium time. There does not appear to be a clear and consistent trend for dependence of Kfoc on pH. In addition, there appears to be no consistent relationship between Kf and organic carbon content or Kf and pH. This suggests that that exposure modelling for parent ought to be conducted using both Kf and Kfoc.

Metabolite X11393729 demonstrated Kfoc values of 26 -151 mg/l and 1/n values of 0.83 – 0.96 following exclusion of the organic soil result. An exploration of Kf in relation to % organic carbon suggests that there is no convincing relationship of increasing adsorption with increasing organic carbon, which again suggests that Kf ought to also be explored as an input parameter for exposure modelling. Unlike the parent, there appears to be reasonably strong evidence that soil adsorption is related to pH, with stronger adsorption at low pH; this is the case for both Kfoc and Kf (see below). This might be expected due to a carboxylic acid group in X11393729 where lower pH would shift the equilibrium towards the undissociated form.

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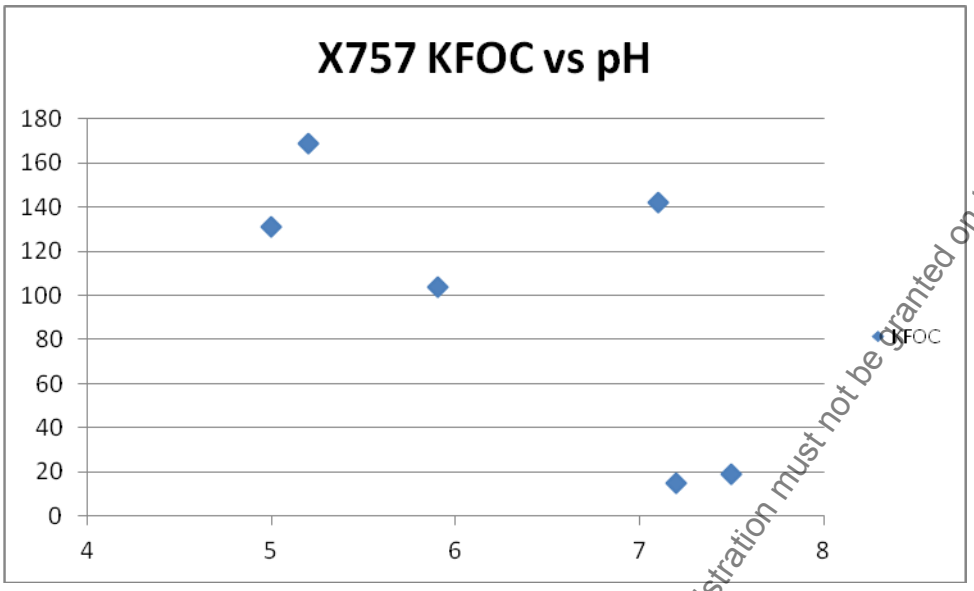


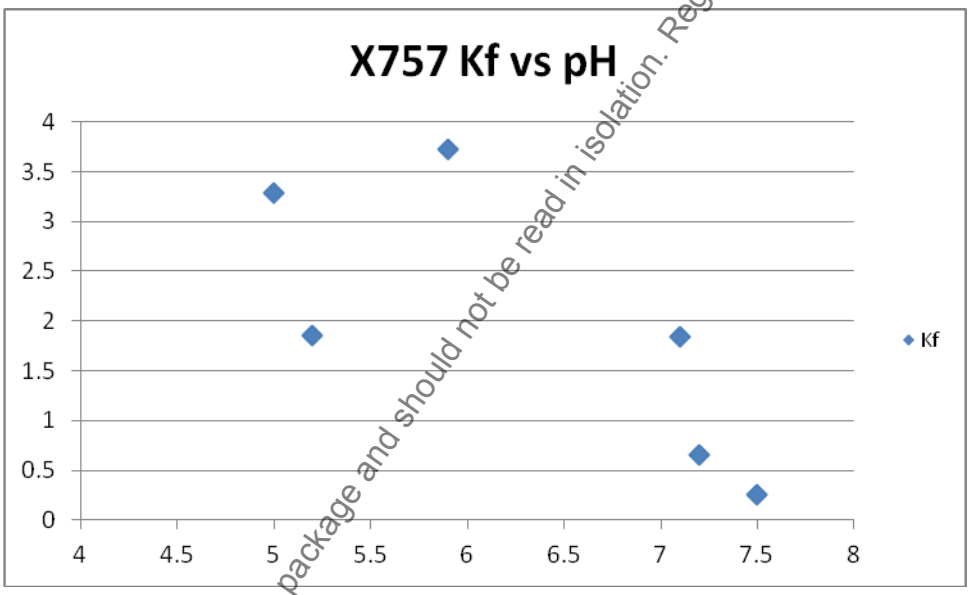


The possibility of pH dependent adsorption is supported by the pKa value of 5.11 for this substance (see section B.2 of the DAR). It is thus proposed that it is appropriate to take pH dependence into account in the environmental exposure assessment of X11393729.

Metabolite X11449757 demonstrated Kfoc values of 15 - 169 mg/l and 1/n values of 0.83 – 0.95 following exclusion of the organic soil result. An exploration of Kf in relation to % organic carbon suggests that there is no convincing relationship of increasing adsorption with increasing organic carbon, which again suggests that Kf ought to also be explored as an input parameter for exposure modelling. As with X11393729, there appears to be reasonably strong evidence that soil adsorption is related to pH, with stronger adsorption at low pH; this is the case for both Kfoc and Kf. This might be expected due to a carboxylic acid group in X11449757 where lower pH would shift the equilibrium towards the undissociated form.

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The possibility of pH dependent adsorption is supported by the pKa value of 5.6 for the carboxylic acid group of this substance and 7.1 for the phenolic group this substance (see section B.2 of the DAR) It is thus proposed that it is appropriate to take pH dependence into account in the environmental exposure assessment of X11449757.

It should be noted that the Applicant has conducted exposure modelling using Kfoc values for all substances included in risk assessment, and the need for exposure modelling using Kf for parent, X11393729 and X11449757 could be the subject of an expert discussion.

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Soil adsorption/desorption (Annex IIA, point 7.1.2)

Parent: XDE-729 methyl‡							
Soil Type (USDA)	OC %	Soil pH	Kd (ml/g)	Koc (ml/g)	Kf (ml/g)	Kfoc (ml/g)	1/n
Clay loam	1.3	7.1	35	2659	24	1812	0.89
Loamy sand	1.1	5.2	25	2294	17	1553	0.88
Loam	2.5	5	39	1576	28	1104	0.90
Silt loam	3.6	5.9	36	1007	24	660	0.88
Sandy loam	1.4	7.5	13	893	9	652	0.89
Clay loam	4.4	7.2	21	473	8	190	0.76
Organic*	33.1	4.1	340	1026	310*	936*	0.98*
Arithmetic mean					18	995	0.87
pH dependence, Yes or No			Very weak, not considered in modelling				

* results excluded from calculation of mean as soil considered unrepresentative

Metabolite: X11393729‡							
Soil Type	OC %	Soil pH	Kd (ml/g)	Koc (ml/g)	Kf (ml/g)	Kfoc (ml/g)	1/n
Clay loam	1.3	7.1	2.23	172	1.48	113	0.83
Loamy sand	1.1	5.2	1.90	172	1.66	151	0.96
Loam	2.5	5	3.87	155	2.40	96	0.83
Silt loam	3.6	5.9	3.63	101	2.40	67	0.84
Sandy loam	1.4	7.5	0.58	41	0.41	29	0.88
Clay loam	4.4	7.2	1.50	34	1.14	26	0.88
Organic*	33.1	4.1	179	539	113*	341*	0.91*
Arithmetic mean/median	Not appropriate, pH dependence						
pH dependence (yes or no)			Yes, increased sorption at low pH				

* results excluded from consideration as soil considered unrepresentative

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Metabolite: X11449757‡							
Soil Type	OC %	Soil pH	Kd (ml/g)	Koc (ml/g)	Kf (ml/g)	Kfoc (ml/g)	1/n
Clay loam	1.3	7.1	2.59	200	1.84	142	0.87
Loamy sand	1.1	5.2	2.73	248	1.86	169	0.86
Loam	2.5	5	4.98	199	3.28	131	0.83
Silt loam	3.6	5.9	6.01	167	3.73	104	0.84
Sandy loam	1.4	7.5	0.34	24	0.26	19	0.90
Clay loam	4.4	7.2	0.76	17	0.66	15	0.95
Organic*	33.1	4.1	195	590	134*	405*	0.93*
Arithmetic mean/median	Not appropriate, pH dependence						
pH dependence (yes or no)			Yes, increased sorption at low pH				

* results excluded from consideration as soil considered unrepresentative

Mobility in soil (Annex IIA, point 7.1.3, Annex IIIA, point 9.1.2)

Column leaching ‡	Not submitted, not required
Aged residues leaching ‡	Not submitted, not required
Lysimeter/ field leaching studies ‡	Not submitted, not required

B.8.3 Predicted environmental concentrations in soil (PECs) (IIIA 9.1)

The worst case GAP for XDE-729 methyl is winter cereals in the autumn at 7.82 g as/ha at crop growth stage BBCH 10-29 (25% interception) followed by a second application in the spring at 6.25 g as/ha at growth stage BBCH 13-45 (25% interception) with a minimum 70 day interval.

i) <u>XDE-729 methyl</u>

In laboratory aerobic degradation studies, XDE-729 methyl degraded relatively rapidly, but exhibited slower degradation in field dissipation studies with a worst case SFO DT50 of 43 days.

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Assuming the above GAP details, mixing over 5 cm depth and bulk density of 1.5 cm^3, the initial PECsoil value after the second application is calculated to be **0.009 mg/kg.**

ii) Metabolites

PECsoil calculations are also needed for metabolites X11393729 and X11449757.

For X11393729, this metabolite showed a worst-case top-down DT50 of 264 days, with worst case molar formation of 40.1% from field dissipation studies. Molecular weight for parent is 345, and 331 for X11393729. Given the apparent persistence of this substance, a maximum total dose approach has been used for PECsoil calculation. Applying molecular weight and observed molar formation corrections, the initial PECsoil for a single years application is calculated to be **0.005 mg/kg**. An accumulation calculation has also been conducted. Based on 5cm depth mixing depth over the course of the calculation and a annual total dose being applied every year, the **peak accumulated concentration of 0.009 mg/kg** occurred in the 6th year application year, with a '**steady state' (bottom of saw teeth) of 0.003 mg/kg**.

For X11449757, this metabolite showed a worst-case top-down DT50 of 197 days, with worst case molar formation of 13.8% from field dissipation studies. Molecular weight for parent is 345, and 317 for X11449757. Given the apparent persistence of this substance, a maximum total dose approach has been used for PECsoil calculation. Applying molecular weight and observed molar formation corrections, the initial PECsoil for a single years application is calculated to be **0.002 mg/kg**. An accumulation calculation has also been conducted. Based on 5cm depth mixing depth over the course of the calculation and a annual total dose being applied every year, the **peak accumulated concentration of 0.0025 mg/kg** occurred in the 5th year application year, with a '**steady state' (bottom of saw teeth) of 0.0007 mg/kg**.

iii) Formulation

A formulation PECsoil has also been calculated. The highest application dose of the formulation "GF-2573" is 1 l product/ha. The relative density of the formulation is 0.905 (section B.2.2.13 of the DAR), thus the application rate is equivalent to 905 g/ha. Whilst the GAP allows up to two applications to winter cereals, it would not be expected that the formulation would remain intact given a minimum interval of 70 days. Thus the PECsoil,formulation has only been calculated on the basis of the initial PECsoil from the highest dose. The same assumptions used above for soil properties and crop interception are made in the PECsoil,formulation calculation. thus, the PECsoil,formulation for "GF-2573" is **0.905 mg/kg.**

iv) Unextracted residue

Given that the Uniform Principles trigger of less than 5% mineralisation and greater than 70% unextracted residues after 100 days was met in at least one laboratory aerobic soil incubation, a consideration of the risk posed by accumulation of unextracted residues is required. The Applicant has attempted to address this requirement for Ecotoxicology by performing a study on earthworms where XDE-729 methyl was dosed into two separate soils at doses between 0.1 mg a.s./kg and 10 mg a.s./kg (see DAR section B.9.8.4 for details). The Applicant considered that based on

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the results of the study at B.8.1.1 c), the mean levels of unextracted radioactivity between 32 and 89 DAT in the 10 mg a.s./kg treatments were 48.6% on the Site E1 soil and 71.0% on the RefSol 03-G soil. Therefore the Applicant considered that the unextracted residue concentrations in the soils during the period of exposure 4.86 mg a.s. equivalent/kg and 7.10 mg a.s. equivalent/kg in the Site E and RefSol 03-G soils respectively.

The total dose of XDE-729 methyl applied in one year is 14.07 g/ha. Using standard soil assumptions and 25% crop interception, this equates to a single year total dose PECsoil of 0.014 mg a.s./kg. The range of dosing in the earthwork study in section B.9.8.4 is therefore equivalent to 7.1x - 714x the annual total dose of XDE-729 methyl.

Taking account of the unextracted residue formed in the aerobic route and rate of degradation study at B.8.1.1 a), the peak amount of unextracted residue seen was 82.5% AR. Considering the annual total dose PECsoil above, the unextracted residue PECsoil for a single year would be 0.012 mg a.s. equivalent/ha. The Applicant considered that on average during the earthworm study, the worms would have been exposed to an unextracted residue of 4.86 – 7.10 mg a.s. equivalent/kg. Therefore these exposure levels are equivalent to 405x – 592x the expected single year unextracted residue.

In section B.8.1.4 b), the Applicants kinetic calculations indicated an upper accumulation factor for unextracted residues of 3.83x of the initial application rate; this would suggest an accumulation of unextracted residue equivalent to 0.054 mg a.s./kg. The RMS has expressed some reservations about the accuracy of these calculations given uncertainty over the calculated kinetic parameters for formation and decline of unextracted residues. However, the application dosing in the earthworm effects study at B.9.8.4 of up to 714x the annual total dose of the parent or 405x - 592x the single year unextracted residue indicates to the RMS that uncertainty over the kinetic calculations are likely to be compensated for by the exaggerated doses used, i.e. even if calculations indicated accumulation of unextracted 10x greater than currently predicted by the Applicant, the earthworm study would have been conducted at doses able to address the likely risk. However, this is on the understanding that there were no observable effects on earthworms at the highest dose of 10 mg a.s./kg (see section B.9.8.4).

B.8.4 Fate and behaviour in water (IIA 7.2.1, IIIA 9.2.1, 9.2.3)

B.8.4.1 Aqueous hydrolysis

The hydrolytic stability of XDE-729 methyl was studied according to OECD Guideline 111, US EPA guidelines OPPTS 835.2120 and GLP.

Sterile aqueous buffer solutions (pH 4, 7 and 9) were prepared containing ^{14}C-XDE-729 methyl radiolabelled in either the phenyl or pyridine ring positions (approx. 1 mg a.s./litre). Samples (20 ml) of each treated buffer were then incubated in the dark at 10, 25 and 50°C; sample containers were sealed and there was no trapping of volatile

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gases. At 0, 1, 3, 7, 14, 21 and 30 days after application, single samples of each buffer were analysed directly by HPLC with UV and radiochemical detection. Substance identification was by co-chromatography using reference standards and additionally using LC-MS and LC-MS/MS.

Degradation rates of the a.s. were determined using SFO kinetics only. Details of software and procedures used were not discussed in the study report. Results of the study are presented below.

Table B.8.131 Results of XDE-729 methyl hydrolysis study (% AR), 10ºC

DAT	Rep	pH 4			pH 7			pH 9		
		% Applied radioactivity	% of HPLC		% Applied radioactivity	% of HPLC		% Applied radioactivity	% of HPLC	
			X11393729	XDE-729 methyl		X11393729	XDE-729 methyl		X11393729	XDE-729 methyl
0	PH	101.4	0.0	98.9	103.2	0.0	98.5	99.8	4.5	94.5
0	PY	100.4	0.0	99.0	99.5	0.0	99.5	99.5	3.9	95.2
1	PH	101.3	0.0	98.6	91.6	0.0	98.9	101.6	10.3	88.9
1	PY	101.1	0.0	99.5	99.5	0.0	99.6	92.1	10.3	89.4
3	PH	101.3	0.5	98.4	100.4	0.0	99.1	100.3	13.0	86.0
3	PY	100.7	0.3	98.9	99.4	0.0	99.0	99.0	14.2	85.2
7	PH	100.0	1.5	97.4	100.1	0.8	97.8	101.2	26.7	72.6
7	PY	102.7	1.6	97.7	100.2	1.8	97.9	100.2	27.8	71.8
14	PH	103.7	3.8	95.3	100.3	1.2	98.1	102.1	42.9	56.0
14	PY	103.9	3.6	95.1	101.5	0.8	97.9	101.9	41.1	58.0
21	PH	103.3	5.1	93.6	97.7	2.5	96.8	99.9	59.8	39.7
21	PY	101.1	5.4	93.5	99.2	1.8	97.6	100.1	55.4	43.5
30	PH	103.4	7.0	91.5	99.4	3.7	95.2	97.5	71.2	27.9
30	PY	100.3	8.1	90.9	98.2	2.6	96.6	100.1	72.0	27.7

Table B.8.132 Results of XDE-729 methyl hydrolysis study (% AR), 25ºC

DAT	Rep	pH 4			pH 7			pH 9		
		% Applied radioactivity	% of HPLC		% Applied radioactivity	% of HPLC		% Applied radioactivity	% of HPLC	
			X11393729	XDE-729 methyl		X11393729	XDE-729 methyl		X11393729	XDE-729 methyl
0	PH	101.4	0.0	98.9	103.2	0.0	98.5	99.8	4.5	94.5
0	PY	100.4	0.0	99.0	99.5	0.0	99.5	99.5	3.9	95.2
1	PH	98.3	0.9	97.9	100.4	0.5	98.7	101.5	26.9	72.1
1	PY	102.4	0.9	98.5	101.1	0.0	98.2	103.6	25.5	73.8
3	PH	103.4	1.9	96.5	102.2	0.9	97.6	102.2	50.6	48.0
3	PY	100.4	2.5	96.6	100.2	0.8	98.1	101.0	52.2	46.9
7	PH	103.4	4.6	94.4	101.4	4.4	94.6	97.7	80.5	18.4
7	PY	100.9	5.1	93.4	100.6	3.6	95.4	102.4	78.7	20.5
14	PH	101.4	10.3	88.7	100.1	5.1	93.7	99.6	94.4	4.5
14	PY	102.1	11.0	87.8	101.4	4.0	94.7	102.1	94.9	4.7
21	PH	101.6	16.6	82.4	99.3	8.2	89.3	103.8	98.5	0.8
21	PY	101.1	16.3	83.5	99.1	7.4	91.5	99.6	98.3	1.1
30	PH	102.9	23.7	75.7	98.4	13.0	85.7	106.2	98.8	0.0
30	PY	98.2	22.6	77.1	99.9	12.0	86.4	101.7	99.3	0.0

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Table B.8.133 Results of XDE-729 methyl hydrolysis study (% AR), 50ºC

DAT	Rep	pH 4			pH 7			pH 9		
		% Applied radioactivity	% of HPLC		% Applied radioactivity	% of HPLC		% Applied radioactivity	% of HPLC	
			X11393729	XDE-729 methyl		X11393729	XDE-729 methyl		X11393729	XDE-729 methyl
0	PH	101.4	0.0	98.9	103.2	0.0	98.5	99.8	4.5	94.5
0	PY	100.4	0.0	99.0	99.5	0.0	99.5	99.5	3.9	95.2
1	PH	102.7	4.7	94.6	101.6	3.4	95.8	101.0	94.8	4.0
1	PY	103.1	5.5	93.6	101.4	3.0	95.5	101.7	95.4	3.9
3	PH	101.3	15.5	83.2	99.8	9.3	89.7	103.8	98.7	0.0
3	PY	100.5	12.4	86.8	100.7	9.8	89.7	100.9	99.6	0.0
7	PH	100.9	31.4	67.0	100.9	25.8	73.0	101.7	98.5	0.0
7	PY	101.4	32.8	67.0	101.9	23.9	75.4	102.3	99.6	0.0
14	PH	102.1	54.8	44.3	101.0	41.6	56.4	101.4	98.8	0.0
14	PY	101.8	52.2	46.8	100.5	40.4	56.4	101.7	99.2	0.0
21	PH	101.0	68.0	30.8	100.0	54.5	43.4	104.2	98.7	0.0
21	PY	99.9	69.7	28.9	100.2	53.6	44.7	100.4	99.6	0.0
30	PH	100.9	80.6	18.1	101.9	66.9	29.8	102.1	99.2	0.0
30	PY	101.5	83.3	16.2	100.9	70.3	26.7	101.5	99.1	0.0

Table B.8.134 SFO hydrolysis rates for XDE-729 methyl

Buffer/Temp	R^2	DT_{50}	DT_{90}
pH 4 10^0C	0.99	245	813
pH 7 10^0C	0.83	660	>1000
pH 9 10^0C	1.00	17.8	59.2
pH 4 25^0C	1.00	80.9	269
pH 7 25^0C	0.97	155	516
pH 9 25^0C	1.00	3.04	10.1
pH 4 50^0C	1.00	12.1	40.2
pH 7 50^0C	1.00	17.1	56.8
pH 9 50^0C	1.00	0.218	0.725

The only metabolite identified was X11393729. Only minor amounts or radioactivity (<5% AR) appear to remain uncharacterised at each sample time.

(Liu *et al* 2011)

B.8.4.2 Aqueous photolysis

a) The aqueous photolysis of XDE-729 methyl was studied according to OECD 316 and US EPA OPPTS 835.2240 guidelines and GLP.

The study used XDE-729 methyl radiolabelled in both the phenyl and pyridine rings, which was dosed into sterile aqueous pH 7 buffer and sterilized natural water collected from a lake in Derbyshire, UK at an initial concentration of 1 mg a.s./l. Samples were exposed to continuous irradiation using a xenon lamp chamber set at 25°C for an equivalent of 34 days and 36 day of summer sunlight at 40° N latitude, in pH 7 buffer and natural water, respectively. The xenon lamp was appropriately filtered to remove wavelengths <295nm.

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Buffered water samples were removed from the xenon lamp chamber at 6, 12, 18, 32, 46, 60, 95, 129, 241 minutes after treatment (MAT) and 1, 3, 7, 11, 14 and 15 days after treatment (DAT) and were directly analysed by LSC and HPLC with UV and radiochemical detection. Natural water samples were removed from the xenon light chamber at 5, 10, 15, 30, 45, 60, 90, 120 MAT and 1, 3, 7, 10 and 14 DAT and were directly analysed by LSC and HPLC with UV and radiochemical detection. Test vessels of irradiated pH 7 buffer and natural water samples were connected to traps for the collection of CO_2 (NaOH) and organic volatiles (ethylene glycol) from 1DAT until termination of the study; the presence of radiolabelled CO_2 in the NaOH traps was confirmed by precipitation with $BaCl_2$. No trapping for volatiles of CO_2 was undertaken for dark controls. Identification of transformation products was performed by co-chromatography with reference standards but also by LC/MS. Dark control of the pH 7 buffer and natural water were removed from the incubator at 1, 3, 7, 10 or 11, and 14 DAT and directly analyzed by LSC and HPLC.

A PNAP/pyridine chemical actinometer solution was used to quantify the amount of light that the samples received. Based on actinometer data, 1 day of continuous irradiation was equivalent to 2.3 days and 2.6 days of irradiation in the summer sun at 40° N latitude to the pH 7 buffer and natural water samples, respectively. Within the wavelength range of 295 – 800 nm, the total light energy supplied by the xenon lamp was 303 W/(m^2nm).

Results of the mass balances for the incubations are shown below. It should be noted that the only identified degradate in the dark control samples was X11393729 and the concentrations of this metabolite for the dark controls are shown in the mass balance tables.

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Table B.8.135 Mass balance in XDE-729 methyl pH7 aqueous buffer solution, dark control

DAT	Label	Rep	% of Applied 14C in Aqueous	(%) XDE-729 Methyl	(%) X11393729
Ph Samples					
0	Ph		100.0	100.0	0.0
1	Ph	A	98.9	97.1	1.1
1	Ph	B	99.1	98.1	1.0
3	Ph	A	100.2	97.3	2.1
3	Ph	B	100.2	96.5	2.5
7	Ph	A	100.3	95.5	3.8
7	Ph	B	101.3	96.2	4.3
10	Ph	A	100.2	93.7	6.5
10	Ph	B	101.8	93.9	6.9
14	Ph	A	100.4.	92.6	7.8
14	Ph	B	100.3.	92.8	7.5
Py Samples					
0	Py		100.0	97.7	0.0
1	Py	A	99.9	97.1	1.5
1	Py	B	100.6	97.9	1.5
3	Py	A	101.2	98.1	2.3
3	Py	B	100.8	97.6	2.2
7	Py	A	101.0	95.8	4.6
7	Py	B	101.3	95.9	4.8
10	Py	A	100.9	94.1	6.9
10	Py	B	100.6	93.3	7.3
14	Py	A	100.8	91.9	8.9
14	Py	B	101.7	93.6	8.0

DAT = Days after treatment (uncorrected for light-energy received by samples)

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Table B.8.136 Mass balance in XDE-729 methyl pH7 aqueous buffer solution, irradiated samples

Sampling Point	Label	Rep	Aqueous	Caustic Trap	Ethylene Glycol Trap	Total
Ph Samples						
0 MAT	Ph	--	100.0	---	---	100.0
6 MAT	Ph	A	99.2	---	---	99.2
6 MAT	Ph	B	99.2	---	---	99.2
12 MAT	Ph	A	97.8	---	---	97.8
12 MAT	Ph	B	99.3	---	---	99.3
18 MAT	Ph	A	97.1	---	---	97.1
18 MAT	Ph	B	98.1	---	---	98.1
32 MAT	Ph	A	98.1	---	---	98.1
32 MAT	Ph	B	97.0	---	---	97.0
46 MAT	Ph	A	95.5	---	---	95.5
46 MAT	Ph	B	96.8	---	---	96.8
60 MAT	Ph	A	96.1	---	---	96.1
60 MAT	Ph	B	96.3	---	---	96.3
95 MAT	Ph	A	95.3	---	---	95.3
95 MAT	Ph	B	96.7	---	---	96.7
129 MAT	Ph	A	96.1	---	---	96.1
129 MAT	Ph	B	91.8	---	---	91.8
241 MAT	Ph	A	92.5	---	---	92.5
241 MAT	Ph	B	91.2	---	---	91.2
1 DAT	Ph	A	83.0	8.0	0.0	91.1
1 DAT	Ph	B	85.0	7.0	0.0	91.9
3 DAT	Ph	A	73.4	21.3	0.1	94.8
3 DAT	Ph	B	73.3	22.2	0.2	95.7
7 DAT	Ph	A	60.4	31.9	0.3	92.6
7 DAT	Ph	B	59.9	31.3	0.3	91.5
11 DAT	Ph	A	57.4	34.1	0.4	91.9
11 DAT	Ph	B	54.9	37.8	0.5	93.2
14 DAT	Ph	A	44.6	43.6	0.5	88.6
14 DAT	Ph	B	48.3	43.0	0.5	91.7
15 DAT	Ph	A	48.3	41.7	0.5	90.5
15 DAT	Ph	B	48.8	42.1	0.6	91.4

MAT = Minutes after treatment (uncorrected for light-energy received by sample)
DAT = Days after treatment (uncorrected for light-energy received by samples)

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Table B.8.137 Mass balance in XDE-729 methyl pH7 aqueous buffer solution, irradiated samples (continued)

Sampling Point	Label	Rep	Aqueous	Caustic Trap	Ethylene Glycol Trap	Total
Py Samples						
0 MAT	Py	--	100.0	---	---	100.0
6 MAT	Py	A	96.3	---	---	96.3
6 MAT	Py	B	98.2	---	---	98.2
12 MAT	Py	A	96.9	---	---	96.9
12 MAT	Py	B	91.7	---	---	91.7
18 MAT	Py	A	95.3	---	---	95.3
18 MAT	Py	B	95.3	---	---	95.3
32 MAT	Py	A	92.3	---	---	92.3
32 MAT	Py	B	92.7	---	---	92.7
46 MAT	Py	A	91.9	---	---	91.9
46 MAT	Py	B	90.6	---	---	90.6
60 MAT	Py	A	89.9	---	---	89.9
60 MAT	Py	B	92.2	---	---	92.2
95 MAT	Py	A	92.0	---	---	92.0
95 MAT	Py	B	89.8	---	---	89.8
129 MAT	Py	A	91.3	---	---	91.3
129 MAT	Py	B	91.7	---	---	91.7
241 MAT	Py	A	89.7	---	---	89.7
241 MAT	Py	B	90.9	---	---	90.9
1 DAT	Py	A	82.1	10.8	0.0	92.9
1 DAT	Py	B	78.4	11.2	0.0	89.6
3 DAT	Py	A	74.1	21.2	0.1	95.3
3 DAT	Py	B	74.5	20.5	0.1	95.1
7 DAT	Py	A	67.1	27.4	0.1	94.7
7 DAT	Py	B	68.0	26.4	0.1	94.5
11 DAT	Py	A	59.9	31.9	0.2	92.0
11 DAT	Py	B	62.7	30.6	0.2	93.5
14 DAT	Py	A	58.7	34.1	0.2	93.0
14 DAT	Py	B	58.6	33.4	0.2	92.2
15 DAT	Py	A	53.6	38.7	0.3	92.6
15 DAT	Py	B	55.3	37.2	0.2	92.8
15 DAT	Py	C	55.8	35.7	0.2	91.7

MAT = Minutes after treatment (uncorrected for light-energy received by sample)
DAT = Days after treatment (uncorrected for light-energy received by samples)

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Table B.8.138 Mass balance in XDE-729 methyl sterile natural water, dark control

Sampling Point	Label	Rep	% of Applied 14C in Aqueous	(%) XDE-729 Methyl	(%) X11393729
Ph Samples					
0 DAT	Ph		100.0	92.7	7.3
1 DAT	Ph	A	99.7	74.1	25.6
1 DAT	Ph	B	100.5	71.3	29.2
3 DAT	Ph	A	101.4	61.4	40.0
3 DAT	Ph	B	101.5	57.4	44.1
7 DAT	Ph	A	101.8	37.2	64.5
7 DAT	Ph	B	101.9	35.4	66.5
10 DAT	Ph	A	101.9	36.7	65.2
10 DAT	Ph	B	102.0	30.7	71.4
14 DAT	Ph	A	101.9	33.6	67.8
14 DAT	Ph	B	102.1	24.7	76.5
Py Samples					
0 DAT	Py		100.0	92.7	7.3
1 DAT	Py	A	99.0	72.7	26.3
1 DAT	Py	B	99.8	72.6	27.2
3 DAT	Py	A	101.0	58.3	42.6
3 DAT	Py	B	100.9	61.4	39.4
7 DAT	Py	A	101.0	38.9	62.1
7 DAT	Py	B	101.2	37.6	63.7
10 DAT	Py	A	101.7	39.1	62.6
10 DAT	Py	B	101.8	35.0	66.9
14 DAT	Py	A	102.2	28.8	73.4
14 DAT	Py	B	102.0	21.6	80.3

DAT = Days after treatment (uncorrected for light-energy received by samples)

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Table B.8.139 Mass balance in XDE-729 methyl sterile natural water, irradiated samples

Sampling Point	Label	Rep	Aqueous	Caustic Trap	Ethylene Glycol Trap	Total
Ph Samples						
0 MAT	Ph	--	100.0	---	---	100.0
5 MAT	Ph	A	99.9	---	---	99.9
5 MAT	Ph	B	101.3	---	---	101.3
10 MAT	Ph	A	100.8	---	---	100.8
10 MAT	Ph	B	100.5	---	---	100.5
15 MAT	Ph	A	98.8	---	---	98.8
15 MAT	Ph	B	101.4	---	---	101.4
30 MAT	Ph	A	100.3	---	---	100.3
30 MAT	Ph	B	100.4	---	---	100.4
45 MAT	Ph	A	98.0	---	---	98.0
45 MAT	Ph	B	98.8	---	---	98.8
60 MAT	Ph	A	100.6	---	---	100.6
60 MAT	Ph	B	98.9	---	---	98.9
90 MAT	Ph	A	99.4	---	---	99.4
90 MAT	Ph	B	99.2	---	---	99.2
120 MAT	Ph	A	98.6	---	---	98.6
120 MAT	Ph	B	97.9	---	---	97.9
1 DAT	Ph	A	84.2	12.6	0.0	96.7
1 DAT	Ph	B	85.2	12.4	0.0	97.6
3 DAT	Ph	A	68.3	27.7	0.2	96.2
3 DAT	Ph	B	69.0	27.1	0.2	96.4
7 DAT	Ph	A	46.4	46.7	0.4	93.4
7 DAT	Ph	B	44.7	43.4	0.3	88.4
10 DAT	Ph	A	38.8	51.8	0.7	91.3
10 DAT	Ph	B	40.0	50.3	0.9	91.2
14 DAT	Ph	A	35.6	51.0	0.9	87.5
14 DAT	Ph	B	31.5	57.5	1.1	90.2

MAT = Minutes after treatment (uncorrected for light-energy received by sample)
DAT = Days after treatment (uncorrected for light-energy received by samples)

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Table B.8.140 Mass balance in XDE-729 methyl sterile natural water, irradiated samples (continued)

Sampling Point	Label	Rep	Aqueous	Caustic Trap	Ethylene Glycol Trap	Total
Py Samples						
0 MAT	Py		100.0	---	---	100.0
5 MAT	Py	A	99.7	---	---	99.7
5 MAT	Py	B	99.1	---	---	99.1
10 MAT	Py	A	93.8	---	---	93.8
10 MAT	Py	B	93.9	---	---	93.9
15 MAT	Py	A	95.4	---	---	95.4
15 MAT	Py	B	96.2	---	---	96.2
30 MAT	Py	A	94.5	---	---	94.5
30 MAT	Py	B	94.2	---	---	94.2
45 MAT	Py	A	89.9	---	---	89.9
45 MAT	Py	B	91.0	---	---	91.0
60 MAT	Py	A	91.9	---	---	91.9
60 MAT	Py	B	92.2	---	---	92.2
90 MAT	Py	A	92.7	---	---	92.7
90 MAT	Py	B	92.7	---	---	92.7
120 MAT	Py	A	93.4	---	---	93.4
120 MAT	Py	B	92.1	---	---	92.1
1 DAT	Py	A	75.8	19.6	0.0	95.3
1 DAT	Py	B	76.1	20.1	0.0	96.3
3 DAT	Py	A	66.2	28.6	0.1	94.9
3 DAT	Py	B	66.4	31.2	0.1	97.7
7 DAT	Py	A	52.2	41.8	0.2	94.2
7 DAT	Py	B	51.6	43.2	0.3	95.1
10 DAT	Py	A	44.8	48.3	0.4	93.6
10 DAT	Py	B	46.3	46.7	0.3	93.3
14 DAT	Py	A	37.8	54.7	0.5	93.1
14 DAT	Py	B	35.6	56.5	0.5	92.6

MAT = Minutes after treatment (uncorrected for light-energy received by samples)
DAT = Days after treatment (uncorrected for light-energy received by samples)

Results of the degradation products in the irradiated samples are shown below. It should be noted that extensive degradation occurred on exposure to light in both water types, and the tables below detail those metabolites found at at least 10% AR. This is because the current guidance on aquatic ecotoxicity states that aqueous photolysis metabolites found at at least 10% AR in aqueous photolysis studies must be subject to an aquatic exposure and risk assessment.

Numerous other metabolites were also found at <10% AR and summary details on the numbers of metabolites are also presented. In the tables below, it is noted that 'Deg 1' with a retention time of 2:10 minutes, appears to a region eluting with the solvent front from the HPLC column. The amount of radioactivity eluting in this region tended to increase over time with maxima around 40% AR at or towards study termination in some incubations. Deg 2 (retention time 3:20 minutes) and Deg 4 (retention time 4:30 minutes) also had concentrations exceeding 10% AR in some incubations. The study authors stated that the regions eluting with retention times <5minutes were not detectable by LC/MS analysis. The authors suggested that this was due to a lack of ionisable functional groups. They suggested that this theory is supported by the short retention time on the HPLC column with both anion and cation exchange capacity in addition to C18 functional groups.

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Efforts to concentrate and isolate Deg 1 under different HPLC conditions were unsuccessful. The Applicant suggests that this region is likely to comprise a number of different fractions or fragments, with a low probability that any would comprise greater than 10% AR.

With respect to Deg 2, this fraction was isolated and injected into different HPLC columns in an attempt to better characterise it. It was stated that the radioactivity was not well retained or separated from the solvent front when injected in an aqueous sample. Attempts to exchange the solvent from water to an organic solvent resulted in low recovery of radioactivity.

Deg 4 fraction was isolated and further analysed using a mixed mode HPLC column. This was found to separate out into two main peaks, each constituting approx 25% of the radioactivity in the Deg 4 region, with numerous smaller peaks accounting for the remaining radioactivity. This provides evidence that Deg 3 is comprised of a number of substances, none of which is likely to be found at ≥10% AR.

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Table B.8.141 Distribution of radioactivity of XDE-729 methyl and photolysis metabolites >10% AR in irradiated sterile pH7 buffer (% AR)

Sampling Point	Rep	% Recovery	XDE-729 Methyl	Deg. 1, Rt:2:10	Deg. 10, Rt:19:40	Deg. 11, Rt:21:40	Deg. 14, Rt:23:40
Ph labelled samples							
0 MAT	---	100.0	100.0				
6 MAT	A	99.2	33.5		6.3	12.1	2.5
6 MAT	B	99.2	36.2		5.8	11.3	1.9
12 MAT	A	97.8	14.4	1.0	6.0	14.8	3.4
12 MAT	B	99.3	14.2		6.1	15.0	3.9
18 MAT	A	97.1	7.0	1.1	4.7	15.7	4.4
18 MAT	B	98.1	6.5	1.1	5.1	14.1	5.7
32 MAT	A	98.1	2.2	1.5	5.5	13.5	7.3
32 MAT	B	97.0	1.0	1.8	5.6	13.2	8.2
46 MAT	A	95.5		2.3	6.9	11.3	8.5
46 MAT	B	96.8		2.0	3.3	11.2	9.3
60 MAT	A	96.1		2.2	5.5	11.2	7.4
60 MAT	B	96.3		2.3	6.0	10.4	8.4
95 MAT	A	95.3		2.7	2.0	5.3	10.4
95 MAT	B	96.7		2.6	2.5	7.0	9.6
129 MAT	A	96.1		3.0	2.6	4.7	11.5
129 MAT	B	91.8		3.2	1.9	4.5	10.2
241 MAT	A	92.5		4.2	2.2	2.2	10.0
241 MAT	B	91.2		4.0	2.1	2.1	9.7
1 DAT	A	91.1		12.8		1.5	2.5
1 DAT	B	91.9		11.6	0.9	1.5	2.2
3 DAT	A	94.8		23.8		2.5	
3 DAT	B	95.7		24.9		1.0	
7 DAT	A	92.6		27.8			
7 DAT	B	91.5		27.4			
11 DAT	A	91.9		29.1			
11 DAT	B	93.2		30.8			
14 DAT	A	88.6		27.2			
14 DAT	B	91.7		30.0			
15 DAT	A	90.5		30.2			
15 DAT	B	91.4		31.8			

MAT = Minutes after treatment (uncorrected for light-energy received by sample)
DAT = Days after treatment (uncorrected for light-energy received by samples)

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Table B.8.142 Distribution of radioactivity of XDE-729 methyl and photolysis metabolites >10% AR in irradiated sterile pH7 buffer (% AR), (continued)

Sampling Point	Rep	% Recovery	XDE-729 Methyl	Deg. 1, Rt:2:10	Deg. 10, Rt:19:40	Deg. 11, Rt:21:40	Deg. 14, Rt:23:40
Py labelled samples							
0 MAT	---	100.0	97.7				
6 MAT	A	96.3	32.7	2.6	6.1	9.0	1.6
6 MAT	B	98.2	33.3	3.1	6.5	9.9	1.8
12 MAT	A	96.9	15.6	4.6	6.9	11.9	2.1
12 MAT	B	91.7	14.2	4.7	11.3	11.3	2.2
18 MAT	A	95.3	6.3	4.4	9.1	12.9	3.5
18 MAT	B	95.3	4.9	4.8	12.6	12.1	3.2
32 MAT	A	92.3	1.2	6.6	9.6	11.7	4.0
32 MAT	B	92.7	1.1	6.9	7.8	10.8	3.7
46 MAT	A	91.9		7.4	9.8	9.4	4.7
46 MAT	B	90.6		7.2	5.6	10.3	3.8
60 MAT	A	89.9		7.4	9.4	8.4	4.5
60 MAT	B	92.2		8.0	5.6	9.0	4.9
95 MAT	A	92.0		8.1	3.5	6.2	6.2
95 MAT	B	89.8		8.1	2.2	6.2	5.7
129 MAT	A	91.3		9.1	5.5	5.1	5.1
129 MAT	B	91.7		9.3	2.3	4.8	5.5
241 MAT	A	89.7		9.4	3.5	2.5	5.8
241 MAT	B	90.9		10.3	1.5	1.3	5.5
1 DAT	A	92.9		17.9		0.9	2.0
1 DAT	B	89.6		17.7		1.2	2.2
3 DAT	A	95.3		30.2			
3 DAT	B	95.1		28.1			
7 DAT	A	94.7		36.0			
7 DAT	B	94.5		36.3			
11 DAT	A	92.0		37.1			
11 DAT	B	93.5		39.3			
14 DAT	A	93.0		40.5			
14 DAT	B	92.2		41.2			
15 DAT	A	92.6		34.1			
15 DAT	B	92.8		34.3			
15 DAT	C	91.7		35.0			

MAT = Minutes after treatment (uncorrected for light-energy received by samples)
DAT = Days after treatment (uncorrected for light-energy received by samples)
[a] Not applicable

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Table B.8.143 Distribution of radioactivity of XDE-729 methyl and photolysis metabolites >10% AR in irradiated sterile natural water (% AR)

Sampling Point	Rep	% Recovery	XDE-729 Methyl	Deg. 1, Rt:2:10	Deg. 2, Rt:3:20	Deg. 4, Rt:4:30	X11393729	Deg. 11 Rt:21:50
Ph labelled samples								
0 MAT	---	100.0	92.7				7.3	
5 MAT	A	99.9	60.0				4.8	6.7
5 MAT	B	101.3	54.5				6.8	8.1
10 MAT	A	100.8	32.1				8.9	12.1
10 MAT	B	100.5	33.1				8.6	11.4
15 MAT	A	98.8	26.6				4.1	12.7
15 MAT	B	101.4	29.2				3.5	11.5
30 MAT	A	100.3	6.3	1.2		1.5	3.4	11.5
30 MAT	B	100.4	6.7	1.2		1.4	3.5	13.8
45 MAT	A	98.0	2.1	1.7		2.0	3.4	12.2
45 MAT	B	98.8	2.3	1.7	1.2	2.4	1.6	12.7
60 MAT	A	100.6	1.1	2.2	2.1	2.9	1.3	10.0
60 MAT	B	98.9		2.4	1.7	3.3	2.1	10.8
90 MAT	A	99.4		2.1	1.4	2.8	1.3	8.3
90 MAT	B	99.2		2.1	1.3	2.5	1.4	8.1
120 MAT	A	98.6		1.9	1.3	3.0	2.9	5.2
120 MAT	B	97.9		2.0	1.3	2.9	3.7	4.3
1 DAT	A	96.7		10.1	5.1	4.3	2.5	
1 DAT	B	97.6		10.3	5.9	2.9	3.2	1.4
3 DAT	A	96.2		14.2	8.1	1.7		1.1
3 DAT	B	96.4		14.1	8.0	0.9		
7 DAT	A	93.4		13.1	7.2	1.2		
7 DAT	B	88.4		13.3	7.0	0.5		
10 DAT	A	91.3		13.0	5.9	0.5		
10 DAT	B	91.2		13.8	7.1	0.9		
14 DAT	A	87.5		12.8	7.0	0.6		
14 DAT	B	90.2		12.6	6.0	0.5		

MAT = Minutes after treatment (uncorrected for light-energy received by sample)
DAT = Days after treatment (uncorrected for light-energy received by samples)

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Table B.8.144 Distribution of radioactivity of XDE-729 methyl and photolysis metabolites >10% AR in irradiated sterile natural water (% AR), (continued)

Sampling Point	Rep	% Recovery	XDE-729 Methyl	Deg. 1, Rt:2:10	Deg. 2, Rt:3:20	Deg. 4, Rt:4:30	X11393729	Deg. 11, Rt:21:50
Py labelled samples								
0 MAT	---	100.0	92.7				7.3	
5 MAT	A	99.7	53.3			6.5	7.7	3.9
5 MAT	B	99.1	47.9			7.0	10.1	4.1
10 MAT	A	93.8	30.5	1.5		9.8	10.4	5.9
10 MAT	B	93.9	25.7	1.7		10.4	10.7	5.8
15 MAT	A	95.4	22.5	2.0		11.4	5.1	6.8
15 MAT	B	96.2	22.8	2.0		11.3	6.4	6.3
30 MAT	A	94.5	5.7	3.1		14.3	6.3	7.2
30 MAT	B	94.2	5.1	3.5	1.0	14.0	3.7	7.7
45 MAT	A	89.9	2.5	3.5	1.0	13.7	2.6	7.0
45 MAT	B	91.0	2.5	3.4	1.0	13.9	2.3	7.0
60 MAT	A	91.9		4.3	1.6	13.9	2.0	6.2
60 MAT	B	92.2		4.3	1.5	14.3	2.0	6.2
90 MAT	A	92.7		4.8	1.6	14.6	1.1	4.6
90 MAT	B	92.7		5.0	1.0	14.4	1.1	5.6
120 MAT	A	93.4		5.4	1.6	14.4	1.2	3.4
120 MAT	B	92.1		5.6	2.1	13.6	2.6	3.3
1 DAT	A	95.3		13.3	8.3	3.2	1.7	1.0
1 DAT	B	96.3		14.4	9.2	2.5	1.2	0.9
3 DAT	A	94.9		19.5	12.2	1.9		
3 DAT	B	97.7		19.6	12.6	1.5	0.7	
7 DAT	A	94.2		19.6	8.1	0.6		
7 DAT	B	95.1		20.4	8.2	1.1		
10 DAT	A	93.6		19.3	7.0	0.9		
10 DAT	B	93.3		18.7	7.1	1.0		
14 DAT	A	93.1		20.0	7.4	0.7		
14 DAT	B	92.6		18.9	8.0	0.6		

MAT = Minutes after treatment (uncorrected for light-energy received by samples)
DAT = Days after treatment (uncorrected for light-energy received by samples)
[a] Not applicable

The extent of degradation under irradiated conditions in terms of the number of separate radiolabelled peaks found during HPLC analysis is demonstrated in the following tables.

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Table B.8.145 Number of peaks recorded in HPLC analysis of irradiated pH7 buffer treated with XDE-729 methyl

Sampling Point	Label/Rep	# of Peaks, % of radiocarbon injected on HPLC				
		< 1%	1%-3%	3%-5%	5%-10%	>10%
Ph Samples						
0 MAT	Ph	0	0	0	0	1
6 MAT	Ph/A	27	9	0	4	2
6 MAT	Ph/B	44	10	0	4	2
12 MAT	Ph/A	37	14	2	4	2
12 MAT	Ph/B	34	15	2	4	2
18 MAT	Ph/A	35	16	5	3	1
18 MAT	Ph/B	28	16	3	6	1
32 MAT	Ph/A	35	13	4	5	1
32 MAT	Ph/B	36	14	4	5	1
46 MAT	Ph/A	39	17	5	3	1
46 MAT	Ph/B	36	18	4	4	1
60 MAT	Ph/A	44	17	3	5	1
60 MAT	Ph/B	37	16	3	5	1
95 MAT	Ph/A	33	21	4	4	1
95 MAT	Ph/B	35	18	4	6	0
129 MAT	Ph/A	28	17	10	2	1
129 MAT	Ph/B	22	18	9	2	1
241 MAT	Ph/A	28	22	6	2	1
241 MAT	Ph/B	32	20	5	3	1
1 DAT	Ph/A	34	16	8	2	1
1 DAT	Ph/B	27	24	3	3	1
3 DAT	Ph/A	32	19	5	1	1
3 DAT	Ph/B	36	22	4	0	1
7 DAT	Ph/A	46	14	2	1	1
7 DAT	Ph/B	27	17	2	1	1
11 DAT	Ph/A	28	11	2	1	1
11 DAT	Ph/B	37	10	0	1	1
14 DAT	Ph/A	30	8	0	2	1
14 DAT	Ph/B	22	7	2	1	1
15 DAT	Ph/A	22	7	2	1	1
15 DAT	Ph/B	26	6	0	2	1

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Table B.8.146 Number of peaks recorded in HPLC analysis of irradiated pH7 buffer treated with XDE-729 methyl (continued)

Sampling Point	Label/Rep	# of Peaks, % of radiocarbon injected on HPLC				
		< 1%	1%-3%	3%-5%	5%-10%	>10%
Py Samples						
0 MAT	Py	5	0	0	0	1
6 MAT	Py/A	42	12	1	4	1
6 MAT	Py/B	37	12	2	3	2
12 MAT	Py/A	36	15	2	4	2
12 MAT	Py/B	34	16	1	3	3
18 MAT	Py/A	33	15	5	4	1
18 MAT	Py/B	34	16	3	4	2
32 MAT	Py/A	34	17	5	2	2
32 MAT	Py/B	31	18	4	4	1
46 MAT	Py/A	37	17	3	4	2
46 MAT	Py/B	42	17	4	4	1
60 MAT	Py/A	38	19	2	5	1
60 MAT	Py/B	39	15	4	6	0
95 MAT	Py/A	34	17	5	5	0
95 MAT	Py/B	36	17	4	6	0
129 MAT	Py/A	39	15	5	5	1
129 MAT	Py/B	30	19	8	3	1
241 MAT	Py/A	33	19	5	3	1
241 MAT	Py/B	31	21	5	3	1
1 DAT	Py/A	23	19	7	2	1
1 DAT	Py/B	28	22	5	2	1
3 DAT	Py/A	34	19	2	0	1
3 DAT	Py/B	32	25	2	0	1
7 DAT	Py/A	38	14	0	1	1
7 DAT	Py/B	25	19	0	1	1
11 DAT	Py/A	36	9	0	1	1
11 DAT	Py/B	27	9	0	1	1
14 DAT	Py/A	20	8	0	1	1
14 DAT	Py/B	17	7	1	1	1
15 DAT	Py/A	24	5	2	1	1
15 DAT	Py/B	27	7	2	1	1
15 DAT	Py/C	28	6	2	1	1

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Table B.8.147 Number of peaks recorded in HPLC analysis of irradiated sterile natural water treated with XDE-729 methyl

Sampling Point	Label/Rep	# of Peaks, % of radiocarbon injected on HPLC				
		< 1%	1%-3%	3%-5%	5%-10%	>10%
Ph Samples						
0 MAT	Ph	0	0	0	1	1
5 MAT	Ph/A	24	4	2	2	1
5 MAT	Ph/B	22	6	1	3	1
10 MAT	Ph/A	24	9	3	2	2
10 MAT	Ph/B	20	10	3	2	2
15 MAT	Ph/A	30	7	5	2	2
15 MAT	Ph/B	24	14	3	2	2
30 MAT	Ph/A	21	13	8	4	1
30 MAT	Ph/B	24	17	6	3	1
45 MAT	Ph/A	14	19	9	2	1
45 MAT	Ph/B	15	22	6	2	1
60 MAT	Ph/A	15	22	8	3	0
60 MAT	Ph/B	19	17	10	2	1
90 MAT	Ph/A	15	24	7	3	0
90 MAT	Ph/B	13	20	7	5	0
120 MAT	Ph/A	17	20	10	3	0
120 MAT	Ph/B	19	21	11	2	0
1 DAT	Ph/A	13	26	5	2	1
1 DAT	Ph/B	17	22	7	2	1
3 DAT	Ph/A	12	27	2	1	2
3 DAT	Ph/B	22	19	2	2	2
7 DAT	Ph/A	40	11	1	1	2
7 DAT	Ph/B	33	13	1	0	3
10 DAT	Ph/A	21	13	1	0	3
10 DAT	Ph/B	34	7	2	0	3
14 DAT	Ph/A	11	14	1	0	3
14 DAT	Ph/B	16	8	0	0	3

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Table B.8.148 Number of peaks recorded in HPLC analysis of irradiated pH7 buffer treated with XDE-729 methyl (continued)

Sampling Point	Label/Rep	# of Peaks, % of radiocarbon injected on HPLC				
		< 1%	1%-3%	3%-5%	5%-10%	>10%
Py Samples						
0 MAT	Py	0	0	0	1	1
5 MAT	Py/A	29	6	1	3	1
5 MAT	Py/B	28	8	1	2	2
10 MAT	Py/A	20	9	2	2	3
10 MAT	Py/B	23	9	2	2	3
15 MAT	Py/A	23	14	1	4	2
15 MAT	Py/B	22	15	2	3	2
30 MAT	Py/A	21	14	4	5	1
30 MAT	Py/B	25	15	6	4	1
45 MAT	Py/A	17	19	7	2	1
45 MAT	Py/B	18	19	6	3	1
60 MAT	Py/A	27	21	5	1	1
60 MAT	Py/B	15	21	6	2	1
90 MAT	Py/A	12	22	8	1	1
90 MAT	Py/B	16	24	2	5	1
120 MAT	Py/A	11	25	7	1	1
120 MAT	Py/B	16	29	3	1	1
1 DAT	Py/A	20	26	3	0	2
1 DAT	Py/B	19	25	4	0	2
3 DAT	Py/A	26	22	0	0	2
3 DAT	Py/B	29	18	2	0	2
7 DAT	Py/A	27	14	0	1	2
7 DAT	Py/B	27	13	0	1	2
10 DAT	Py/A	26	11	0	0	3
10 DAT	Py/B	19	14	0	0	3
14 DAT	Py/A	2	8	0	0	3
14 DAT	Py/B	5	7	0	0	3

The following degradation rates were calculated from the study. The actual photolysis rate was calculated by accounting for the degradation rate in the dark control.

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Table B.8.149 Degradation rates of XDE-729 methyl in pH7 buffer and sterile natural water, uncorrected for light intensity

Condition	Degradation rate (DAT^{-1})	DT50 (days)	r^2
Sterile pH7 buffer			
Dark	0.0044	157.5	0.911
Irradiated (total)	242.50	4.1 min	0.997
Photolysis	242.50	4.1 min	N/A
Sterile natural water			
Dark	0.0946	7.3	0.931
Irradiated (total)	141.12	7.1 min	0.983
Photolysis	141.02	7.1 min	N/A

The study authors also calculated the quantum yield of XDE-729 methyl as 5.63. Using published tables of sunlight energy as a function of latitude and season and the quantum yield, the study authors calculated DT50 for sterile pH 7 buffer and sterile natural water at a range of latitudes and seasons.

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Table B.8.150 Estimated environmental aqueous photolysis rates for XDE-729 methyl in pH 7 buffer

Latitude	Season	ΣεcλLλ	Degradation rate (k, days-1)	DT50 (days)	DT90 (days)	DT50 (hours)	DT90 (hours)
0 N	Spring	23.37	131.66	0.005	0.017	0.126	0.420
10 N	Spring	24.03	135.34	0.005	0.017	0.123	0.408
20 N	Spring	23.15	130.37	0.005	0.018	0.128	0.424
30 N	Spring	20.90	117.71	0.006	0.020	0.141	0.469
40 N	Spring	17.45	98.32	0.007	0.023	0.169	0.562
50 N	Spring	13.49	75.96	0.009	0.030	0.219	0.727
60 N	Spring	9.72	54.72	0.013	0.042	0.304	1.010
0 N	Summer	21.79	122.76	0.006	0.019	0.136	0.450
10 N	Summer	24.12	135.88	0.005	0.017	0.122	0.407
20 N	Summer	25.28	142.41	0.005	0.016	0.117	0.388
30 N	Summer	24.28	136.76	0.005	0.017	0.122	0.404
40 N	**Summer**	**22.95**	**129.29**	**0.005**	**0.018**	**0.129**	**0.427**
50 N	Summer	20.43	115.09	0.006	0.020	0.145	0.480
60 N	Summer	17.26	97.21	0.007	0.024	0.171	0.569
0 N	Autumn	24.10	135.73	0.005	0.017	0.123	0.407
10 N	Autumn	21.57	121.50	0.006	0.019	0.137	0.455
20 N	Autumn	18.14	102.17	0.007	0.023	0.163	0.541
30 N	Autumn	14.00	78.86	0.009	0.029	0.211	0.701
40 N	Autumn	9.57	53.88	0.013	0.043	0.309	1.026
50 N	Autumn	5.33	30.02	0.023	0.077	0.554	1.841
60 N	Autumn	2.23	12.56	0.055	0.183	1.325	4.401
0 N	Winter	22.37	126.02	0.006	0.018	0.132	0.439
10 N	Winter	18.53	104.36	0.007	0.022	0.159	0.530
20 N	Winter	13.90	78.32	0.009	0.029	0.212	0.706
30 N	Winter	9.03	50.88	0.014	0.045	0.327	1.086
40 N	Winter	4.69	26.40	0.026	0.087	0.630	2.093
50 N	Winter	1.74	9.79	0.071	0.235	1.700	5.646
60 N	Winter	0.39	2.21	0.313	1.040	7.516	24.968

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Table B.8.151 Estimated environmental aqueous photolysis rates for XDE-729 methyl in sterile natural water

Latitude	Season	Sunlight ka in days-1 for PNAPa	Correction Factor Days/DATb	Degradation rate DT50 (days)c	DT90 (days)d	DT50 (hours)	DT90 (hours)
0 N	Spring	505	2.72	0.013	0.044	0.321	1.066
10 N	Spring	525	2.62	0.013	0.043	0.309	1.026
20 N	Spring	514	2.67	0.013	0.044	0.315	1.048
30 N	Spring	483	2.84	0.014	0.046	0.336	1.115
40 N	Spring	431	3.19	0.016	0.052	0.376	1.249
50 N	Spring	362	3.80	0.019	0.062	0.448	1.487
60 N	Spring	286	4.80	0.024	0.078	0.567	1.883
0 N	Summer	477	2.88	0.014	0.047	0.340	1.129
10 N	Summer	523	2.63	0.013	0.043	0.310	1.030
20 N	Summer	551	2.49	0.012	0.041	0.294	0.977
30 N	Summer	551	2.49	0.012	0.041	0.294	0.977
40 N	**Summer**	**532**	**2.58**	**0.013**	**0.042**	**0.305**	**1.012**
50 N	Summer	496	2.77	0.014	0.045	0.327	1.086
60 N	Summer	445	3.09	0.015	0.050	0.364	1.210
0 N	Autumn	513	2.68	0.013	0.044	0.316	1.050
10 N	Autumn	470	2.92	0.014	0.048	0.345	1.146
20 N	Autumn	409	3.36	0.017	0.055	0.396	1.316
30 N	Autumn	333	4.13	0.020	0.067	0.487	1.617
40 N	Autumn	245	5.61	0.028	0.092	0.662	2.198
50 N	Autumn	154	8.92	0.044	0.146	1.052	3.496
60 N	Autumn	76.1	18.06	0.089	0.295	2.130	7.075
0 N	Winter	482	2.85	0.014	0.047	0.336	1.117
10 N	Winter	417	3.29	0.016	0.054	0.389	1.291
20 N	Winter	327	4.20	0.021	0.069	0.496	1.647
30 N	Winter	233	5.90	0.029	0.096	0.696	2.311
40 N	Winter	139	9.88	0.049	0.161	1.166	3.874
50 N	Winter	63.7	21.57	0.106	0.352	2.545	8.453
60 N	Winter	19.7	69.75	0.343	1.139	8.228	27.332

(Blakeslee *et al* 2011)

b) A study was conducted to determine the aqueous photolysis of XDE-729 methyl under the test conditions of a study performed on *Myriophyllum* aquatic plants. The ecotoxicological study on this aquatic plant is presented in section B.9.2.1.1.4. The study was stated to have been conducted to GLP but no specific study guideline was stated to have been followed.

^{14}C-XDE-729 methyl labelled in both Ph and Py positions was dosed into the test medium at a dose of 501 µg/l Ph labelled material and 407 µg/l Py labelled material. The composition of the test medium is shown below.

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Table B.8.152 Composition of test medium used to determine aqueous photolysis under Myriophyllum test conditions

Solution	Ingredient	Concentration per litre
Solution 1	$CaCl_2$ x 2 H_2O	9.17 mg/L
Solution 2	$MgSO_4$ x 7 H_2O	6.90 mg/L
Solution 3	$NaHCO_3$	5.84 mg/L
	$KHCO_3$	1.54 mg/L

Medium for test: 100 mL of each solution was added to 9.7 L water. Each test vessel was filled with 1 L medium

Incubation vessels were prepared to allow dark control and illuminated samples. Incubation temperatures were 19.72±0.04ºC with average pH 7.55. The study was conducted for 14 days with sampling of incubation vessels at 0 and 6 hours after treatment and 1, 3, 7 and 14 DAT. Light intensity in the illuminated samples was measured once during the course of the study but was not reported; the RMS assumes that the same light source used in the *Myriphyllum* study was also used in this test. Water samples were directly subjected to HPLC following addition of acetonitrile. Identity of radiolabelled fractions was by co-chromatography with reference standards. There was no trapping of volatile radioactivity.

Results of the gross radioactivity in water phase are given below.

Table B.8.153a Radioactivity in water phase for Ph labelled XDE-729 methyl

Sampling interval [days]		0	0.25	1	3	7	14
	Test item 1	%AR					
Radioactivity in water phase	Light	87	95	93	91	75	67
	Dark	94	94	95	95	80	76

Table B.8.153b Radioactivity in water phase for Py labelled XDE-729 methyl

Sampling interval [days]		0	0.25	1	3	7	14
	Test Item 2	%AR					
Radioactivity in water phase	Light	79	88	85	81	54	52
	Dark	84	90	90	88	74	70

Results of analysis of identity of radioactivity in the water phase are given below.

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Table B.8.154 Composition of radioactivity in water phase treated with Ph labelled XDE-729 methyl

Sampling interval [days]		0	0.25	1	3	7	14
	Test Item 1	%AR					
Parent	Light	87	95	45	9	6	0
	Dark	94	94	95	88	67	56
XDE 729 acid	Light	0	0	0	6	4	4
	Dark	0	0	0	7	13	20
X11449757	Light	0	0	0	3	1	4
	Dark	0	0	0	0	0	0
X11406790	Light	0	0	6	5	8	3
	Dark	0	0	0	0	0	0

Table B.8.155 Composition of radioactivity in water phase treated with Py labelled XDE-729 methyl

Sampling interval [days]		0	0.25	1	3	7	14
	Test Item 2	%AR					
Parent	Light	79	88	33	7	3	2
	Dark	84	90	90	84	65	51
XDE 729 acid	Light	0	0	4	6	4	3
	Dark	0	0	0	4	5	18
X11449757	Light	0	0	0	6	3	3
	Dark	0	0	0	0	0	0
X11406790	Light	0	0	4	5	4	4
	Dark	0	0	0	0	0	0

Dissipation rates for illuminated samples were calculated using FOCUS Degradation Kinetics principles and KinGUI 1.1. Only SFO kinetics were applied. The following parameters were obtained.

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Table B.8.156 Kinetic parameters for Ph labelled ('Test Item 1') and Py labelled ('Test Item 2') in illuminated Myriophyllum test medium.

Test Item	Kinetic Model	DT50 [d]	DT90 [d]	Chi2 Error [%]	Visual Assessment *
1	SFO	0.7	3.3	15.09	+
2	SFO	0.8	2.9	18.14	+

* Visual Assessment: + = good, o = moderate, - = poor

Scrutiny of chromatograms illustrates a very large number of degradates in illuminated samples from 1 DAT onward. Most of these were unidentified.

(Hellstern, 2012)

B.8.4.3 Ready biodegradation

Ready biodegradation of the metabolite X11393729 was studied according to OECD guideline 310, 2006 and GLP.

The ready biodegradability of X11393729 was determined in a CO_2 Headspace Test. The test item was exposed to activated sludge (4 g dry material/l) from the aeration tank of a domestic waste water treatment plant for 28 days. The concentration of X11393729 was approximately 42 mg/l. The dosed media were incubated in glass flasks sealed with Teflon-coated septa at 20ºC in darkness for 28 days whilst being constantly agitated. The biodegradation was determined by following the CO_2 evolution of the test item in the incubation flasks during exposure. Sodium benzoate was used as a reference item and was tested simultaneously under the same conditions as test item and was a procedural control.

At the end of the 28 day incubation period, it was calculated that the mean biodegradation (i.e. mineralisation) was 7.7%. Given that mineralisation did not exceed 60% in 28 days, X11393729 was considered to be not readily biodegradable. The sodium benzoate control was completely mineralised during the incubation period.

(Feil 2011)

B.8.4.4 Water/sediment studies

a) An aerobic sediment/water study was conducted according to OECD 308 and US EPA OPPTS 835.4300 guidelines and the GLP.

Samples of untreated Derbyshire pond water and Staffordshire pond water and their associated sediments were equilibrated in flasks for 1 week at 20ºC in the dark; the sediment depth was approximately 2.5cm and water was added to give a sediment:water ratio of 1:3 – 1:4 w/v. Details of the water/sediment systems are given below.

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Table B.8.157 Properties of water in XDE-729 methyl water/sediment study

Parameter	Results	
Geographic Location	Swiss Lake, Chatsworth, Derbyshire, England	Calwich Abbey Lake, Calwich, Staffordshire, England
Storage Temperature	4 °C	4 °C
pH	7.0	8.3
Initial Redox Potential (mv)	161	51
Final Redox Potential (mv)	199	79
Initial Dissolved Oxygen (mg/L)	7.2	3.5
Final Dissolved Oxygen (mg/L)	7.2	5.0
Dissolved Organic Carbon (ppm) b	11.5	5.0
Hardness (mg equivalent CaCO3/L) c	25	224
Conductivity (mmhos/cm) d	0.12	0.48

Table B.8.158 Properties of sediment in XDE-729 methyl water/sediment study

Parameter	Results	
Geographic Location	Swiss Lake, Chatsworth, Derbyshire, England	Calwich Abbey Lake, Calwich, Staffordshire, England
USDA Texture Class	Loamy Sand	Silt Loam
% Sand	85	37
% Silt	13	55
% Clay	2	8
International Texture Class	Sand	Loam
% Sand	95	57
% Silt	3	35
% Clay	2	8
pH	5.8	7.7
% Organic Carbon	1.3	5.7
Initial Redox Potential (mv)	-408	-389
Final Redox Potential (mv)	-317	-370
Initial Biomass (µg/g)	51.3	581.6
Final Biomass (µg/g)	24.4	35.0
CEC (meq/100g)	3.7	15.3
Bulk Density (g/cm3)	1.04	0.66

Following equilibration, XDE-729 methyl radiolabelled in either the phenyl and pyridine ring positions was added to the water layer to separate flasks (nominal concentration of 0.02 mg a.s./litre). Treated flasks were supplied with humidified air and attached to a NaOH trap for CO_2. All flasks were then incubated at 20°C in the dark for up to 103 days.

As with the pre-treatment stage of the study, treated flasks were incubated in the dark at 20ºC. Duplicate flasks were analysed at day 0 and ten additional representative sample points. It must be noted that at day 0, the water phase only was present, i.e. there was no sediment layer present in samples taken at day 0. The RMS notes that this does not appear to be in strict compliance with the OECD 308 guideline which states that "*Concentrations of test substance and transformation products at every*

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sampling time in water and sediment should be measured and reported..." (para 41). However, a correct mass balance is available for day 0 as only the water phase was dosed with no sediment present, thus no partitioning to sediment could have taken place. The Applicant argued separately that such a procedure is often employed in water/sediments studies for two reasons: 1) A true zero time sample cannot contain sediment residues by definition. 2) Even if the sample is processed immediately after dosing, there are likely to be residues detected in the sediment which result from disruption/mixing of the water layer during centrifugation and decanting process and not by passive mechanisms (sorption/osmosis/diffusion). In addition they argued that FOCUS kinetics guidance recommends that any residues in sediment at Day 0 should be added to the water layer for kinetics analysis negating the value of having sediment present at Day 0. Whilst the RMS agrees with the individual points 1) and 2) that have been made, the RMS does not agree that the value of having a day 0 sample is negated by the principle for kinetic assessment of adding any sediment residues back into the water layer as parent residues. Day 0 sediment samples can still give important information on any immediate partitioning and/or transformation behaviour. Extraction and analysis of day 0 sediment samples is also in-line with the OECD 308 guideline. Overall, whilst the RMS considers the Applicant's approach to be a departure from the OECD guideline, the RMS considers that the departure is not sufficient to invalidate the study as the subsequent sampling and analysis is sufficient to elucidate the overall fate and behaviour of the substance and its metabolites. As all the residues in the day 0 samples are in the water phase due to the absence of sediment, there should be no implication for kinetic analysis as long as any metabolites at day 0 are added to the parent residue.

The water layer was removed from the incubation flask following centrifugation (day 2 samples onwards). The aqueous phase was concentrated prior to HPLC analysis by passing through an SPE cartridge following acidification to pH 2 with H_3PO_4. The cartridge was eluted with methanol/water/H_3PO_4 and methanol/glycerin added to the eluant. The resulting solution was evaporated under a stream of nitrogen and reconstituted in methanol. The resulting solution was analysed by HPLC with UV and radio-chemical detection.

Sediment was initially extracted twice with methanol/water. This was then concentrated under nitrogen and reconstituted in H_3PO_4. This was then passed through an SPE cartridge, eluted with methanol/water/H_3PO_4 and methanol/glycerin added to the eluant. The resulting solution was evaporated under a stream of nitrogen and reconstituted in water/acetonitrile/formic acid. The resulting solution was analysed by HPLC with UV and radio-chemical detection. On all occasions except day 0, sediment was also subject to an ASE extraction similar to that described in Section B.8.1. A 10-g subsample of each air-dried sediment sample was mixed with approximately 4 g of diatomaceous earth and transferred to an ASE extraction cell. Each sample was subjected to six discrete ASE extractions, collecting each in a separate weighed and labelled glass vial. Samples were extracted twice at 50ºC using methanol/water, twice at 80ºC using methanol/water and, finally, twice at 100ºC using methanol/0.1% phosphoric acid. Triplicate aliquots of each extract were assayed separately by LSC and the remainder of the six extractions were combined prior to concentration and HPLC analysis. ASE extracts were concentrated under nitrogen and 0.1% H_3PO_4 solution was added prior to SPE concentration/clean-up. The reconstituted ASE sample was loaded onto an SPE cartridge and eluted with methanol/water/H_3PO_4. A

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methanol/glycerol solution was added to the sample eluants and the samples were evaporated to approximately 100 µL under a stream of nitrogen with a water bath temperature set at 30 °C. Sample residues were reconstituted with water/acetonitrile/formic acid. Samples were then centrifuged. The supernatant was transferred to an autosampler vial. Aliquots of the concentrated samples were analysed by HPLC with UV and radio-chemical detection.

Identity of radiolabelled components was by co-chromatography with reference standards and LC/MS.

Extracted sediment samples were also subject to combustion to determine unextracted residues. Confirmation of the presence of $^{14}CO_2$ in NaOH traps was by precipitation with $BaCl_2$.

At each sample time, an additional flask was taken and analysed for water phase pH and dissolved oxygen, and water and sediment redox potential. Results of these measurements are given below. The measurements suggest that the aqueous layer was aerobic and the sediment layer anaerobic throughout the course of the incubation.

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Table B.8.159 Measurements of pH, dissolved oxygen and redox potential in XDE-729 methyl water/sediment study

M805

DAT	pH	O_2 (ppm)	Aqueous Potential (mV)	Aqueous E_h7 [a] (mV)	Sediment Potential (mV)	Sediment E_h7 [a] (mV)
0	7.8	7.2	209	161	-360	-408
2	7.8	6.6	168	120	-285	-334
5	7.9	7.0	173	122	-293	-344
8	7.6	7.2	195	160	-271	-306
14	5.5	7.0	170	259	-331	-242
22	5.5	7.6	276	367	-264	-173
30	6.6	7.4	216	240	-279	-255
43	6.8	7.1	289	303	-361	-348
60	6.8	6.7	212	225	-290	-278
83	7.3	7.5	204	188	-307	-323
103	7.1	7.2	205	199	-311	-317

[a] E_h for pH 7 calculated using the expression $E_h + \Delta E_h$, with $\Delta E_h = -59.2 \text{ mV} \times (\text{pH} - 7)$.

M806

DAT	pH	O_2 (ppm)	Aqueous Potential (mV)	Aqueous E_h7 [a] (mV)	Sediment Potential (mV)	Sediment E_h7 [a] (mV)
0	7.9	3.5	105	51	-335	-389
2	8.1	4.6	104	37	-326	-393
5	8.1	6.7	105	39	-306	-371
8	7.8	6.4	98	52	-277	-323
14	7.5	6.1	67	35	-310	-342
22	7.3	4.8	106	86	-329	-348
30	7.8	5.5	95	48	-314	-362
43	7.5	5.8	150	118	-405	-437
60	7.3	3.3	84	65	-315	-334
83	7.9	6.8	158	106	-297	-349
103	7.7	5.0	122	79	-327	-370

[a] E_h for pH 7 calculated using the expression $E_h + \Delta E_h$, with $\Delta E_h = -59.2 \text{ mV} \times (\text{pH} - 7)$.

Note: M805 = Swiss lake sand water/sediment system; M806 = Calwich Abbey Lake loam water/sediment system

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In the following tables of results, the phenyl-ring labelled results are shaded to aid differentiation from the pyridine-ring labelled results. Results of mass balance are given below.

Table B.8.160 Mass balance in XDE-729 methyl Swiss Lake sand water/sediment system

Radiolabel	DAT	Caustic Trap	Aqueous Layer	Organic Extract	ASE Extract	NER	Total
PH	0	NA	94.6	NA	NA	NA	94.6
PY	0	NA	96.8	NA	NA	NA	96.8
PH	2	0.0	77.8	19.6	NA	1.9	99.4
PY	2	0.1	85.2	13.9	NA	1.3	100.6
PH	5	0.0	59.9	29.9	6.2	2.0	98.1
PY	5	0.1	60.1	29.3	7.0	3.0	99.5
PH	8	0.0	60.4	27.6	7.1	3.7	98.7
PY	8	0.1	80.4	13.4	3.1	1.0	98.1
PH	14	0.1	61.5	18.7	10.2	4.6	95.1
PY	14	0.2	61.5	22.6	9.6	7.8	101.7
PH	22	0.6	50.2	16.9	12.8	16.3	96.8
PY	22	0.3	57.0	18.4	12.9	7.8	96.4
PH	30	0.7	49.6	18.0	12.0	17.8	98.1
PY	30	0.5	37.8	19.0	20.9	22.4	100.6
PH	43	1.1	36.4	18.9	20.2	17.0	93.6
PY	43	0.7	30.7	18.1	26.0	16.6	92.1
PH	62	6.9	15.3	9.4	17.8	42.3	91.8
PY	62	1.6	26.3	15.8	22.5	32.8	99.1
PH	79	11.9	9.6	6.4	15.8	46.5	90.3
PY	79	3.7	10.4	5.8	10.9	72.4	103.2
PH	103	15.8	7.5	4.6	15.1	45.4	88.4
PY	103	5.1	8.3	4.2	19.4	54.8	91.8

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Table B.8.161 Mass balance in XDE-729 methyl Calwich Abbey Lake loam water/sediment system

Sample ID	DAT	Caustic Trap	Aqueous Layer	Organic Extract	ASE Extract	NER	Total
PH	0	NA	96.6	NA	NA	NA	96.6
PY	0	NA	99.2	NA	NA	NA	99.2
PH	2	0.0	62.7	24.7	8.4	3.5	99.4
PY	2	0.1	61.5	25.1	9.4	2.9	99.0
PH	5	0.0	59.9	19.7	12.9	5.7	98.2
PY	5	0.1	55.6	20.7	10.4	12.9	99.1
PH	8	0.2	50.1	20.8	16.8	11.2	99.1
PY	8	0.3	48.2	21.5	18.0	11.5	99.6
PH	14	0.4	39.7	21.8	16.2	21.1	99.4
PY	14	0.5	38.5	22.6	18.7	20.7	100.9
PH	22	0.6	25.0	22.2	24.7	23.7	96.1
PY	22	0.4	22.3	21.9	27.8	27.7	100.1
PH	30	0.9	14.0	22.5	27.2	34.4	99.1
PY	30	0.4	15.5	20.8	30.1	36.2	103.0
PH	43	1.2	11.9	22.7	24.4	37.8	98.0
PY	43	0.7	13.2	21.3	20.1	47.1	102.3
PH	62	1.7	9.5	20.3	23.0	42.5	96.9
PY	62	0.9	10.1	19.7	19.7	52.7	103.1
PH	79	2.1	9.6	19.2	19.8	51.4	102.0
PY	79	0.8	9.4	18.9	17.1	56.6	102.8
PH	103	1.0	8.1	18.3	24.5	42.5	94.4
PY	103	1.2	7.5	15.0	21.8	51.2	96.8

Results of the distribution of active substance and metabolites in water and sediment and total system are given below.

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Table B.8.162 Distribution of radioactivity as XDE-729 methyl and its metabolites in water and sediment in Swiss Lake sand water/sediment system

	Aqueous layer				Sediment			
Label & DAT	729 methyl[a]	X729[b]	X757[c]	X790[d]	729 methyl	X729	X757	X790
PH-0	89.7	4.9	0.0	0.0	NA	NA	NA	NA
PY-0	85.4	11.4	0.0	0.0	NA	NA	NA	NA
PH-2	63.2	6.8	1.3	5.2	12.2	1.7	1.5	3.5
PY-2	71.2	7.7	1.9	4.4	8.7	1.5	1.2	2.5
PH-5	19.3	15.8	12.1	12.8	8.8	5.0	11.0	10.6
PY-5	22.8	17.3	8.1	10.6	11.7	6.1	10.2	7.6
PH-8	16.5	20.0	15.0	7.8	8.4	3.5	14.4	7.5
PY-8	57.8	11.6	4.4	5.7	6.2	1.2	6.3	2.8
PH-14	5.7	13.6	33.7	7.9	2.4	1.0	21.5	3.3
PY-14	2.7	11.6	39.0	5.3	2.7	1.5	23.8	3.3
PH-22	0.0	2.9	46.7	0.5	0.8	0.5	25.4	1.4
PY-22	0.0	7.1	48.3	1.6	1.4	0.3	27.3	1.8
PH-30	0.3	1.4	46.6	0.8	0.3	0.0	28.2	0.7
PY-30	0.0	5.4	31.3	0.0	1.1	3.0	33.5	0.9
PH-43	0.0	2.5	33.0	0.0	1.2	0.6	35.4	1.1
PY-43	0.0	3.0	25.7	0.0	1.3	1.1	36.9	1.1
PH-62	0.0	1.8	6.4	0.0	0.9	0.7	23.9	0.7
PY-62	0.0	1.8	21.1	0.0	0.4	0.3	35.4	0.0
PH-79	0.0	1.3	4.9	0.0	1.3	1.0	14.6	0.8
PY-79	0.0	1.7	3.9	0.0	0.6	0.9	10.5	0.6
PH-103	0.0	0.5	2.5	0.0	0.3	1.0	13.8	0.2
PY-103	0.0	0.8	2.9	0.0	0.4	1.6	12.9	0.6

[a] 729 methyl = XDE-729 methyl
[b] X729 = X11393729
[c] X757 = X11449757
[d] X790 = X11406790

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Table B.8.163 Distribution of radioactivity as XDE-729 methyl and its metabolites in total Swiss Lake sand water/sediment system

	Total system				
Label & DAT	XDE-729 Methyl	X11393729	X11449757	X11406790	Other
PH-0	89.7	4.9	0.0	0.0	0.0
PY-0	85.4	11.4	0.0	0.0	0.0
PH-2	75.3	8.6	2.8	8.6	2.4
PY-2	79.9	9.2	3.1	6.9	0.0
PH-5	28.1	20.8	23.1	23.4	0.3
PY-5	34.5	23.4	18.3	18.2	2.0
PH-8	24.9	23.5	29.4	15.3	2.2
PY-8	64.0	12.8	10.7	8.6	0.9
PH-14	8.2	14.6	55.2	11.1	1.3
PY-14	5.5	13.0	62.8	8.6	3.8
PH-22	0.8	3.4	72.1	1.9	1.7
PY-22	1.4	7.5	75.6	3.4	0.4
PH-30	0.7	1.4	74.8	1.5	1.1
PY-30	1.1	8.4	64.8	0.9	2.5
PH-43	1.2	3.1	68.4	1.1	1.7
PY-43	1.3	4.1	62.6	1.1	5.7
PH-62	0.9	2.5	30.3	0.7	8.2
PY-62	0.4	2.0	56.4	0.0	5.9
PH-79	1.3	2.2	19.5	0.8	8.0
PY-79	0.6	2.6	14.4	0.6	8.9
PH-103	0.3	1.5	16.3	0.2	8.8
PY-103	0.4	2.4	15.8	0.6	12.7

The Other ^{14}C is a summation of the radioactivity incorporated in numerous components. No individual component accounts for more than 5% of the applied radioactivity.

It is noted in the kinetic assessment that the Applicant excluded the results from the PY label at day 8 from the kinetic assessment. It is noted that the amount of parent XDE-729 methyl in this sample was significantly higher than in the PH sample and in samples from sampling times before and after. The Applicant stated that they could see no obvious explanation for the higher parent concentration at this time point. However, they considered that it was acceptable to exclude this sample on the basis of FOCUS Kinetic guidance which states:

"Statistical tests for identifying outliers in an objective manner may not be appropriate given the limited number of data available. Therefore, all measurements should initially be included in the optimisation. Samples that clearly differ from others can then be eliminated based on expert judgement and the fitting procedure repeated. The removal of any data points as outliers must be clearly documented and justified in the report. Experimental errors should be identified wherever possible." (FOCUS Degradation Kinetics, Section 6.1.5).

The Applicant conducted fits including and excluding the results from this sample, and thus the RMS considers that the approach taken to be acceptable given the significant deviation of this sample from the overall results obtained.

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Table B.8.164 Distribution of radioactivity as XDE-729 methyl and its metabolites in water and sediment in Calwich Abbey Lake loam water/sediment system

	Aqueous layer				Sediment			
Label & DAT	729 methyl[a]	X729[b]	X757[c]	X790[d]	729 methyl	X729	X757	X790
PH-0	93.0	3.6	0.0	0.0	NA	NA	NA	NA
PY-0	94.7	4.5	0.0	0.0	NA	NA	NA	NA
PH-2	13.0	11.3	21.9	16.5	7.3	2.0	15.8	7.0
PY-2	12.1	13.3	20.3	15.0	6.7	3.2	17.5	6.5
PH-5	0.8	5.8	44.4	7.2	1.2	0.7	27.7	2.8
PY-5	0.8	5.5	41.6	5.9	1.9	1.0	24.7	3.0
PH-8	0.0	2.7	42.9	0.9	0.6	0.8	33.8	1.3
PY-8	0.0	4.3	40.7	1.3	1.4	1.1	35.1	1.5
PH-14	0.0	0.8	39.0	0.0	0.7	0.0	35.5	0.3
PY-14	0.0	0.7	36.8	0.0	0.0	0.0	39.8	0.8
PH-22	0.0	0.0	25.0	0.0	0.5	0.0	45.4	0.3
PY-22	0.0	0.0	22.3	0.0	0.4	0.0	47.5	0.3
PH-30	0.0	0.0	14.0	0.0	0.5	0.0	48.5	0.5
PY-30	0.0	0.3	15.0	0.0	0.3	0.0	50.6	0.0
PH-43	0.0	0.0	11.9	0.0	0.0	0.0	46.8	0.0
PY-43	0.0	0.0	13.2	0.0	0.3	0.0	37.0	0.4
PH-62	0.0	0.0	8.8	0.0	0.7	0.0	40.5	0.0
PY-62	0.0	0.0	10.1	0.0	0.0	0.0	34.6	0.3
PH-79	0.0	0.0	9.4	0.0	0.2	0.5	35.7	0.0
PY-79	0.0	0.0	9.4	0.0	0.7	0.0	33.7	0.3
PH-103	0.0	0.0	8.0	0.0	0.1	0.0	35.3	0.1
PY-103	0.0	0.0	7.1	0.0	0.0	0.0	28.7	0.2

[a] 729 methyl = XDE-729 methyl
[b] X729 = X11393729
[c] X757 = X11449757
[d] X790 = X11406790

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Table B.8.165 Distribution of radioactivity as XDE-729 methyl and its metabolites in total Calwich Abbey Lake loam water/sediment system

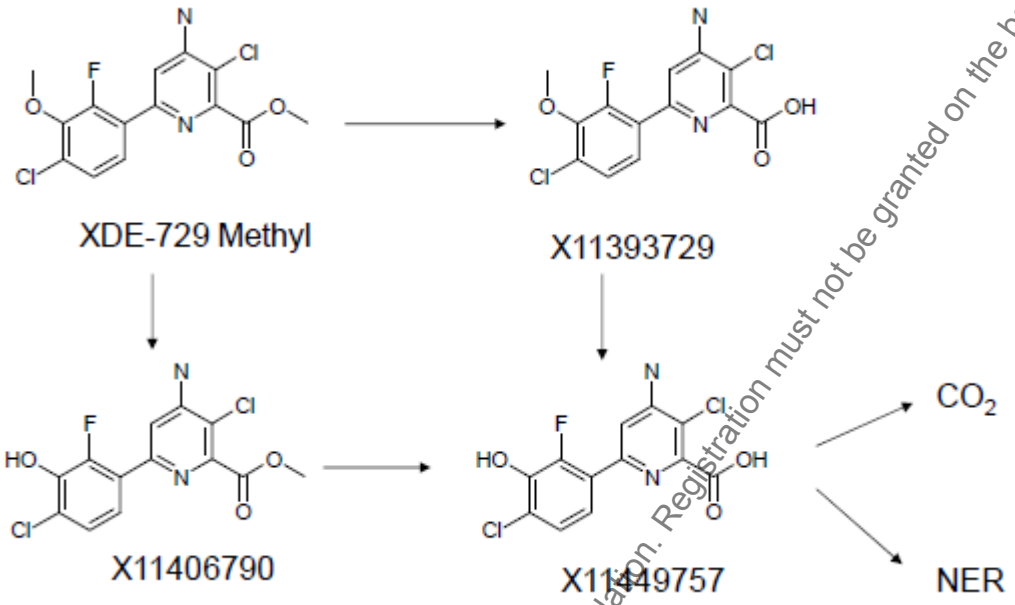
	Total system				
Label & DAT	XDE-729 Methyl	X11393729	X11449757	X11406790	Other
PH-0	93.0	3.6	0.0	0.0	0.0
PY-0	94.7	4.5	0.0	0.0	0.0
PH-2	20.3	13.3	37.7	23.6	1.0
PY-2	18.8	16.4	37.8	21.5	1.5
PH-5	1.9	6.5	72.1	10.0	1.9
PY-5	2.7	6.5	66.3	9.0	2.3
PH-8	0.6	3.5	76.7	2.1	4.7
PY-8	1.4	5.3	75.8	2.8	2.4
PH-14	0.7	0.8	74.5	0.3	1.6
PY-14	0.0	0.7	76.6	0.8	1.6
PH-22	0.5	0.0	70.4	0.3	0.7
PY-22	0.4	0.0	69.8	0.3	1.6
PH-30	0.5	0.0	62.4	0.5	0.3
PY-30	0.3	0.3	65.6	0.0	0.2
PH-43	0.0	0.0	58.7	0.0	0.3
PY-43	0.3	0.0	50.1	0.4	3.7
PH-62	0.7	0.0	49.3	0.0	2.7
PY-62	0.0	0.0	44.8	0.3	4.5
PH-79	0.2	0.5	45.1	0.0	2.2
PY-79	0.7	0.0	43.1	0.3	3.2
PH-103	0.1	0.0	43.3	0.1	1.0
PY-103	0.0	0.0	35.7	0.2	1.6

The Other ^{14}C is a summation of the radioactivity incorporated in numerous components. No individual component accounts for more than 5% of the applied radioactivity.

The study authors applied the principles of the FOCUS Degradation Kinetics guidance document to the results of the water/sediment study to derive dissipation parameters appropriate for both comparison against regulatory 'triggers' and for use in environmental exposure modelling. In particular it is noted that for day 0 samples, only the water phase in the absence of sediment was treated. Any metabolite residues in the day 0 samples were added to the active substance in compliance with FOCUS Kinetics recommendations. The conceptual model used in the kinetic model was as based on the following metabolic pathway. The RMS confirms that in the modelling, each compartment had a flow to the sink compartment in line with FOCUS Degradation Kinetics recommendations, although it is recognised that this is not shown in the figure below. For the purpose of kinetic assessment, the LOD was set at 1% AR.

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Figure B.8.200 Proposed metabolic pathway for XDE-729 methyl in water/sediment systems

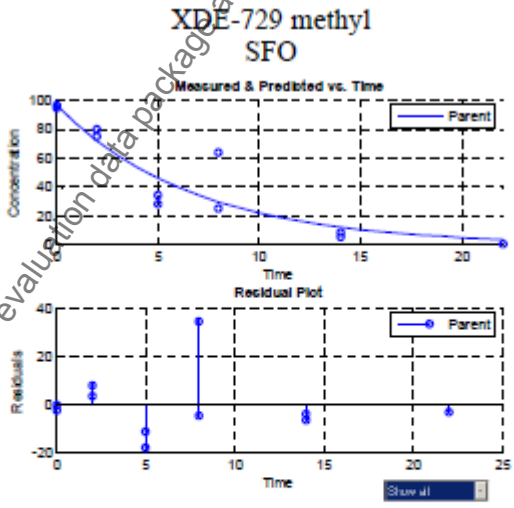


Swiss Lake sand water/sediment system

Parent total system

The initial fitting of parent results indicated a potential outlier with PY label results at 8 DAT (as described above).

Figure B.8.201 Initial SFO fitting for XDE-729 methyl in Swiss Lake total system



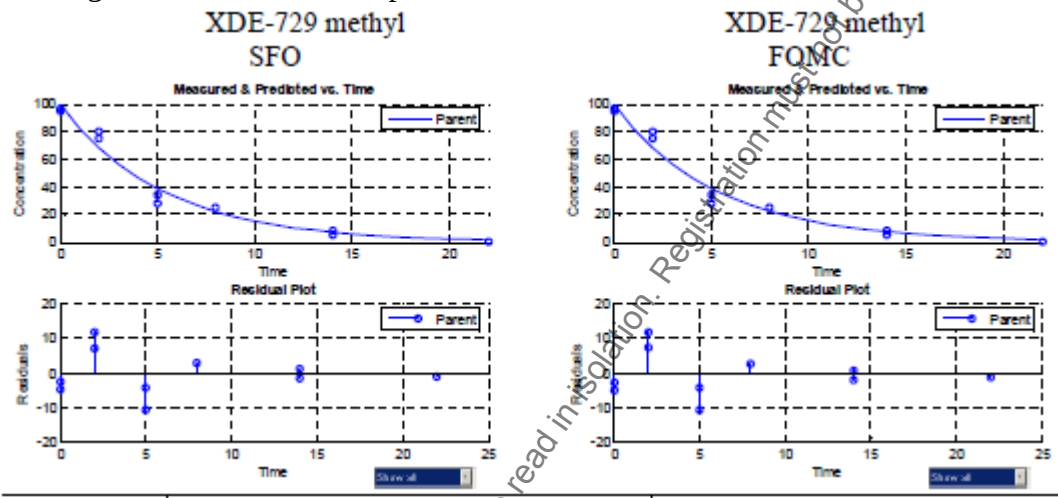
Model parameters	SFO Parameter ± error	Confidence Interval	Prob>t
M_0	96.9 ± 8.9	76.8-116.9	
Parent k_1	0.1491 ± 0.0304	0.0804-0.2178	4.2E-4
% error where χ^2 passes	15.8		
r^2	0.8638		
$DegT_{50}$ (days)	5		
$DegT_{90}$ (days)	15		

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The study authors considered that the data at this sample point was an outlier and subsequently removed it from all further assessments of a.s. and metabolites. As explained above, this seems to be a reasonable and consistent approach taking into account FOCUS Degradation Kinetics recommendations, in spite of there being no obvious scientific or experimental explanation.

The dataset minus the PY 8DAT data were refitted to SFO and FOMC kinetics.

Fig B.8.202 SFO and FOMC fitting for XDE-729 methyl in Swiss Lake total system omitting 8 DAT PY label data point



Model parameters	SFO Parameter ± error	Confidence Interval	Prob>t	FOMC Parameter ± error	Confidence Interval	Prob>t
M_0	99.4 ± 4.4	89.4-109.5		99.5 ± 5.0	87.8-111.3	
Parent k_1	0.1879 ± 0.0195	0.1428-0.2329	5.7E-6			
alpha				37.8 ± 402.9	-915-991	0.4639
beta				243± 716	<-1000->1000	0.4645
% error where χ^2 passes	9.4			10.4		
r^2	0.9723			0.9718		
$DegT_{50}$ (days)	4			4		
$DegT_{90}$ (days)	12			12		
	Best-fit endpoint					

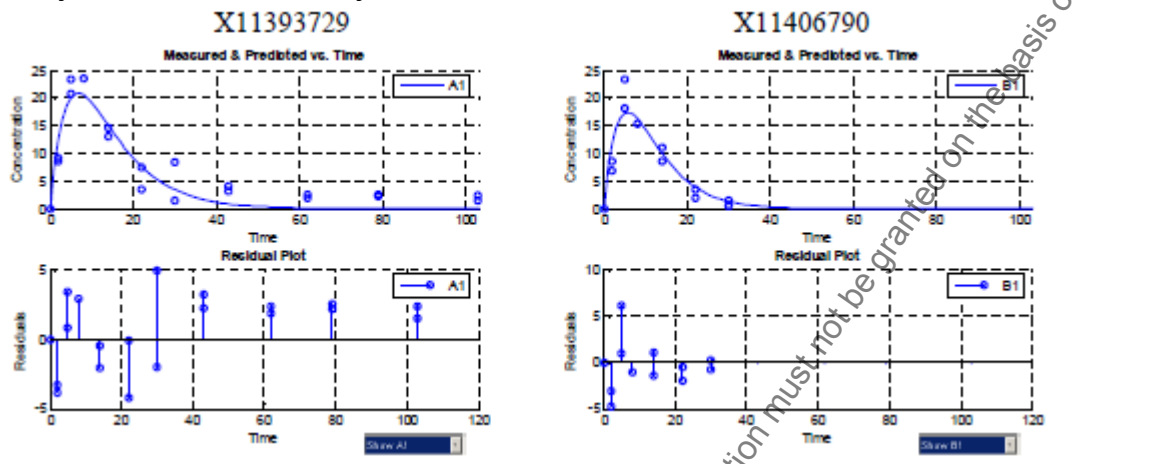
The study author considered SFO to be the superior fit in view of the slightly better χ^2 value and that the errors associated with the FOMC alpha and beta parameters were greater than the optimised values. RMS also notes that the confidence intervals around the alpha and beta parameters include zero. RMS agrees that SFO represents the best fit for parent in whole system

<u>Metabolites total system</u>

Data on metabolites X11393729 and X11406790 were added to the parent SFO model. Both metabolites were added as they appeared to be formed at similar times to each other.

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Figure B.8.203 SFO fitting for X11393729 and X11406790 in series with XDE-729 methyl in Swiss Lake total system



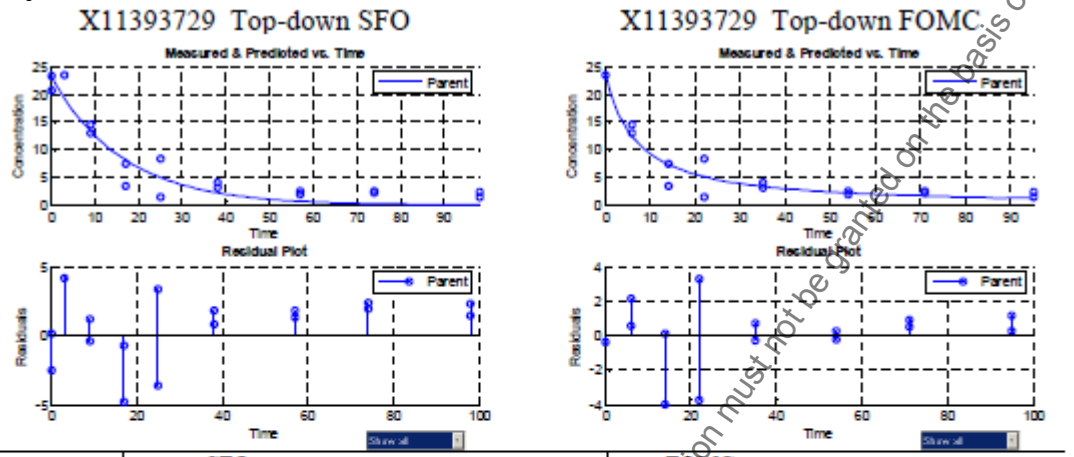
Model parameters	X113729 (metabolite A1) Parameter ± error	Confidence Interval	Prob>t	X11406790 (metabolite B1) Parameter ± error	Confidence Interval	Prob>t
FF	0.4512 ± 0.0692	0.3112-0.5912		0.4450 ± 0.2050	0.0300-0.8600	
Metabolite, k	0.1125 ± 0.0235	0.0648-0.1602	1.3E-5	0.1634 ± 0.0445	0.0733-0.2534	3.7E-4
% error where χ^2 passes	25.9			23.5		
r^2	0.8906			0.8917		
$DegT_{50}$ (days)	6			4		
$DegT_{90}$ (days)	20			14		

FF = metabolite formation fraction

For both metabolites, χ^2 errors are reasonably large. For X11393729, visual and residual fits demonstrate a systematic under prediction of residues at the last four sample times. The spread of residuals for X11406790 appears random and therefore acceptable. The peak of formation is underestimated for both metabolites, particularly for X11406790. The study authors considered that overall the fits for these metabolites were not sufficiently good and decided to calculate kinetics with a 'top down' approach from peak observed concentrations. This is likely to be a more conservative approach as it only takes into account the overall decline which is a function of both formation and degradation. In addition, a top down approach was also employed for the terminal metabolite X11449757. Note that because the FOCUSsw models do not simulate the sequential formation of metabolites in water, the conservative use of top down kinetics is acceptable in this case.

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Figure B.8.204 'Top down' SFO and FOMC fitting for X11393729 in Swiss Lake total system

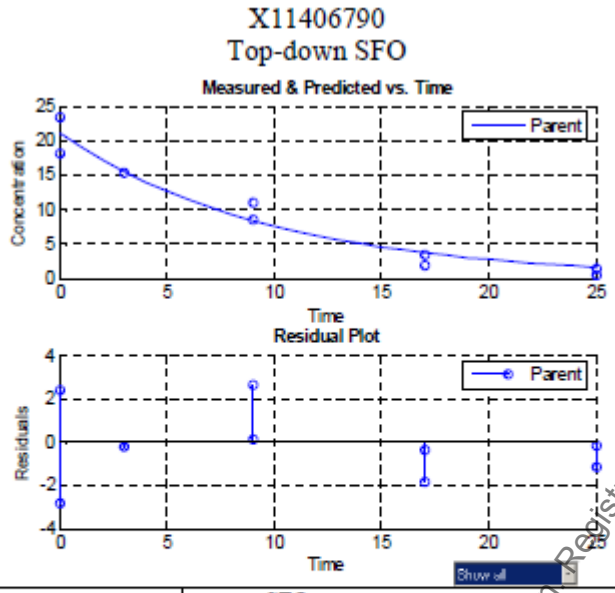


Model parameters	SFO Parameter ± error	SFO Confidence Interval	SFO Prob>t	FOMC Parameter ± error	FOMC Confidence Interval	FOMC Prob>t
M_0	23.3 ± 1.6	19.9-26.6		23.9± 2.0	19.5-28.2	
Parent k_1	0.0614 ± 0.0087	0.0428-0.0800	2.0E-6			
alpha				1.2 ± 0.4	0.18-2.13	0.0123
beta				7.9± 5.5	-4.1-20.0	0.0881
% error where χ^2 passes	20.7			12.7		
r^2	0.9153			0.9141		
$DegT_{50}$ (days)	11			7		
$DegT_{90}$ (days)	38			50		
Best-fit Endpoint						

Whilst the overall fit was better with FOMC (observed fit, residuals and χ^2 error), the fact that the FOMC beta parameter had a large error and confidence interval incorporated zero were considered to be inappropriate. As a consequence, SFO was considered to be the better fitter by the study authors. The RMS considers that neither SFO or FOMC show ideal fits or parameters, but the SFO parameters are appropriate to use being more conservative than SFO in series with the parent.

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Figure B.8.205 'Top down' SFO fitting for X11406790 in Swiss Lake total system



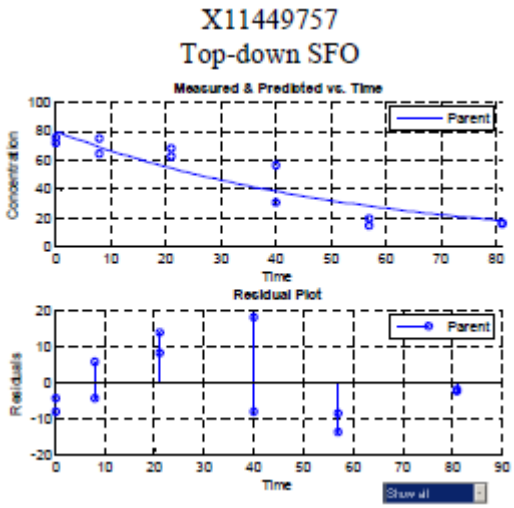
Model parameters	SFO Parameter ± error	Confidence Interval	Prob>t
M_0	21.0 ± 1.3	18.1-24.0	
Parent k_1	0.1011 ± 0.0135	0.0692-0.1330	6.9E-5
% error where χ^2 passes	7.4		
r^2	0.9541		
$DegT_{50}$ (days)	7		
$DegT_{90}$ (days)	23		

SFO top down fitting only was used for X11406790, however, the fit and statistics appear to be reasonable and the RMS can accept these endpoints.

Given the use of a top-down approach for the two preceding metabolites, a top down approach was also used for the secondary metabolite, X11449757.

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Figure B.8.206 'Top down' SFO fitting for X11449757 in Swiss Lake total system



Model parameters	SFO Parameter ± error	Confidence Interval	Prob>t
M_0	80.0 ± 5.6	67.5-92.6	
Parent k_1	0.0184 ± 0.0031	0.0115-0.0253	7.3E-5
% error where χ^2 passes	12.1		
r^2	0.8578		
$DegT_{50}$ (days)	38		
$DegT_{90}$ (days)	125		

The RMS considers that the fit and statistics appear reasonable and that the SFO parameters can be accepted in spite of biphasic kinetics not being fitted.

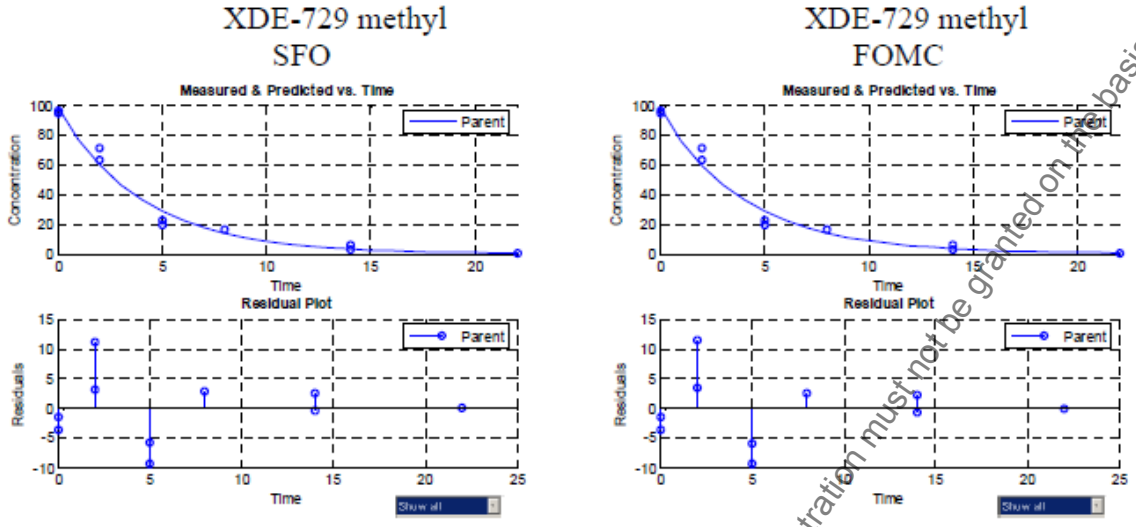
Parent water phase dissipation

Data omitting the 8 DAT PY label data for parent were fitted using SFO and FOMC kinetics.

Both kinetics gave similar fits, with a slightly superior $\chi 2$ value for SFO. Additionally, confidence intervals around the FOMC alpha and beta parameters included zero and the errors around the optimised alpha and beta values were greater than the optimised values themselves. SFO was chosen as the superior fit.

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Fig B.8.207 SFO and FOMC fitting for XDE-729 methyl in Swiss Lake water phase



Model parameters	SFO Parameter ± error	Confidence Interval	Prob>t	FOMC Parameter ± error	Confidence Interval	Prob>t
M_0	98.2 ± 4.0	88.9-107.5		98.2 ± 4.5	87.6-108.9	
Parent k_1	0.2468 ± 0.0236	0.1924-0.3012	3.0E-6			
alpha				37.2 ± 365.2	-826-901	0.4608
beta				148± >1000	<-1000->1000	0.4615
% error where χ^2 passes	9.2			10.2		
r^2	0.9723			0.9777		
DT_{50} (days)	3			3		
DT_{90} (days)	9			9		
	Best-fit endpoint					

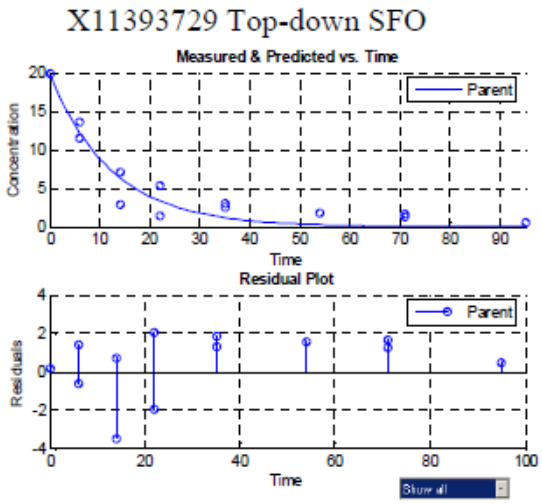
Metabolites water phase

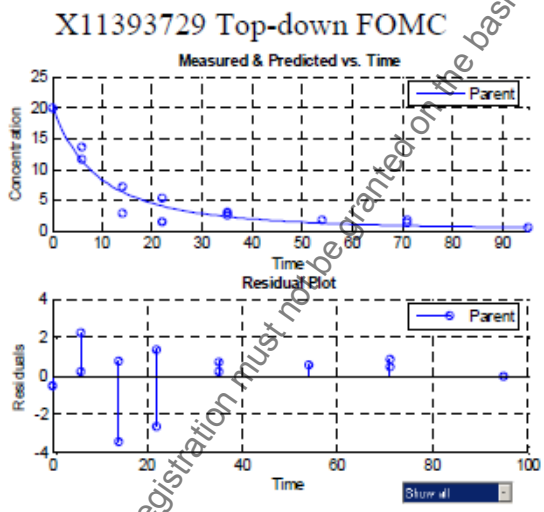
Given that water column dissipation only was being calculated, the study authors only calculated top down dissipation values for the metabolites as follows.

For X11393729, FOMC was a better fit visually, in terms of residuals and for χ^2, however, the error around the FOMC parameters was of a similar magnitude to the optimised values, and the confidence intervals included zero. The Study author thus considered that SFO was the preferred choice. The RMS considers that this is overall an acceptable choice.

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Fig B.8.208 SFO and FOMC top down fitting for X11393729 in Swiss Lake water phase



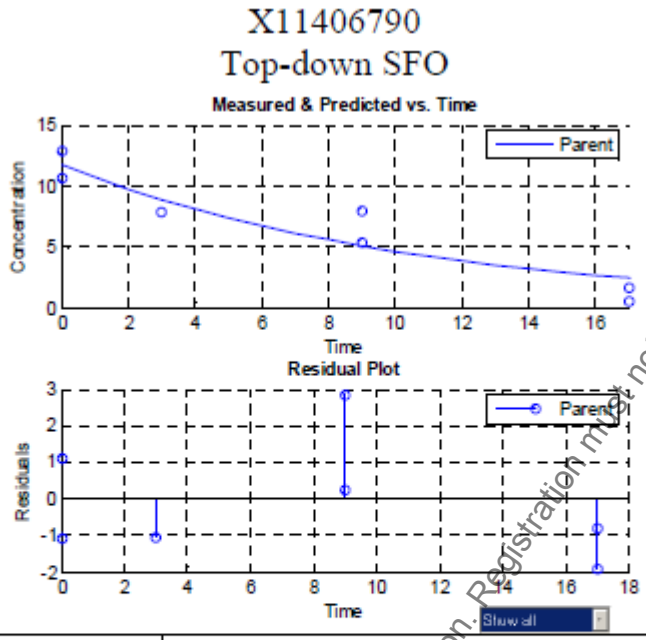


Model parameters	SFO Parameter ± error	Confidence Interval	Prob>t	FOMC Parameter ± error	Confidence Interval	Prob>t
M_0	19.8 ± 1.6	16.4-23.3		20.5 ± 1.6	17.0-24.0	
Parent k_1	0.0809 ± 0.0110	0.0569-0.1048	4.4E-6			
alpha				1.98 ± 1.13	-0.50-4.46	0.0533
beta				17.33± 14.14	-13.79-48.45	0.1230
% error where χ^2 passes	16.1			12.6		
r^2	0.9315			0.9352		
DT_{50} (days)	9			7		
DT_{90} (days)	28			38		
	Best-fit endpoint					

Top down SFO kinetics appear to have been only used for the other two metabolites. Given the relatively limited scope for use of dissipation-only water phase values in EU risk assessment, the use of SFO-only kinetics for these metabolites is considered acceptable by the RMS. In addition, the RMS considers that the fits presented are reasonable and can be accepted in their own right.

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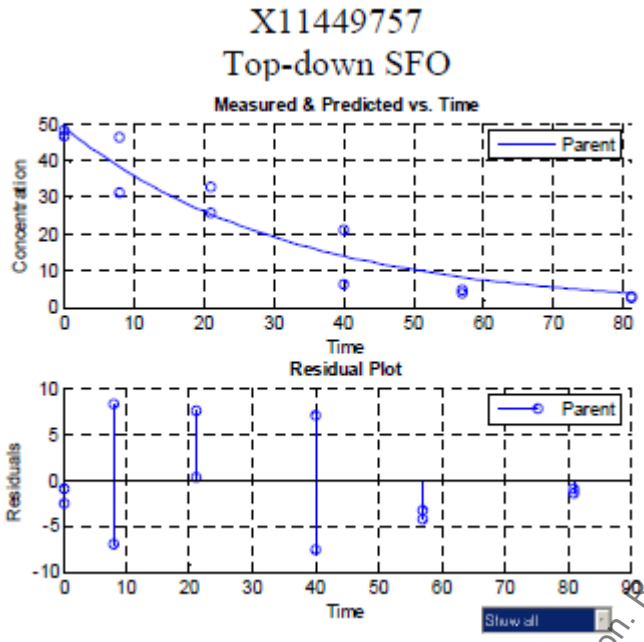
Figure B.8.209 SFO top down fitting for X11406790 in Swiss Lake water phase



Model parameters	SFO Parameter ± error	Confidence Interval	Prob>t
M_0	11.7 ± 1.2	8.7-14.7	
Parent k_1	0.0928 ± 0.0225	0.0350-0.1506	4.5E-3
% error where χ^2 passes	14.1		
r^2	0.8715		
DT_{50} (days)	7		
DT_{90} (days)	25		

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Figure B.8.210 SFO top down fitting for X11449757 in Swiss Lake water phase



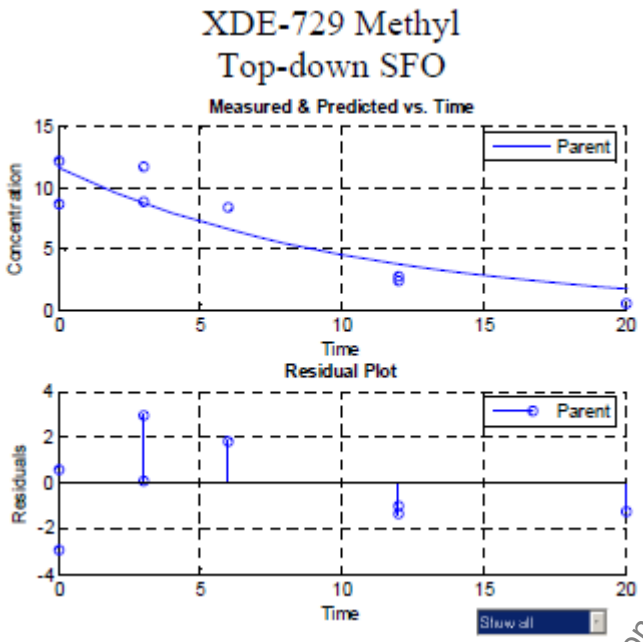
Model parameters	SFO Parameter ± error	Confidence Interval	Prob>t
M_0	49.2 ± 3.4	41.6-56.8	
Parent k_1	0.0314 ± 0.0048	0.0208-0.0421	3.1E-5
% error where χ^2 passes	8.4		
r^2	0.9150		
DT_{50} (days)	22		
DT_{90} (days)	73		

Parent, sediment phase

A top-down approach was used to calculate the dissipation rate of XDE-729 methyl from sediment. SFO kinetics only was attempted. Given the limited use of sediment dissipation rates in EU assessment, this is considered to be acceptable. The RMS considers that the fits are reasonable and can be accepted.

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Fig B.8.211 SFO top down fitting for XDE-729 methyl in Swiss Lake sediment phase



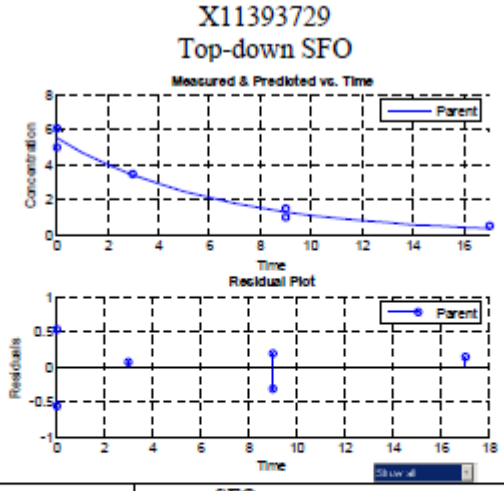
Model parameters	SFO Parameter ± error	Confidence Interval	Prob>t
M_0	11.6 ± 1.3	8.5-14.8	
Parent k_1	0.0945 ± 0.0272	0.0279-0.1612	6.6E-3
% error where χ^2 passes	16.2		
r^2	0.8243		
DT_{50} (days)	7		
DT_{90} (days)	24		

Metabolites, sediment phase

A top down approach was also taken for decline of the metabolites in sediment.

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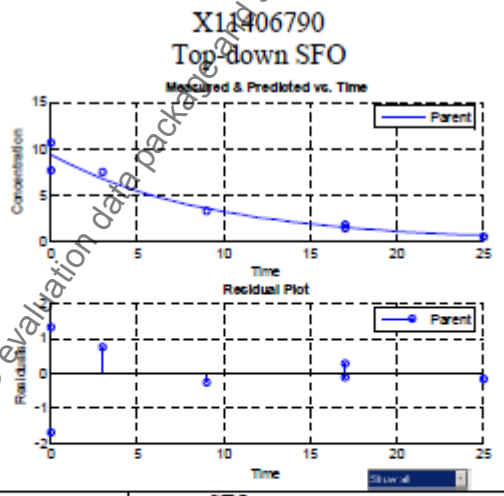
Fig B.8.212 SFO top down fitting for X11393729 methyl in Swiss Lake sediment phase



Model parameters	SFO Parameter ± error	Confidence Interval	Prob>t
M_0	5.6 ± 0.3	4.7-6.4	
Parent k_1	0.1603 ± 0.0229	0.0968-0.2239	1.1E-3
% error where χ^2 passes	2.3		
r^2	0.9712		
DT_{50} (days)	4		
DT_{90} (days)	14		

The RMS considers that in spite of only four sample times being available, the fit is good and the optimised parameters reflect the decline of this metabolite from the observed peak in sediment.

Fig B.8.213 SFO top down fitting for X11406790 methyl in Swiss Lake sediment phase

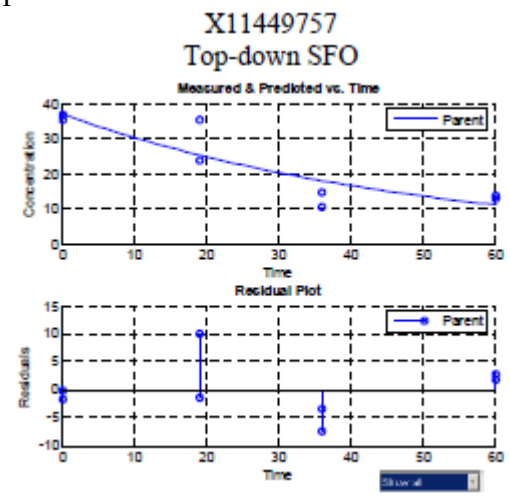


Model parameters	SFO Parameter ± error	Confidence Interval	Prob>t
M_0	9.3 ± 0.6	7.7-10.8	
Parent k_1	0.1064 ± 0.0167	0.0656-0.1471	3.5E-4
% error where χ^2 passes	6.7		
r^2	0.9412		
DT_{50} (days)	7		
DT_{90} (days)	22		

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The RMS considers that the optimised parameters can be accepted for the decline of this metabolite in sediment.

Fig B.8.214 SFO top down fitting for X11449757 methyl in Swiss Lake sediment phase



Model parameters	SFO Parameter ± error	Confidence Interval	Prob>t
M_0	37.1± 3.7	28.1-46.1	
Parent k_1	0.0201 ± 0.0047	0.0086-0.0315	2.6E-3
% error where χ^2 passes	13.1		
r^2	0.7982		
DT_{50} (days)	35		
DT_{90} (days)	115		

The RMS considers that in spite of only four sample times being available, the fit is good and the optimised parameters reflect the decline of this metabolite from the observed peak in sediment.

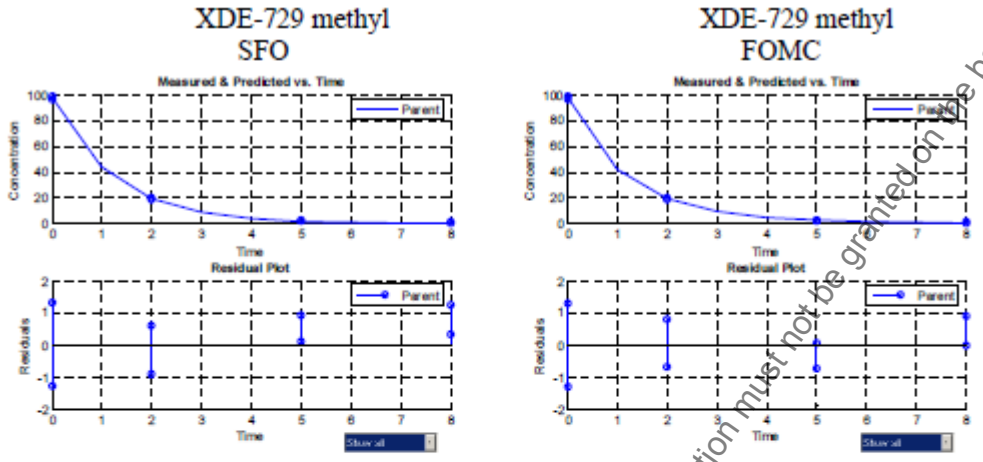
Calwich Abbey loam water/sediment system

Parent total system

Setting LOD to 1% results in availability of only four sample times for the parent, i.e. to 8 DAT. Both SFO and FOMC kinetics were tested with the following results being obtained.

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Figure B.8.215 SFO and FOMC fits for XDE-729 methyl in Calwich Abbey water/sediment total system



Model parameters	SFO Parameter ± error	Confidence Interval	Prob>t	FOMC Parameter ± error	Confidence Interval	Prob>t
M_0	97.9 ± 0.8	96.0-99.8		97.9 ± 0.8	95.9-99.9	
Parent k_1	0.8017 ± 0.0194	0.7543-0.8491	6.7E-8			
alpha				10 ± 7	-10-29	0.1306
beta				11 ± 9	-13-35	0.1502
% error where χ^2 passes	1.3			0.9		
r^2	0.9995			0.9995		
$DegT_{50}$ (days)	0.8			0.8		
$DegT_{90}$ (days)	2.9			3.0		
	Best fit endpoint					

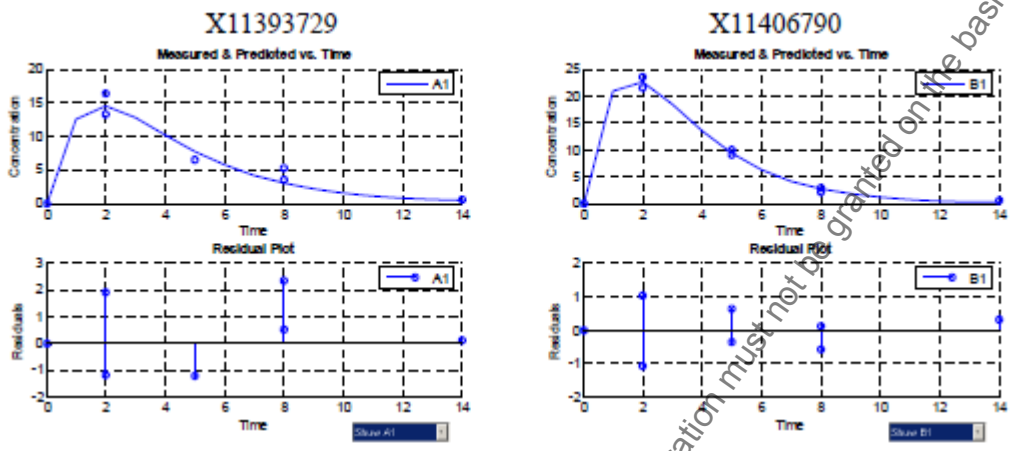
Both kinetics give good fits to the data. Whilst $\chi 2$ is marginally better with FOMC, the error around the alpha and beta parameters are large and confidence intervals include zero, thus the RMS agrees with the SFO fit being the most appropriate.

Metabolites total system

Data on metabolites X11393729 and X11406790 were added to the parent SFO model. Both metabolites were added as they appeared to be formed at similar times to each other.

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Figure B.8.216 SFO fitting for X11393729 and X11406790 in series with XDE-729 methyl in Calwich Abbey total system



Model parameters	X11393729 (metabolite A1) Parameter ± error	Confidence Interval	Prob>t	X11406790 (metabolite B1) Parameter ± error	Confidence Interval	Prob>t
FF	0.2806 ± 0.0238	0.2310-0.3303		0.4983 ± 0.0518	0.3903-0.6063	
Metabolite k	0.3448 ± 0.0390	0.2635-0.4262	1.2E-8	0.4606 ±0.0375	0.3825-0.5388	4.4E-11
% error where χ^2 passes	13.5			2.2		
r^2	0.9506			0.9953		
$DegT_{50}$ (days)	2.0			1.5		
$DegT_{90}$ (days)	6.7			5.0		
	Best-fit endpoint			Best-fit endpoint		

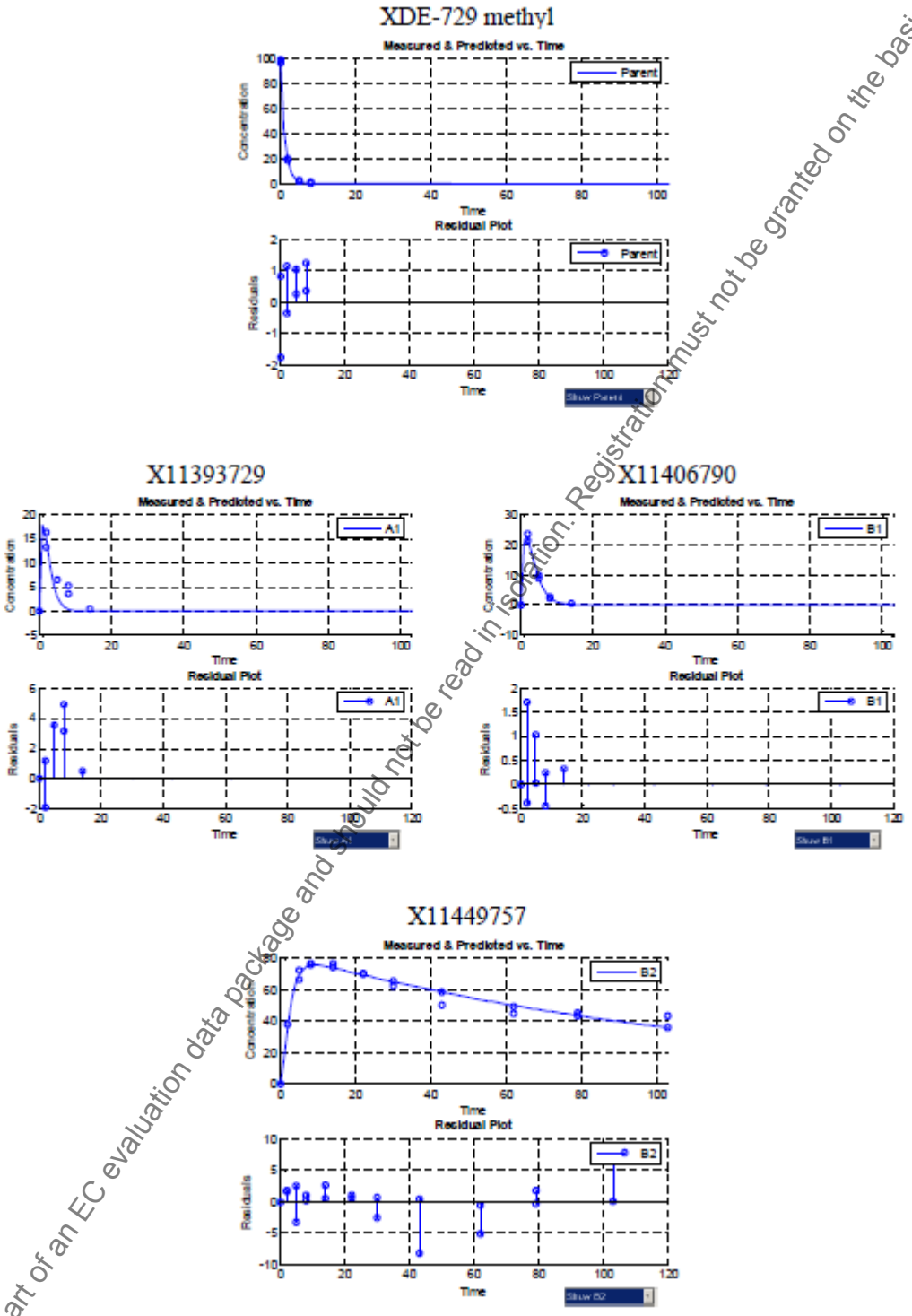
FF = metabolite formation fraction

The RMS agrees that the fits look reasonable for both metabolites and the statistics are also acceptable. This may be related to the relatively low number of sample times available, however, the RMS accepts the optimised SFO parameters for X11393729 and X11406790 in the total system.

The data for X11449757 was subsequently added to the parent/X11393729/X11406790 model. The model was run in the FOCUS Kinetics recommended way, i.e. precursor substance parameters fixed and optimise X11449757 parameters, then allow all simulated substances to freely optimise.

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Figure B.8.217 SFO fitting for X11449757 (in series with XDE-729 methyl, X11393729 and X11406790) in Calwich Abbey total system



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Figure B.8.218 SFO fitting for X11449757 (in series with XDE-729 methyl, X11393729 and X11406790) in Calwich Abbey total system (continued)

	XDE-729 methyl		
Model parameters	Parameter ± error	Confidence Interval	Prob>t
M_0	98.4± 1.9	94.6-102.2	
Parent k_1	0.8183 ± 0.0487	0.7198-0.9168	9.2E-20
% error where χ^2 passes	1.6		
r^2	0.9996		
$DegT_{50}$ (days)	0.85		
$DegT_{90}$ (days)	2.8		

	X11393729 (metabolite A1)			X11406790 (metabolite B1)		
Model parameters	Parameter ± error	Confidence Interval	Prob>t	Parameter ± error	Confidence Interval	Prob>t
FF	0.5220 ± 0.1992	0.1192-0.9249		0.4780 ± 0.1726	-0.4779-1.4338	
Metabolite k	0.8925 ± 0.3502	0.1841-1.6009	7.4E-3	0.4601 ± 0.0918	0.2743-0.6458	6.1E-6
% error where χ^2 passes	38.3			4.8		
r^2	0.8789			0.9852		
$DegT_{50}$ (days)	0.78			1.5		
$DegT_{90}$ (days)	2.6			5.0		

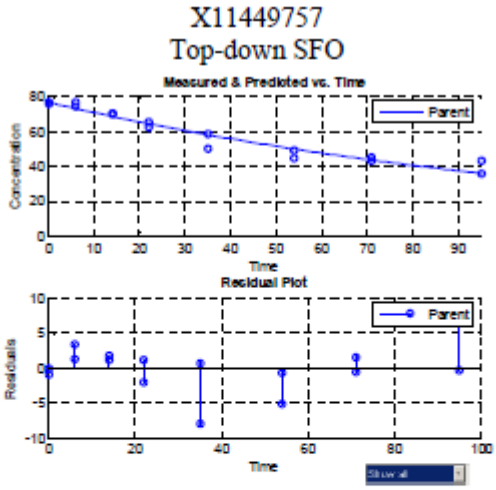
FF = metabolite formation fraction

	X11449757 (metabolite B2)		
Model parameters	Parameter ± error	Confidence Interval	Prob>t
A1_FF	0.9942 ± 0.9481	-0.9235-2.9120	
B1_FF	0.6410 ± 0.6487	-0.6711-1.9531	
Metabolite k	0.0082 ± 0.0005	0.0073-0.0092	1.4E-20
% error where χ^2 passes	3.5		
r^2	0.9810		
$DegT_{50}$ (days)	84		
$DegT_{90}$ (days)	280		

As can be seen, the overall fits for all four substances are still very good with the exception X11393729, where the addition of X11449757 leads to a deterioration in the fit. It is noted, however, that the confidence intervals around the formation fraction for X11406790 includes zero and the error around the optimised value is approaching the optimised value. A similar situation exists for X11449757. With this in mind, and wishing to preserve the better fits for the metabolites X11393729 and X11406790, a top down approach was attempted for X11449757.

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Figure B.8.219 SFO top down fitting for X11449757 in Calwich Abbey total system



Model parameters	SFO Parameter ± error	Confidence Interval	Prob>t
M_0	76.7± 1.5	73.5-80.0	
Parent k_1	0.0080 ± 0.0006	0.0067-0.0092	6.0E-10
% error where χ^2 passes	3.1		
r^2	0.9444		
$DegT_{50}$ (days)	87		
$DegT_{90}$ (days)	289		
	Best-fit endpoint		

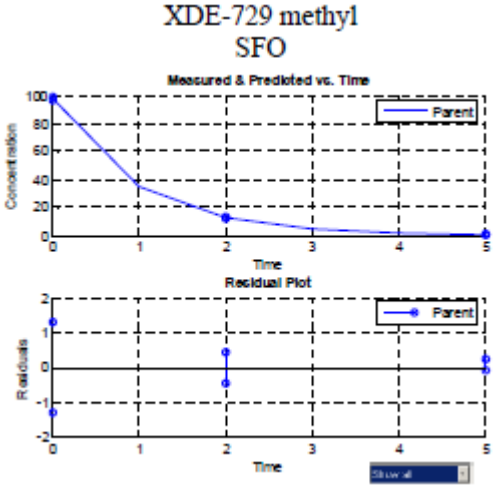
The RMS considers that the top down fit for X11449757 is acceptable and appropriate and that the optimised parameters can be accepted.

Parent water phase dissipation

Given that data were only effectively available from the first three sample times, SFO fitting only was attempted for the parent in the water phase. Note that this is a dissipation calculation rather than a degradation calculation.

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Fig B.8.220 SFO fitting for XDE-729 methyl in Calwich Abbey water phase



Model parameters	SFO Parameter ± error	Confidence Interval	Prob>t
M_0	97.9 ± 0.7	96.0-99.8	
Parent k_1	1.0268 ±0.0276	0.9501-1.1035	1.6E-6
% error where χ^2 passes	0.1		
r^2	0.9997		
DT_{50} (days)	0.67		
DT_{90} (days)	2.24		
	Best-fit endpoint		

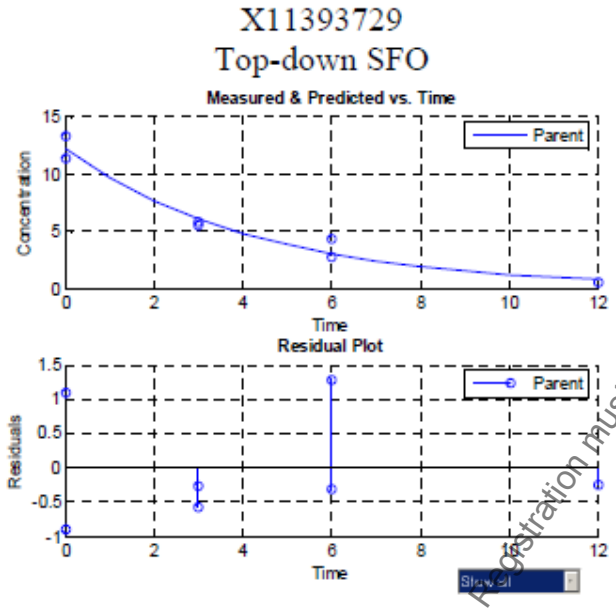
The RMS considers that the fit is appropriate and the optimised parameters can be accepted.

Metabolites water phase dissipation

Metabolites in the water phase were only considered with SFO and using a top down approach.

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Fig B.8.221 SFO top down fitting for X11393729 in Calwich Abbey water phase

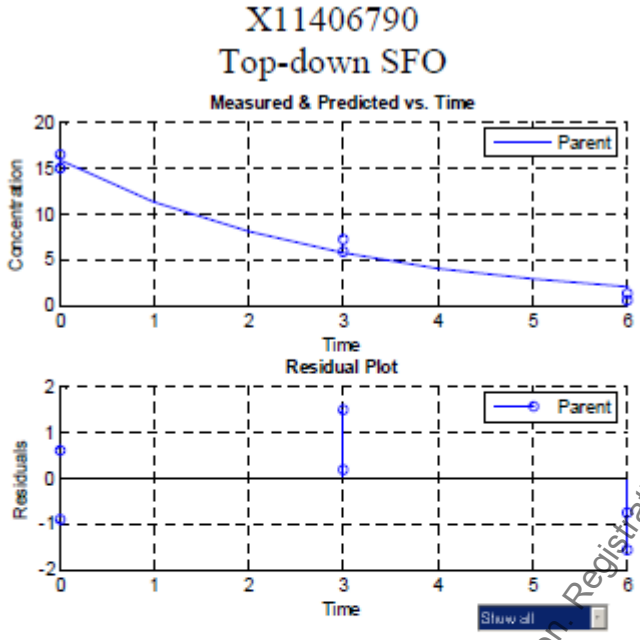


Model parameters	SFO Parameter ± error	Confidence Interval	Prob>t
M_0	12.2 ± 0.6	10.6-13.8	
Parent k_1	0.2329 ± 0.0276	0.1619-0.3038	1.9E-4
% error where χ^2 passes	4.5		
r^2	0.9664		
DT_{50} (days)	3		
DT_{90} (days)	10		

The RMS accepts the optimised top down parameters.

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Fig B.8.222 SFO top down fitting for X11406790 in Calwich Abbey water phase

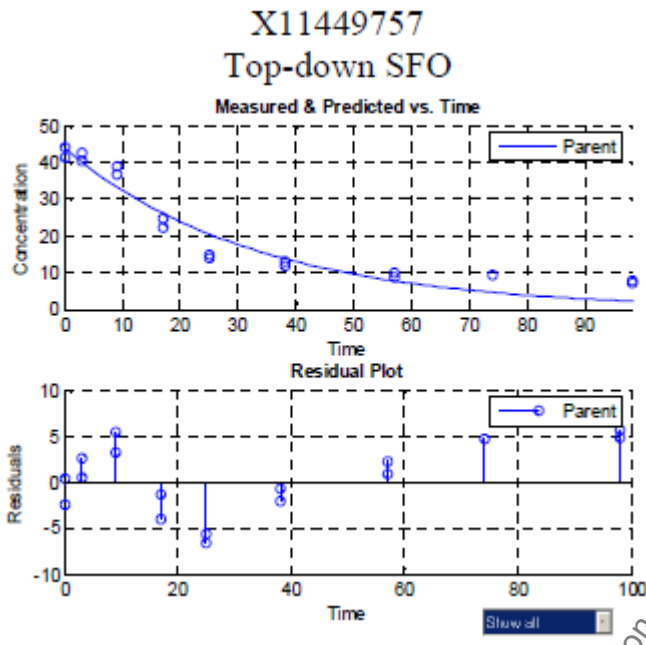


Model parameters	SFO Parameter ± error	Confidence Interval	Prob>t
M_0	15.9± 0.9	13.4-18.4	
Parent k_1	0.3409 ± 0.0450	0.2158-0.4660	8.2E-4
% error where χ^2 passes	9.5		
r^2	0.9737		
DT_{50} (days)	2		
DT_{90} (days)	7		

The RMS accepts the optimised top down parameters whilst noting the small number of data points available.

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Fig B.8.223 SFO top down fitting for X11449757 in Calwich Abbey water phase



Model parameters	SFO Parameter ± error	Confidence Interval	Prob>t
M_0	44.0 ± 2.0	39.8-48.2	
Parent k_1	0.0303 ± 0.0032	0.0236-0.0371	2.7E-8
% error where χ^2 passes	13.3		
r^2	0.9350		
DT_{50} (days)	23		
DT_{90} (days)	76		

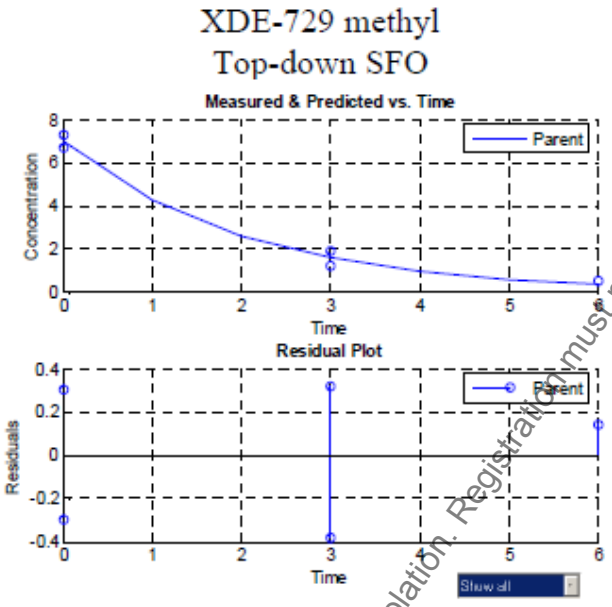
Whilst the RMS makes the observation that the fitted curve underestimates the concentrations at the later time points and that the decline curve is probably biphasic, the RMS considers that the fit is good enough as dissipation rates are not used in FOCUSsw modelling at Step 1-2.

Parent sediment layer dissipation

An SFO top down approach was only attempted on data on parent in sediment.

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Fig B.8.224 SFO top down fitting for XDE-729 methyl in Calwich Abbey sediment phase



Model parameters	SFO Parameter ± error	Confidence Interval	Prob>t
M_0	7.0 ± 0.3	6.1279-7.8648	
Parent k_1	0.4955 ± 0.0562	0.3168-0.6743	1.5E-3
Alpha			
Beta			
% error where χ^2 passes	2.1		
r^2	0.9893		
DT_{50} (days)	1.3		
DT_{90} (days)	4.6		
Endpoint	Best fit endpoints		

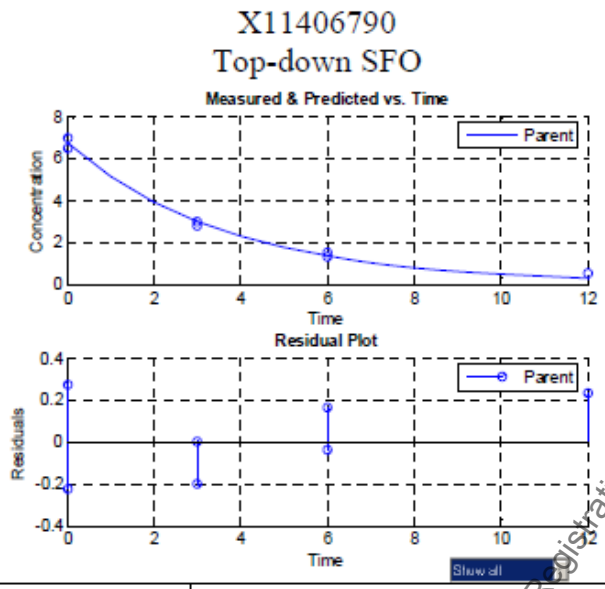
In view of the fact that sediment phase dissipation rates have limited application in FOCUSsw modelling, the optimised parameters can be accepted.

Metabolites sediment phase dissipation

Given that only two sample times were effectively available for X11393729, no fitting was attempted for this metabolite. The RMS considers this acceptable. Sufficient data were available for the other two metabolites to perform a top down approach.

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Fig B.8.225 SFO top down fitting for X11406790 in Calwich Abbey sediment phase

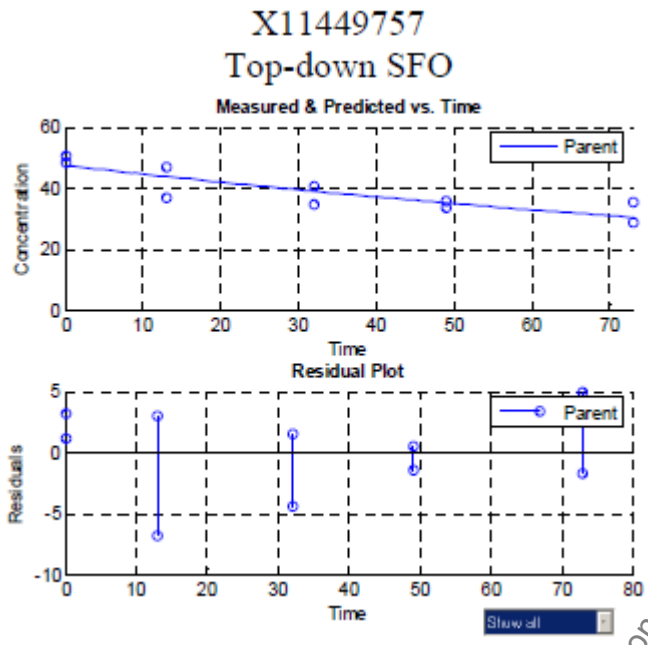


Model parameters	SFO		
	Parameter ± error	Confidence Interval	Prob>t
M_0	6.7 ± 0.2	6.3-7.1	
Parent k_1	0.2692 ± 0.0141	0.2329-0.3056	3.7E-6
% error where χ^2 passes	3.3		
r^2	0.9942		
DT_{50} (days)	3		
DT_{90} (days)	9		

The RMS can accept the optimised parameters from this fit.

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Fig B.8.226 SFO top down fitting for X11449757 in Calwich Abbey sediment phase



Model parameters	SFO Parameter ± error	Confidence Interval	Prob>t
M_0	47.4 ± 2.1	42.8-52.2	
Parent k_1	0.0061 ± 0.0013	0.0032-0.0090	6.7E-4
% error where χ^2 passes	3.3		
r^2	0.7497		
DT_{50} (days)	114		
DT_{90} (days)	378		

The RMS can accept the optimised parameters from this fit.

(Laughlin and Balcer 2011, updated 2012)

b) A supplementary aerobic water/sediment study was conducted according to OECD 308 and US EPA OPPTS 835.4300 guidelines and the GLP. The study was conducted because the Applicant wished to clarify the behaviour of XDE-729 methyl at the beginning of the study. In the study described in B.8.4.4a) above, whilst there were four sampling times in the first eight days following treatment, XDE-729 methyl degraded to less than 10% AR in the total Calwich Abbey system within this time and to 25 – 64% AR in total Swiss Lake system by the same time point with a further reduction to less than 10% AR by 14 DAT. Therefore to obtain a better definition of fate in the early part of this type of study, the study was repeated on water and sediment samples collected from the same locations as those used in the initial study, using more sample times and terminating the study at 30 DAT.

Water and sediment properties of the two systems are shown below.

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Table B.8.166 Properties of water in supplementary aerobic water/sediment study

Parameter	Results	
Geographic Location	Chatsworth, Derbyshire, England	Calwich, Staffordshire, England
Storage Temperature	4 °C	4 °C
pH	6.8	8.2
Initial Redox Potential (mv)	235	121
Final Redox Potential (mv)	376	103
Initial Final Dissolved Oxygen (ppm)	6.91	5.04
Final Dissolved Oxygen (ppm)	7.18	6.87
Dissolved Organic Carbon (ppm)	6.2	2.0
Hardness (mg equivalent $CaCO_3$/L)	24	244
Conductivity (mmhos/cm)	0.14	0.47

Table B.8.167 Properties of sediment in supplementary aerobic water/sediment study

Parameter	Results	
Geographic Location	Site C – Swiss Lake, Chatsworth, Derbyshire, England	Site A – Calwich Abbey Lake, Calwich, Staffordshire, England
USDA Texture Class	Sand	Sandy Loam
% Sand	88	46
% Silt	7	47
% Clay	5	7
International Texture Class	Loamy Sand	Sandy Loam
% Sand	94	70
% Silt	1	23
% Clay	5	7
pH (1:1 soil:water)	5.4	7.2
% Organic Carbon	0.90	4.80
Initial Redox Potential (mv)	-293	-398
Final Redox Potential (mv)	-131	-376
Initial Biomass (µg/g)	160.8	376.8
Final Biomass (µg/g)	20.6	38.1
CEC (meq/100g)	2.9	15.7
Bulk Density (g/cm^3)	1.14	0.75

The sediment/water ratios used were 1:3 (w:v) for the Swiss Lake system and 1:4 (w:v) for Swiss Lake system. XDE-729 methyl was dosed at a nominal concentration of 0.02 mg/l. The substance was radiolabelled in both PH and PY rings. Prior to treatment, the water/sediment systems were established and allowed to equilibrate in the dark at 20ºC for five days with a supply of moistened air. Incubation containers were connected to a 2N NaOH trap for volatiles.

Following dosing, samples were analysed at 0, 1 and 4 hours after treatment and 1, 2, 4, 7, 10, 15, 21 and 30 DAT. Incubation conditions continued to be in darkness at

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20ºC. At each sample time, the entire incubation contained and its volatile trap were sacrificed. Duplicate samples were taken at each sample time, although only one replicate was available per radiolabel. Note that for day 0 samples, the test substance was dosed onto the water layer and the water layer immediately decanted from the sediment.

At each sample time, water and sediment were separated following centrifugation. Water samples were acidified to pH 2 with 20% H_3PO_4 and subjected to solid phase extraction with elution with methanol:water:H_3PO_4. A methanol:glycerol solution was added to the eluant prior to concentration to less than 0.5ml under a stream of nitrogen. The concentrated sample was then analysed by HPLC with UV and radiochemical detection. Metabolite identification was by co-chromatography with reference standards.

Sediment was extracted twice with methanol:water. If the unextracted residue in the sediment exceeded 6% AR, the sediment was subject to an ASE procedure as previously described for the soil studies. Sediment extracts were concentrated in a similar manner to the water samples. Analysis and metabolite identification was by the same procedures as for the water samples.

Extracted sediment was subject to combustion to determine unextracted radioactivity.

Measurements of pH, dissolved oxygen, redox potential and redox potential corrected to pH 7 were taken at every daily sample time. The magnitude of the values suggested that the water remained aerobic and sediment anaerobic over the course of the study.

Details of mass balance are presented below.

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Table B.8.168 Details of mass balance in Swiss Lake water/sediment supplementary study

Label	DAT	Caustic Trap	Aqueous Layer	Organic Extract	ASE Extract	NER	Total
PH	0	NA[a]	97.1	1.2	NA	0.1	98.3
PY	0	NA	97.8	1.4	NA	0.1	99.3
PH	0.04	0.0	91.1	6.5	NA	0.3	98.0
PY	0.04	0.0	89.3	7.0	NA	0.3	96.7
PH	0.16	0.0	88.8	9.4	NA	0.8	98.9
PY	0.16	0.7	86.9	10.8	NA	0.4	98.8
PH	1	0.0	90.0	8.9	NA	0.5	99.3
PY	1	0.0	88.5	9.2	NA	0.5	98.2
PH	2	NR[b]	NR	NR	NR	NR	NR
PY	2	NR[c]	NR	NR	NR	NR	NR
PH	4	0.0	65.6	28.4	NA	5.7	99.8
PY	4	0.1	89.2	8.1	NA	0.8	98.2
PH	7	0.0	65.6	23.0	9.0	0.0	97.7
PY	7	0.0	58.6	29.5	7.5	2.6	98.2
PH	10	0.0	46.4	35.1	11.6	3.6	96.7
PY	10	0.0	60.2	23.9	10.1	3.6	97.8
PH	15	0.3	51.9	22.4	18.0	5.8	98.3
PY	15	0.0	52.7	21.1	17.6	4.7	96.1
PH	21	0.0	54.3	17.1	15.2	4.7	91.3
PY	21	0.1	44.0	24.6	18.5	2.3	89.5
PH	30	0.4	43.0	18.8	20.2	10.6	93.0
PY1	30	0.1	42.9	18.5	20.2	11.4	93.1

[a] NA = Not Applicable
[b] NR = Not Reported. Sample results not included due to low mass balance.
[c] NR = Not Reported. Sample results not included due to high mass balance.

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Table B.8.169 Details of mass balance in Calwich Abbey water/sediment supplementary study

Label	DAT	Caustic Trap	Aqueous Layer	Organic Extract	ASE Extract	NER	Total
PH	0.0	NA[a]	98.4	0.8	NA	0.0	99.3
PY	0.0	NA	96.1	0.9	NA	0.1	97.1
PH	0.04	0.0	84.3	12.3	NA	1.1	97.8
PY	0.04	0.1	87.8	9.5	NA	1.1	98.5
PH	0.16	NR[b]	NR	NR	NR	NR	NR
PY	0.16	0.0	68.5	23.9	NA	2.5	95.0
PH	1	0.0	79.5	17.6	NA	3.1	100.2
PY	1	0.0	70.2	23.8	NA	4.9	98.8
PH	2	0.0	71.0	18.9	7.7	1.1	98.6
PY	2	0.0	72.3	19.5	6.6	1.7	100.2
PH	4	0.0	72.3	18.4	8.3	1.1	100.2
PY	4	0.0	61.2	20.9	14.7	3.2	100.1
PH	7	0.0	53.7	17.5	17.7	7.6	96.6
PY	7	0.0	54.1	18.4	18.6	6.5	97.6
PH	10	0.1	49.0	20.2	22.3	7.5	99.0
PY	10	0.1	49.4	18.4	19.9	11.2	99.0
PH	15	NR[c]	NR	NR	NR	NR	NR
PY	15	0.0	40.3	18.2	22.9	14.9	96.4
PH	21	0.7	37.0	17.7	23.2	18.3	97.0
PY	21	0.0	33.2	21.9	27.9	13.6	96.6
PH	30	1.8	27.0	16.9	25.6	30.5	101.8
PY	30	0.1	25.5	23.4	31.0	17.7	97.6

[a] NA = Not Applicable
[b] NR = Not Reported. Sample lost during incubation.
[c] NR = Not Reported. Sample results not included due to high mass balance.

Results of quantification of parent and metabolites are presented below.

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Table B.8.170 Distribution of radioactivity as XDE-729 methyl and its metabolites in water and sediment in Swiss Lake water/sediment system, supplementary study

	Aqueous layer				Sediment layer			
Label & DAT	729 methyl[d]	X729[b]	X757[a]	X790[c]	729 methyl	X729	X757	X790
PH-0	92.6	4.5	0.0	0.0	1.2	0.0	0.0	0.0
PY-0	91.8	6.0	0.0	0.0	1.4	0.0	0.0	0.0
PH-0.04	85.9	5.1	0.0	0.0	6.3	0.2	0.0	0.0
PY-0.04	83.1	5.7	0.0	0.0	7.0	0.0	0.0	0.0
PH-0.16	84.3	4.5	0.0	0.0	9.1	0.3	0.0	0.0
PY-0.16	80.3	6.6	0.0	0.0	10.5	0.3	0.0	0.0
PH-1	84.0	5.5	0.0	0.5	8.1	0.3	0.0	0.5
PY-1	81.3	7.2	0.0	0.0	8.4	0.5	0.0	0.3
PH-2	NR	NR	NR[e]	NR	NR	NR	NR	NR
PY-2	NR	NR	NR[f]	NR	NR	NR	NR	NR
PH-4	38.5	6.7	4.9	15.5	11.5	0.7	3.1	13.1
PY-4	81.7	5.5	0.9	1.2	6.5	0.2	0.6	0.7
PH-7	29.4	7.5	11.7	17.1	5.3	0.5	14.3	11.9
PY-7	17.9	7.1	12.5	21.0	7.0	0.9	12.1	16.9
PH-10	10.0	10.4	14.0	11.9	12.1	3.0	14.8	16.7
PY-10	13.0	7.0	20.7	19.5	2.6	1.0	16.4	14.0
PH-15	8.3	5.0	24.6	14.0	2.2	1.0	27.7	9.4
PY-15	10.7	4.3	24.7	12.9	2.6	0.3	24.5	11.4
PH-21	19.6	5.8	21.1	7.8	2.3	0.3	26.2	3.5
PY-21	1.9	6.2	31.6	4.2	4.5	1.5	27.9	9.0
PH-30	0.6	2.9	37.1	2.3	1.2	0.3	33.9	3.7
PY-30	0.0	1.7	39.2	2.1	0.8	0.0	33.4	4.6

[a] X757 = X11449757
[b] X729 = X11393729
[c] X790 = X11406790
[d] 729 methyl = XDE-729 methyl
[e] NR = Not Reported. Sample results not included due to low mass balance.
[f] NR = Not Reported. Sample results not included due to high mass balance.

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Table B.8.171 Distribution of radioactivity as XDE-729 methyl and its metabolites in Swiss Lake water/sediment total system, supplementary study

	Total				
Label & DAT	729 methyl[d]	X729[b]	X757[a]	X790[c]	Other[e]
PH-0	93.8	4.5	0.0	0.0	0.0
PY-0	93.2	6.0	0.0	0.0	0.0
PH-0.04	92.2	5.4	0.0	0.0	0.0
PY-0.04	90.1	5.7	0.0	0.0	0.5
PH-0.16	93.3	4.8	0.0	0.0	0.0
PY-0.16	90.8	7.0	0.0	0.0	0.0
PH-1	92.1	5.8	0.0	1.0	0.0
PY-1	89.7	7.7	0.0	0.3	0.0
PH-2	NR	NR	NR	NR	NR
PY-2	NR	NR	NR	NR	NR
PH-4	50.0	7.4	8.1	28.6	0.0
PY-4	88.2	5.7	1.5	1.9	0.0
PH-7	34.7	8.0	26.1	28.9	0.0
PY-7	24.9	8.0	24.6	37.9	0.0
PH-10	22.2	13.4	28.8	28.7	0.0
PY-10	15.6	8.0	37.1	33.5	0.0
PH-15	10.5	6.0	52.4	23.4	0.0
PY-15	13.3	4.7	49.2	24.2	0.0
PH-21	21.9	6.1	47.3	11.3	0.0
PY-21	6.4	7.8	59.6	13.2	0.2
PH-30	1.8	3.1	71.0	6.0	0.0
PY-30	0.8	1.7	72.6	6.7	0.0

[a] X757 = X11449757
[b] X729 = X11393729
[c] X790 = X11406790
[d] 729 methyl = XDE-729 methyl
[e] The Other ^{14}C is a summation of the radioactivity incorporated in numerous components. The other ^{14}C accounts for up to 0.5% of the applied radioactivity.
[f] NR = Not Reported. Sample results not included due to low mass balance.
[g] NR = Not Reported. Sample results not included due to high mass balance.

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Table B.8.172 Distribution of radioactivity as XDE-729 methyl and its metabolites in water and sediment in Calwich Abbey water/sediment system, supplementary study

	Aqueous Layer				Sediment Layer			
Label & DAT	729 methyl[d]	X729[b]	X757[a]	X790[c]	729 methyl	X729	X757	X790
PH-0	90.1	8.3	0.0	0.0	0.8	0.0	0.0	0.0
PY-0	86.5	9.1	0.0	0.0	0.9	0.0	0.0	0.0
PH-0.04	74.6	9.7	0.0	0.0	11.3	0.4	0.0	0.6
PY-0.04	78.1	9.3	0.0	0.0	8.4	0.4	0.0	0.6
PH-0.16	NR	NR	NR[e]	NR	NR	NR	NR	NR
PY-0.16	58.9	9.3	0.3	0.0	21.1	1.4	0.0	1.2
PH-1	57.7	11.2	5.0	5.6	10.0	1.0	1.6	5.1
PY-1	44.6	10.0	7.4	7.7	13.3	1.2	2.9	6.2
PH-2	25.8	8.1	23.0	14.1	6.8	0.5	13.2	5.7
PY-2	33.3	10.5	18.8	9.8	8.0	1.1	10.8	6.1
PH-4	48.5	7.8	12.2	3.8	8.2	0.5	14.1	3.8
PY-4	1.7	6.3	41.5	11.7	2.3	1.5	26.3	5.6
PH-7	0.8	2.9	45.7	2.6	0.2	0.2	33.0	1.3
PY-7	0.0	1.9	49.2	3.1	0.9	0.0	34.5	1.6
PH-10	1.6	2.4	39.7	4.0	0.5	0.2	40.5	1.3
PY-10	0.0	0.7	47.9	0.8	0.3	0.0	37.4	0.6
PH-15	NR	NR	NR[f]	NR	NR	NR	NR	NR
PY-15	0.0	0.0	40.3	0.0	0.4	0.0	40.5	0.2
PH-21	0.0	0.0	37.0	0.0	0.1	0.0	40.3	0.2
PY-21	0.0	0.0	33.2	0.0	0.2	0.0	49.2	0.4
PH-30	0.0	0.0	26.6	0.0	0.3	0.0	42.0	0.2
PY-30	0.0	0.0	25.5	0.0	0.0	0.0	54.1	0.0

[a] X757 = X11449757
[b] X729 = X11393729
[c] X790 = X11406790
[d] 729 methyl = XDE-729 methyl
[e] NR = Not Reported. Sample lost during incubation.
[f] NR = Not Reported. Sample results not included due to high mass balance.

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Table B.8.173 Distribution of radioactivity as XDE-729 methyl and its metabolites in Calwich water/sediment total system, supplementary study

	Total				
Label & DAT	729 methyl[d]	X729[b]	X757[a]	X790[c]	Other[e]
PH-0	90.9	8.3	0.0	0.0	0.0
PY-0	87.4	9.1	0.0	0.0	0.5
PH-0.04	85.9	10.2	0.0	0.6	0.0
PY-0.04	86.5	9.8	0.0	0.6	0.4
PH-0.16	NR	NR	NR	NR	NR
PY-0.16	80.0	10.7	0.3	1.2	0.2
PH-1	67.8	12.1	6.6	10.6	0.0
PY-1	57.9	11.3	10.4	13.9	0.4
PH-2	32.6	8.6	36.2	19.8	0.3
PY-2	41.3	11.6	29.6	15.9	0.0
PH-4	56.8	8.3	26.3	7.7	0.0
PY-4	4.0	7.8	67.8	17.3	0.0
PH-7	1.5	3.1	78.8	4.0	1.6
PY-7	0.9	1.9	83.7	4.7	0.0
PH-10	2.2	2.6	80.3	5.3	1.2
PY-10	0.3	0.7	85.3	1.4	0.0
PH-15	NR	NR	NR	NR	NR
PY-15	0.4	0.0	80.9	0.2	0.0
PH-21	0.1	0.0	77.3	0.2	0.3
PY-21	0.2	0.0	82.4	0.4	0.0
PH-30	0.3	0.0	68.6	0.2	0.4
PY-30	0.0	0.0	79.6	0.0	0.3

[a] X757 = X11449757
[b] X729 = X11393729
[c] X790 = X11406790
[d] 729 methyl = XDE-729 methyl
[e] The Other ^{14}C is a summation of the radioactivity incorporated in numerous components. The other ^{14}C accounts for up to 1.6% of the applied radioactivity.
[f] NR = Not Reported. Sample lost during incubation.
[g] NR = Not Reported. Sample results not included due to high mass balance.

With respect to kinetics, the study authors only considered XDE-729 methyl. For degradation in total system, water phase decline and decline from peak concentration in sediment, degradation/decline rates were very similar between the supplementary study for both systems and the original study at B.8.4.4a). A summary of the kinetic parameters is given below.

Table B.8.174 Summary of kinetic parameters from supplementary water/sediment study

Sediment Name	Model Type	DT_{50} (days)	DT_{90} (days)	χ^2
Swiss Lake Loamy sand				
Water	SFO	4	15	11.0
Sediment	Top-down SFO	12	39	15.1
Total system	SFO	5	17	9.9
Calwich Abbey Sandy loam				
Water	SFO	1.6	5.2	15.9
Sediment	Top-down SFO	1.4	4.8	13.3
Total system	SFO	1.9	6.2	8.9

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Given that the kinetic parameters are very similar and that the study is relatively short in relation to a normal water/sediment study, the RMS proposes that the kinetic parameters from the original study may be used. In addition, it should be noted that that the outcome of FOCUSsw modelling at Step 3 is generally relatively insensitive to water and sediment degradation rates, thus it is considered that there is unlikely to be any major impact arising from any differences that do exist between results for XDE-729 methyl from these two studies.

With respect to metabolites, on the basis of total system occurrence, the observed patterns of formation and decline were in general quite similar. The exception to this is X11449757 which appeared to have peaked before 30 DAT in the Swiss Lake system in the original study but appeared to be still increasing at 30 DAT in the supplementary study. As all the metabolites contain both radiolabelled positions, it is acceptable to calculate a mean of the two radiolabel results as they can essentially be treated as replicates at each sample time. A comparison of peak metabolite levels and the sample time at which they occurred in the two studies is given below.

Table B.8.175 Comparison of total system peak metabolite levels in original and supplementary aerobic water/sediment studies (values are mean of two replicates)

	Original study	Supplementary study
	Max % observed (DAT)	Max % observed (DAT)
X11393729: Swiss Lake	22.1% (5 DAT)	10.7% (10 DAT)
X11393729: Calwich Abbey	14.8% (2 DAT)	11.7% (1 DAT)
X11449757: Swiss Lake	73.8% (22 DAT)	71.8 (30 DAT, study end)
X11449757: Calwich Abbey	76.3% (8 DAT)	82.8% (10 DAT)
X11406790: Swiss Lake	20.8% (5 DAT)	33.4% (7 DAT)
X11406790: Calwich Abbey	22.6% (2 DAT)	17.8% (2 DAT)

Following correspondence between the RMS and the Applicant, the Applicant produced a further assessment to calculate kinetics of the metabolites from this study. This was performed using a top-down approach with SFO kinetics. A summary of the calculated values is presented below.

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Table B.8.176 Kinetics parameters for metabolites of XDE-729 methyl from the supplementary water/sediment study

System Phase	Substance	No. of Time Points	Model	DT50 (days)	X^2 error (%)	Original Study DT50 (days)
Swiss Lake Loamy Sand						
Whole System	XDE-729 Acid	4	SFO top-down	11	18.5	11
	X-790	5	SFO top-down	11	7.8	7
	X-757[1]	NC	NC	NC	NC	NC
Water	XDE-729 Acid	4	SFO top-down	13	17.3	9
	X-790	5	SFO top-down	9.4	10.0	7
	X-757[1]	NC	NC	NC	NC	NC
Sediment	XDE-729 Acid[2]	NC	NC	NC	NC	4
	X-790	4	SFO top-down	9.4	3.9	7
	X-757[1]	NC	NC	NC	NC	NC
Calwich Abbey Sandy Loam						
Whole System	XDE-729 Acid	5	SFO top-down	3.4	10.0	2.0
	X-790	5	SFO top-down	2.9	7.8	1.5
	X-757[3]	NC	NC	NC	NC	NC
Water	XDE-729 Acid	5	SFO top-down	3.4	8.5	3
	X-790	4	SFO top-down	2.9	6.9	2
	X-757	5	SFO top-down	28	1.9	23
Sediment	XDE-729 Acid[2]	NC	NC	NC	NC	NC
	X-790	6	SFO top-down	3.1	13.0	3
	X-757[1]	NC	NC	NC	NC	NC

NC = not calculated
[1] no decline during the 30 day study
[2] levels too low
[3] kinetics parameters not reliable (see Appendix)

The RMS has checked the visual and residual fits and concurs that the calculated values are appropriate. It is noted that for some of the fits, only four sample times were available. Higher χ^2 values e.g. above 10, tended to be associated with variable residues data between sample times and relatively widely spaced replicate values. In the case of the calculation of X-757 whole system decline in the Calwich Abbey system, it was noted that the degradation was very slow, only four data points were available and that the confidence intervals around the optimised rate constant included zero. Within the limits of this particular study, X-757 appears to be persistent in Calwich Abbey system, and had not reached the maximum formation in the Swiss Lake system. However, this study needs to be considered in the context of the original study which clearly showed that X-757 declined after reaching maxima earlier in the study. The RMS considers it reasonable to assume that similar behaviour would have been seen had the supplementary study been conducted for longer.

Overall, the parent and metabolite endpoints are very similar, and it is considered acceptable to use the metabolite endpoints from the original study at B.8.4.4a) which has been conducted for an appropriate duration in accordance with OECD 308.

(Laughlin, Boulton and Jonas, 2012)

c) The Applicant submitted an anaerobic water/sediment study (Yoder, Lehman and Balcer, 2012) in addition to the aerobic water/sediment study described above in B.8.4.4a). The RMS understands the water/sediment study in the EU data

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requirements to relate to water/sediment systems with aerobic water phase as this is the typical situation considered to be appropriate to water bodies adjacent to agricultural fields. With this in mind, the RMS has not evaluated the anaerobic water/sediment study and it is not relied upon for EU approval purposes; consequently it is cited in the reference list at the end of this section of the DAR. However, the RMS has briefly scrutinised the results which did not raise any particular concerns in light of the aerobic water/sediment studies and the anaerobic soil study, e.g. no novel metabolites formed, no unusual substance behaviour.

B.8.4.6 Summary & assessment – fate and behaviour in water

Aqueous hydrolysis

A study on the aqueous hydrolysis of XDE-729 methyl was submitted. The study was conducted under sterile conditions at pH 5, 7 and 9, and degradation at temperatures of 10, 25 and 50ºC was investigated at each pH value. As might be expected, XDE-729 methyl degraded faster at higher temperatures. In addition, it exhibited clear pH dependence of degradation. The slowest degradation occurred at pH 7,faster degradation at pH 4 and fastest degradation at pH 9 (this would be consistent with acid and base catalysed ester hydrolysis). At 25ºC, SFO DT50 values were 80.9 days at pH 4, 155 days at pH 7 and 3 days at pH 9. The magnitude of the degradation rates suggest that in the soil environment, abiotic hydrolysis is not solely responsible for degradation of XDE-729 methyl, but could be partially responsible. Metabolite X11393729 was the only identified metabolite which appeared to be stable in the study, tending to accumulate to a maximum at or towards the end of the study. The maximum accumulation was 99.6% AR at the penultimate time point at pH 9 and 50ºC. The total of XDE-729 methyl and X11393729 accounted for the majority of radioactivity at each sample time, with less than 5% AR unidentified at any point.

Aqueous photolysis

Data on molar extinction of XDE-729 methyl (Section B.2.1.10 of the DAR) indicate significant light absorbance at 290 nm (e.g. 3798 L $mol^{-1}cm^{-1}$), which suggests that the a.s. will be susceptible to aqueous photolysis.

An aqueous photolysis study was performed on XDE-729 methyl in both sterile pH 7 buffer and natural water. An artificial xenon light source appropriately filtered for wavelengths (cut-off 295nm) was utilised. XDE-729 methyl degraded extremely quickly under irradiated conditions with complete disappearance of the a.s. within 1 hour after the start of the study in both water systems. The SFO DT50 values were of the order of 4 minutes in buffer solution and 7 minutes in the natural water. Degradation was extensive with a very large number of radiolabelled components detected in both systems. As an example, in the buffer solution treated with phenyl-labelled material, up to 46 separate peaks, each of which comprised <1% AR, were seen in one replicate of the 7 DAT sample, and a total of 64 separate peaks were detected in this replicate in total. There was a trend for an increasing amount of radioactivity to be eluted at the solvent front during incubations; approximately 12-40% AR was recorded in this region at or towards the study end in the irradiated incubations. This region was termed ‘Deg 1’ and is further discussed below.

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Over the whole of the study, four separate metabolites were found to exceed 10% AR in individual replicates and could be allocated structures following LC/MS. These were: X11393729 accounting for 10.7% AR 10 minutes after treatment in natural water; Deg 10 accounting for 12.6 %AR 18 minutes after treatment in buffer solution; Deg 11 accounting for 15.7% AR 18 minutes after treatment in buffer solution; Deg 14 accounting for 11.5% AR 129 minutes after treatment in buffer solution. The RMS recommends that the four major aqueous photolysis metabolites should be subject to aquatic exposure and risk assessment. It was noted that Deg 10, Deg 11 and Deg 14 had all fallen below 10% AR within 4 hours of the start of the study, and thus appear to be transient.

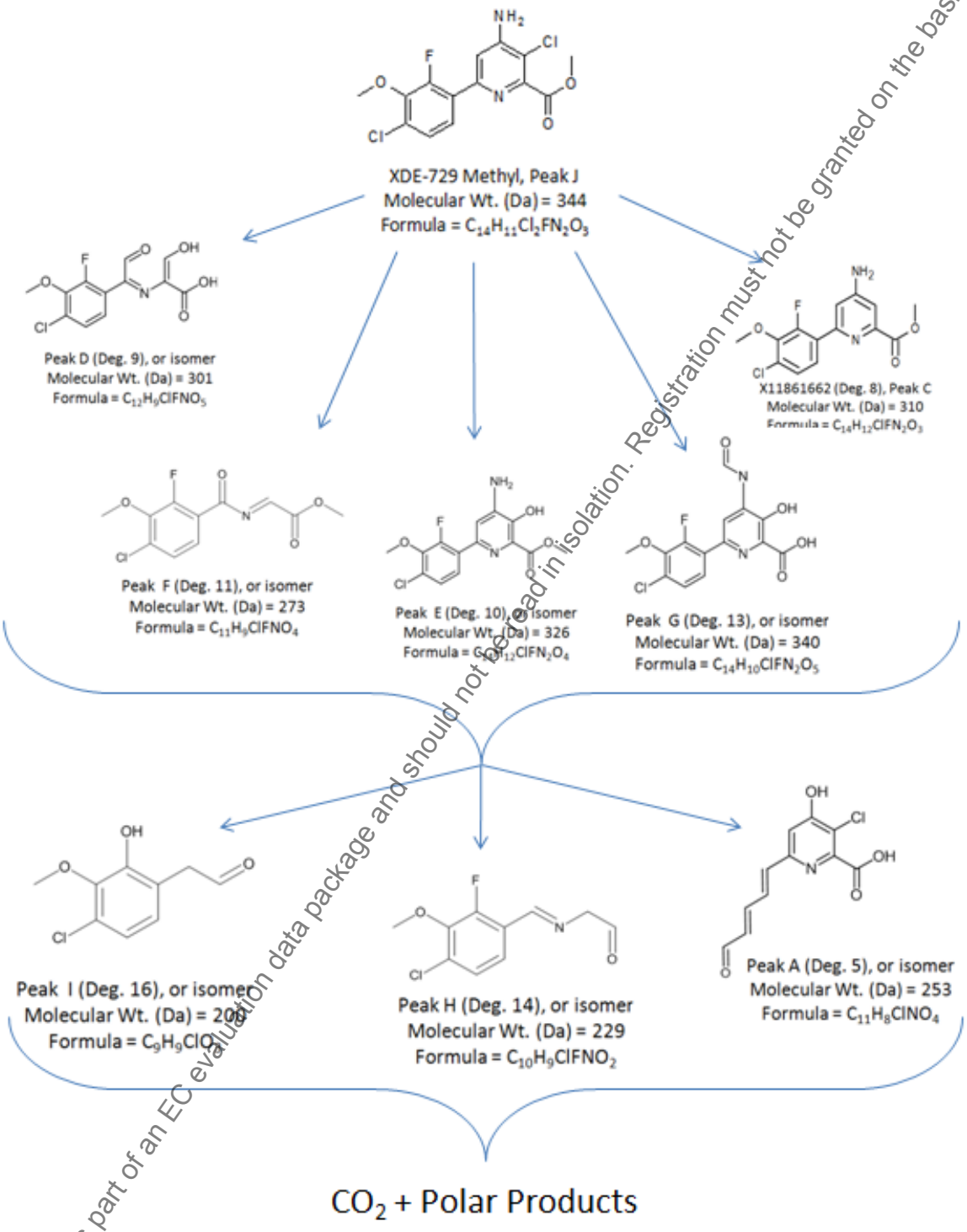
Three other chromatographic regions were detected which exceeded 10% AR, Deg 1, Deg 2 and Deg 4. These all eluted within 5 minutes of the HPLC run, and could not be detected by LC/MS suggesting that these regions did not contain any ionisable functional groups. Attempts to further characterise Deg 1 and Deg 2 failed to provide significant additional information, but Deg 4 was found to comprise a number of different components, none greater than 10% AR. Deg 1 and 2 are likely to also comprise radiolabelled fragments which could not be sufficiently retained by the HPLC columns used. Therefore, RMS considers that the chromatographic regions Deg 1, Deg 2 and Deg 4 do not require any additional risk assessment consideration.

Given the results of the aqueous photolysis study, the RMS considers it very likely that XDE-729 methyl will undergo photolysis in natural waters following exposure via spray drift. Given the apparent susceptibility of the a.s. to photolytic processes, it is possible that photo-degradation could also contribute to degradation were the a.s. to enter surface water via run-off or drainflow events. However, the RMS considers that in reality this is unlikely as drainage or run-off water containing residues of XDE-729 methyl is likely to be relatively turbid and reduce the propensity for photodegradation. The RMS notes that the main soil metabolite, X11393729, which was also a major metabolite in both the hydrolysis study and the photolysis study with natural water, is also susceptible to aqueous photolysis and would not be expected to persist in an optically clear water body exposed to sunlight. Data in the phys/chem. properties section (Section B.2.1.10) indicates a molar extinction coefficient for X11393729 of 4301 L $mol^{-1}cm^{-1}$ at neutral pH at 290 nm, suggesting, as for the parent, that the substance is susceptible to photolysis. Soil metabolite X11449757 also appears to be susceptible to photo-degradation with a molar extinction coefficient of 5535 L $mol^{-1}cm^{-1}$ at neutral pH at 290 nm. However, the simulation of such rapid photo-degradation rate in FOCUS exposure modelling is not simple given that the water body is not differentiated by depth layers but by segment of horizontal distance. The Applicant has proposed a strategy for addressing aquatic risk as a result of rapid and extensive photolytic degradation in surface water, this being discussed in the section dealing with PECsw calculations (B.8.6.1). However, given that the a.s. and the two main soil metabolites appear to be very susceptible to aqueous photolysis, it is considered likely that these can be accommodated by the risk assessment by assessing the four identified aqueous photolysis metabolites.

The following degradation pathways were proposed for aqueous photolysis in pH 7 buffer and in natural water.

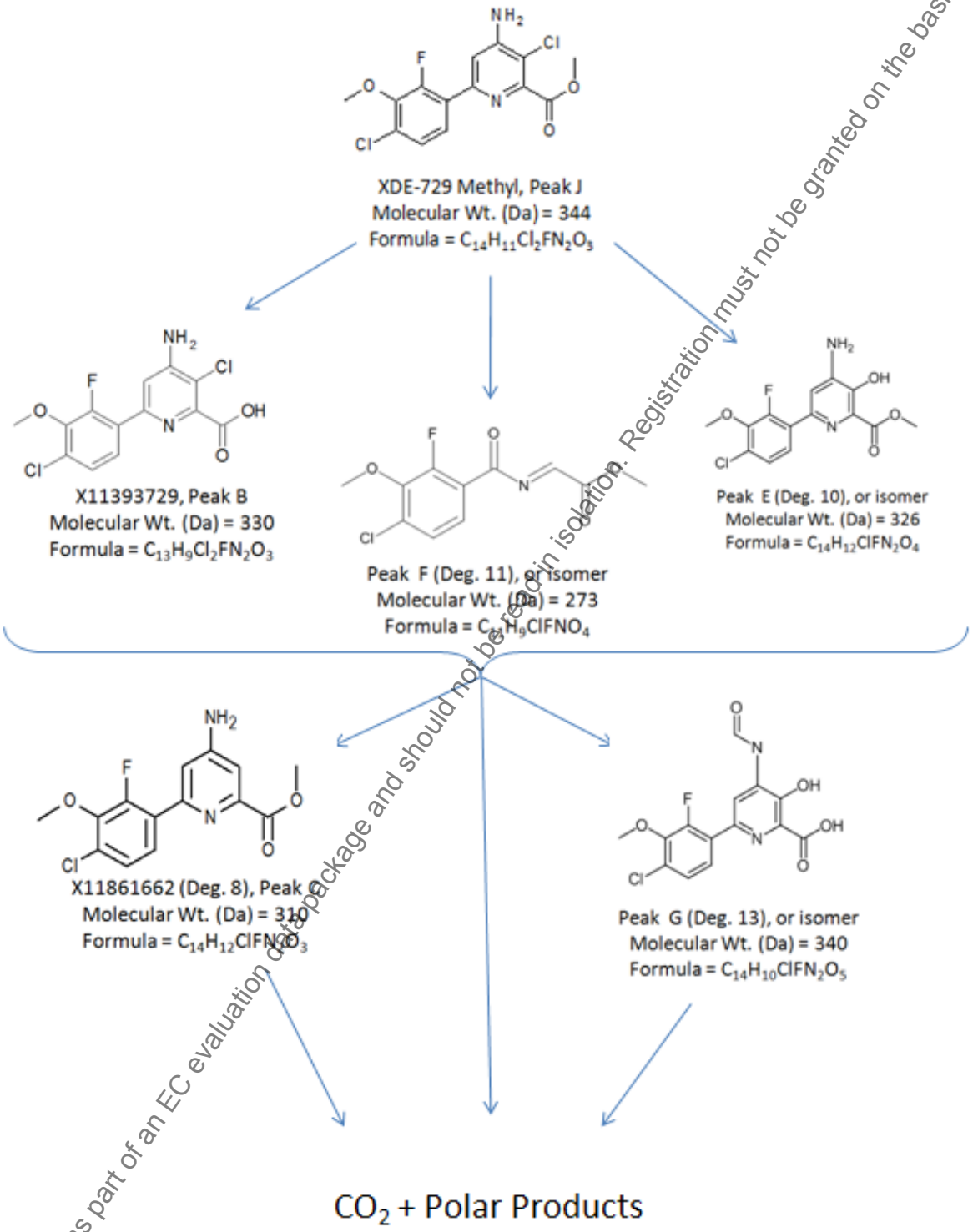
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Figure B.8.227 Proposed photolytic degradation pathway for XDE-729 methyl in pH 7 buffer



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Figure B.8.228 Proposed photolytic degradation pathway for XDE-729 methyl in natural water



A further non-guideline study to investigate aqueous photolysis under conditions of an Ecotox study on *Myriophyllum* sp indicated rapid degradation with DT50 less than 1 day (SFO kinetics) under unknown light conditions. By contrast, in dark conditions in the test medium at pH 7, 51 – 56% AR remained as unchanged XDE-729 methyl at study end (14 days). Scrutiny of chromatograms from illuminated samples suggested extensive degradation with multiple, mostly unidentified, peaks. This is generally in

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agreement with the findings of the standard aqueous photolysis study which indicates that XDE-729 methyl degrades rapidly with formation of a large number of minor metabolites.

Ready biodegradability

A ready biodegradability study was conducted on the metabolite X11393729. Given the rapid degradation of XDE-729 methyl to X11393729 in the environment, this is considered acceptable. The study demonstrated that X11393729 would be classified as 'not readily biodegradable'. It is considered that this conclusion can be extrapolated to XDE-729 methyl.

Water/sediment study

A standard water/sediment study was conducted on XDE-729 methyl using two systems. The sediment properties ranged from weakly acid to weakly alkaline with a range of organic carbon content. The water/sediment systems are considered by the RMS to be appropriate. Measurements of redox potential suggest that the systems had aerobic water layers and anaerobic sediments. Mass balances recorded during the study were generally acceptable. However, it was noted that for day 0, the results were taken from water samples that specifically did not have any sediment associated with them at the time of dosing. The OECD 308 guideline suggests that both water and sediment should be analysed at all sample times. In terms of kinetic assessment, this does not pose an issue as any metabolite residues in the water at day 0 were added to the measured a.s. concentration. However, the main issue is whether this departure from the OECD guideline is sufficiently serious to invalidate the study. In the view of the RMS, whilst potentially important information on initial degradation and partitioning behaviour during the first minutes or hours after dosing in the complete system is absent, this is not a sufficiently serious departure to invalidate the study. Essentially, an absolute time zero sample should only contain parent and there should be no time for partitioning to sediment to occur, thus residues should only be present in the water layer at the immediate time of dosing the system.

XDE-729 methyl degraded rapidly in both systems with <10% AR remaining in the total system at 5 – 14 DAT. The more rapid degradation occurred in the Calwich Abbey Lake water/sediment system which had a higher microbial biomass, organic carbon and clay content and the higher pH. Dissipation from the water layer was also rapid with some partitioning into sediment. The highest amount of observed partitioning occurred in the Swiss Lake system, with up to 12.2% AR at 2 DAT. Interestingly, this was the system that theoretically would have had the lower adsorption potential of the two systems tested, but the higher level of observed partitioning may be related to the overall slower degradation of XDE-729 methyl in this system, e.g. the actual level of partitioning into sediment in the Calwich Abbey Lake system may be disguised by the rapid degradation. The highest observed partitioning into sediment in the Calwich Abbey Lake system was 7.3% AR at 2 DAT.

Extensive metabolite formation was also seen in both systems. Three metabolites were positively identified. Metabolite X11393729 was seen at 16.4 – 23.5% AR at 2 – 8 DAT in the total system but appeared to occur in greater amounts in the water phase, with 13.3 – 20.0% AR at 2 – 8 DAT in the water phase and 3.2 – 6.1% AR at 2 – 5

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DAT in sediment. Decline was moderate in the Swiss Lake total system with a pronounced 'tail' 1.5 – 4% AR from 43 DAT to the study end. However, X11393729 was only sporadically detected at under 1% AR from 14 DAT in the Calwich Abbey Lake total system.

X11449757 was the principal metabolite with 75.6 – 76.7% AR at 8 – 22 DAT formed in total system. Similar concentrations were seen in water and sediment but peak concentrations appeared to occur earlier in water. This may indicate formation in both water and sediment and potential partitioning from water into sediment. Peak concentrations in the water phase were 44.4 – 48.3% AR at 5 – 22 DAT. In sediment, concentrations were 36.9 – 50.6% AR at 30 – 43 DAT. Dissipation from total system appeared to be relatively slow in the Calwich Abbey Lake system with 35 – 43% AR remaining at study end, but appeared to be more rapid in Swiss Lake system, with 16% remaining at study end.

A further metabolite, X11406790, was identified. This reached 23.4 – 23.6% AR in total system at 2-5 DAT, with maximum amounts observed in water and sediment at the same sample time. Maximum amounts in water were 12.8 - 16.5% AR at 2 - 5 DAT and in sediment were 7.0 – 10.6% at 2 – 5 DAT. Levels had declined to <5% AR by 8 – 22 DAT. X11406790 appeared to be formed at similar times to X11393729 and the proposed structure is the same as parent except for demethylation of the phenyl ring as opposed to demethylation of the pyridine ring as in X11393729. As such it is proposed as an additional precursor to formation of X11449757 which is formed by demethylation of both ring structures.

It is noted that these three metabolites were all identified as soil metabolites, but only X11393729 and X11449757 occurred at greater than 10% in soil. In addition, X11393729 was the principal metabolite in soil whereas X11449757 appears to be the principal metabolite in water/sediment systems. All three of these metabolites must be subject to an aquatic exposure assessment.

No other metabolites were identified. 'Other' radioactivity rose to a peak of 12.7% AR in the Swiss Lake system at study end, but this was the sum of numerous small chromatographic peaks, none of which accounted for >5% AR at any time.

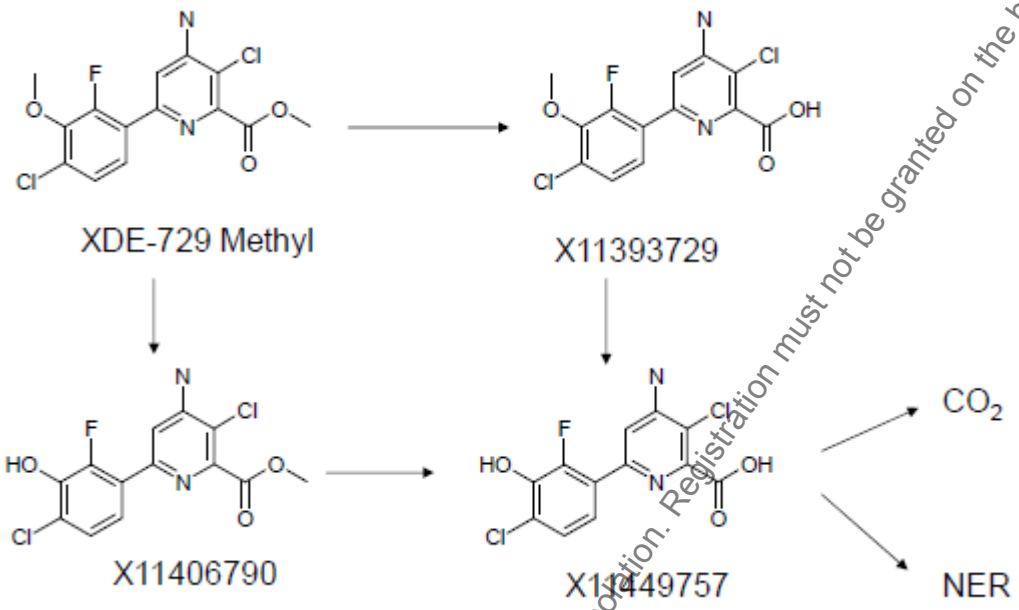
Mineralisation was limited, particularly in the Calwich Abbey Lake system with <2% AR in the NaOH trap at study end (103 DAT). In the Swiss Lake system, there was 15.8% AR as CO^2 at study end with the phenyl labelled material, but only 5.1% AR with pyridine labelled material.

Similar levels of unextracted residues were observed in both systems at study end, with 42.5 – 45.4% AR with phenyl labelled material and 51.2 – 54.8% AR with pyridine labelled material.

The following degradation pathway was proposed for XDE-729 methyl in dark aerobic water/sediment systems.

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Figure B.8.229 Proposed metabolic pathway for XDE-729 methyl in dark aerobic water/sediment systems



The study authors only attempted calculations of degradation rates for parent and metabolites in the total system. These are shown below.

Table B.8.177 Summary of SFO DegT50 values (days) for XDE-729 methyl and metabolites in water/sediment total system

System	XDE-729 methyl	X11393729	X11406790	X11449757
Swiss Lake	4	11*	7*	38*
Calwich Abbey	0.8	2	1.5	87

*dissipation rate, calculated by top down approach

The Applicant considered that whilst there was relatively frequent sampling during the initial part of the water/sediment study, XDE-729 methyl had dissipated so quickly that the behaviour in the early part of the study needed to be investigated further. To this end, a 'supplementary' study was performed over 30 days with more frequent sampling particularly in the first week. Essentially the study was repeated with water/sediment systems sourced from the same locations as originally used. Phys/chem properties of the water/sediment systems were similar but not identical to those in the original study. Behaviour of XDE-729 methyl in the supplementary study was very similar. Metabolites X11393729, X11449757 and X11406790 were all observed and with similar behaviour. In the 'supplementary' study, X11393729 was formed at slightly lower levels in both systems, X11449757 was formed at higher levels in the Calwich Abbey system and X11406790 was formed at higher levels in the Swiss Lake system. Kinetic assessment of the new study for parent and metabolites showed very similar values. It is thus considered that it is acceptable to use the

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supplementary study as supportive information to the original water/sediment study and to use kinetic endpoints derived from the original study.

Hydrolytic degradation of the active substance and metabolites > 10 %, DT50 ‡	pH 4: 245 d at 10°C 80.9 d at 25ºC 12.1 d at 50ºC SFO, r^2 > 0.99 Met X11393729: max 8.1% at 10ºC, 23.7% at 25ºC, 83.3%AR at 50ºC, all at study end (30 DAT)
	pH 7: 660 d at 10°C 155 d at 25ºC 17.1 d at 50ºC SFO, r^2= 0.83 – 1.00 Met X11393729: max 3.7% at 10ºC, 13.0% at 25ºC, 70.3%AR at 50ºC, all at study end (30 DAT)
	pH 9: 17.8 d at 10°C 3.04 d at 25ºC 0.218 d at 50ºC SFO, r^2 = 1.00 Met X11393729: max 72.0% at 30 DAT at 10ºC, 99.3% at 30 DAT at 25ºC, 99.6%AR at 21 DAT at 50ºC

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Photolytic degradation of active substance and metabolites above 10 % ‡	Xenon lamp, 14 – 15 days continuous illumination equivalent to 34 – 36 days natural summer sunlight at 40°N DT_{50} sterile buffer: 4.1 minutes (SFO) DT_{50} natural water: 7.1 minutes (SFO) Estimated DT_{50} at 40°N in summer: 7.7 minutes in sterile buffer; 18.3 minutes in natural water. Identified metabolites exceeding 10% AR (values are maximums in individual reps): Deg 10: 12.6 %AR (18 minutes, buffer) Deg 11: 15.7% AR (18 minutes, buffer) Deg 14: 11.5% AR (129 minutes, buffer) X11393729: 10.7% AR (10 minutes, natural water)
Quantum yield of direct phototransformation in water at Σ > 290 nm	5.6 mol $Einstein^{-1}$
Readily biodegradable ‡ (yes/no)	Study on metabolite X11393729, considered not readily biodegradable.

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Degradation in water / sediment

Parent	Distribution (Max. sed 7.3 – 12.2 % after 2 d)									
Water / sediment system	pH water phase	pH sed	t. °C	$DegT_{50}$-$DegT_{90}$ whole sys.	St. (χ^2)	$DisT_{50}$-$DisT_{90}$ water	St. (χ^2)	$DisT_{50}$-$DisT_{90}$ sed	St. (r^2)	Method of calculation
Swiss Lake	7.0	5.8	20	4 / 12 days	9.4	3 / 9 days	9.2 (11)	7 / 24 days	16.2	SFO (WS) SFO (WP) SFO TD (SP)
Calwich Abbey Lake	8.3	7.7	20	0.8 / 2.9 days	1.3	0.67 / 2.24 days	0.1 (15.9)	1.3 / 4.6 days	2.1	SFO (WS) SFO (WP) SFO TD (SP)
Geometric mean				1.8 / 5.9						

WS = whole system WP = water phase TD = top down SP = sediment phase

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Metabolite X11393729	Distribution (max in water 13.3 – 20.0% after 2 - 8 d. Max. sed 3.2 – 6.1 % after 2-5 d)									
Water / sediment system	pH water phase	pH sed	t. °C	DT_{50}-DT_{90} whole sys.	St. (χ^2)	$DisT_{50}$-$DisT_{90}$ water	χ^2	$DisT_{50}$-$DisT_{90}$ sed	St. (χ^2)	Method of calculation
Swiss Lake	7.0	5.8	20	11 / 38 days (dissipation)	20.7	9 / 28 days	16.1	4 / 14 days	2.3	SFO TD (WS) SFO TD (WP) SFO TD (SP)
Calwich Abbey Lake	8.3	7.7	20	2 / 6.7 days (degradation)	1.3	3 / 10 days	4.5	Not calculated Insufficient data		SFO IS (WS) SFO TD (WP)
Geometric mean				4.7/16.0						

TD = top down WS = whole system WP – water phase IS = in series with parent SP = sediment phase

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Metabolite X11449757	Distribution (max in water 44.4 – 48.3% after 5 - 22 d. Max. sed 36.9 – 50.6% after 30 - 43 d)									
Water / sediment system	pH water phase	pH sed	t. °C	$DisT_{50}$-$DisT_{90}$ whole sys.	St. (χ^2)	$DisT_{50}$-$DisT_{90}$ water	χ^2	$DisT_{50}$-$DisT_{90}$ sed	St. (χ^2)	Method of calculation
Swiss Lake	7.0	5.8	20	38 / 125	12.1	22 / 73 days	8.4	35 / 115 days	13.1	SFO TD (WS) SFO TD (WP) SFO TD (SP)
Calwich Abbey Lake	8.3	7.7	20	87 / 289 days	3.1	23 / 76 days	13.3	114 / 378 days	3.3	SFO TD (WS) SFO TD (WP) SFO TD (SP)
Geometric mean				57.5 / 190						

TD = top down WS = whole system WP – water phase SP = sediment phase

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Metabolite X11406790	Distribution (max in water 12.8 – 16.5% after 2 - 5 d. Max. sed 7.0 – 10.6% after 2 - 5 d)									
Water / sediment system	pH water phase	pH sed	t. °C	DT_{50}-DT_{90} whole sys.	St. (χ^2)	$DisT_{50}$-$DisT_{90}$ water	χ^2	$DisT_{50}$-$DisT_{90}$ sed	St. (χ^2)	Method of calculation
Swiss Lake	7.0	5.8	20	7 / 23 days (dissipation)	7.4	7 / 25 days	14.1	7 / 22 days	6.7	SFO TD (WS) SFO TD (WP) SFO TD (SP)
Calwich Abbey Lake	8.3	7.7	20	1.5 / 5 days (degradation)	2.2	2 / 7 days	9.5	3 / 9 days	3.3	SFO IS (WS) SFO TD (WP) SFO TD (SP)
Geometric mean				3.2 / 10.7						

TD = top down WS = whole system WP – water phase IS = in series with parent SP = sediment phase

Mineralization and non extractable residues					
Water / sediment system	pH water phase	pH sed	Mineralization x % after 103 d. (end of the study).	Non-extractable residues in sed. Max x % after n d	Non-extractable residues in sed. Max x % after 103 d (end of the study)
Swiss Lake	7.0	5.8	15.8% (phenyl label) 5.1% (pyridine label)	46.5% at 79 d (phenyl label) 72.4% at 79 d (pyridine label)	45.4% (phenyl label) 54.8% (pyridine label)
Calwich Abbey Lake	8.3	7.7	1.0% (phenyl label) 1.2% (pyridine label)	51.4% at 79 d (phenyl label) 56.6% at 79 d (pyridine label)	42.5% (phenyl label) 51.2% (pyridine label)

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B.8.5 Impact on water treatment procedures (Annex IIIA 9.2.2)

Not submitted and not required for the representative use of XDE-729 methyl. For potential effects on sewage sludge, see section B.9.10.

B.8.6 Predicted environmental concentrations in surface water and groundwater (PECsw and PECgw) (IIIA 9.2.1, 9.2.3)

B.8.6.1 Surface Water & Sediment

B.8.6.1.1 Steps 1-2

The worse case GAP in terms of total dose applied is winter cereals in the autumn at 7.82 g as/ha at crop growth stage BBCH 10-29 followed by a second application in the spring at 6.25 g as/ha at growth stage BBCH 13-45 with a minimum 70 day interval. The application interval is set at 70 days. For Steps 1-2, the Applicant considered that because the application interval is quite wide and because the active substance degrades relatively rapidly in both soil and water, the single applications are likely to represent the worst case. However, it appears that the Steps 1-2 calculations were performed before the latest kinetic calculations from field dissipation studies. Therefore the RMS has re-calculated Steps 1-2 values for XDE-729 methyl, X11393729, X11449757 and X11406790. The soil DT50 used was the geometric mean normalised field DegT50 of 20 days. In addition, the RMS assumed the GAP was 2 x 7.82 g/ha as the Steps 1-2 software cannot simulate different application doses. The RMS realises this is conservative. An application interval of 70 days was assumed. The input parameters are shown below.

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Table B.8.178 Input parameters for FOCUSsw Steps 1-2 for XDE-729 methyl and its metabolites

Parameter	Value	Comments
XDE-729 methyl		
Molecular mass:	345	
Aqueous solubility (mg/L, 20ºC):	1.7	Measured value (List of End Points)
Koc (mol/g)	987	Average Kfoc value (n = 7)
DT50 in soil(days):	20	Geomean (n = 8) SFO after 10mm rain from normalised field dissipation studies
DT50 in sediment/water (days)	1.8	Geomean of two water/sediment systems
DT50 in water (days)	1.8	Geomean of two whole system DT50
DT50 in sediment	1000	FOCUS recommended default
X11393729		
Molar mass	331	
Aqueous solubility (mg/L, 20ºC):	3070	Measured value (List of End Points)
Maximum observed in water/sediment	23.5%	
Maximum observed in soil	40.1%	From field studies
Koc	28	Average Kfoc from the highest pH soils
DT50 soil (days)	72.6	Geomean normalised top down DT50 from two alkaline field soils
DT50 in sediment/water (days)	4.7	Geomean of two water/sediment systems
DT50 in water (days)	4.7	Geomean whole system of two water/sediment systems
DT50 in sediment	1000	FOCUS recommended default
X11449757		
Molar mass	317	
Aqueous solubility (mg/L, 20ºC):	265	Measured value (List of End Points)
Maximum observed in water/sediment	76.7%	
Maximum observed in soil	13.8%	From laboratory studies
Koc	17	Average Kfoc from the highest pH soils
DT50 soil (days)	67	Geomean of field normalised top-down SFO DT50
DT50 in sediment/water (days)	57.5	Geomean of two water/sediment systems
DT50 in water (days)	57.5	Geomean whole system of two water/sediment systems
DT50 in sediment	1000	FOCUS recommended default
X11406790		
Molar mass	331	
Aqueous solubility (mg/L, 20ºC):	3070	Taken as identical to X11393729 in absence of data
Maximum observed in water/sediment	23.6%	
Maximum observed in soil	1.4%	From laboratory studies
Koc	0/1000*	Default, no data available
DT50 soil (days)	1000	Worst case default, no data available
DT50 in sediment/water (days)	3.2	Geomean of two water/sediment systems
DT50 in water (days)	3.2	Geomean whole system of two water/sediment systems
DT50 in sediment	1000	FOCUS recommended default

*In absence of data, "worst" and "best" cases used as Koc determines partitioning into sediment at Step 1-2

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Results are shown in the following tables.

Table B.8.179 Steps 1-2 PECsw for XDE-729 methyl, two applications to winter cereals (values in brackets are from single application)

Time (d)	Step 1		Step 2, North, Oct-Feb		Step 2, South, Oct-Feb	
	Actual	TWA	Actual	TWA	Actual	TWA
0	1.197	---	0.412 (0.381)	---	0.332 (0.308)	---
1		0.992		0.346 (0.321)		0.279 (0.259)

Table B.8.180 Steps 1-2 PECsed for XDE-729 methyl, two applications to winter cereals (values in brackets are from single application)

Time (d)	Step 1		Step 2, North, Oct-Feb		Step 2, South, Oct-Feb	
	Actual	TWA	Actual	TWA	Actual	TWA
0	11.11	---	4.076 (3.773)	---	3.287 (3.048)	---
1		9.438		4.073 (3.770)		3.284 (3.044)

Table B.8.182 Steps 1-2 PECsw for X11393729, two applications to winter cereals (values in brackets are from single application)

Time (d)	Step 1		Step 2, North, Oct-Feb		Step 2, South, Oct-Feb	
	Actual	TWA	Actual	TWA	Actual	TWA
0	0.983	---	0.536 (0.358)	---	0.430 (0.288)	---
1		0.915		0.499 (0.333)		0.401 (0.268)

Table B.8.183 Steps 1-2 PECsed for X11393729, two applications to winter cereals (values in brackets are from single application)

Time (d)	Step 1		Step 2, North, Oct-Feb		Step 2, South, Oct-Feb	
	Actual	TWA	Actual	TWA	Actual	TWA
0	0.271	---	0.150 (0.100)	---	0.120 (0.081)	---
1		0.254		0.140 (0.094))		0.112 (0.075)

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Table B.8.184 Steps 1-2 PECsw for X11449757, two applications to winter cereals (values in brackets are from single application)

Time (d)	Step 1		Step 2, North, Oct-Feb		Step 2, South, Oct-Feb	
	Actual	TWA	Actual	TWA	Actual	TWA
0	0.748		0.233 (0.164)		0.198 (0.141)	
1		0.742		0.231 (0.163)		0.197 (0.140)

Table B.8.185 Steps 1-2 PECsed for X11449757, two applications to winter cereals (values in brackets are from single application)

Time (d)	Step 1		Step 2, North, Oct-Feb		Step 2, South, Oct-Feb	
	Actual	TWA	Actual	TWA	Actual	TWA
0	0.252		0.040 (0.028)		0.034 (0.024)	
1		0.122 (day 4)		0.039 (0.028)		0.033 (0.024)

Table B.8.186 Steps 1-2 PECsw for X11406790, two applications to winter cereals (values in brackets are from single application) assuming Koc = 0

Time (d)	Step 1		Step 2, North, Oct-Feb		Step 2, South, Oct-Feb	
	Actual	TWA	Actual	TWA	Actual	TWA
0	0.051		0.032 (0.020)		0.026 (0.017)	
1		0.046		0.028 (0.018)		0.024 (0.016)

Table B.8.187 Steps 1-2 PECsed for X11406790, two applications to winter cereals (values in brackets are from single application) assuming Koc = 0

Time (d)	Step 1		Step 2, North, Oct-Feb		Step 2, South, Oct-Feb	
	Actual	TWA	Actual	TWA	Actual	TWA
0	0.000		0.000 (0.000)		0.000 (0.000)	
1		0.000		0.000 (0.000)		0.000 (0.000)

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Table B.8.188 Steps 1-2 PECsw for X11406790, two applications to winter cereals (values in brackets are from single application) assuming Koc = 1000

Time (d)	Step 1		Step 2, North, Oct-Feb		Step 2, South, Oct-Feb	
	Actual	TWA	Actual	TWA	Actual	TWA
0	0.031		0.015 (0.016)		0.014 (0.016)	
1		0.024		0.014 (0.012)		0.010 (0.012)

Table B.8.189 Steps 1-2 PECsed for X11406790, two applications to winter cereals (values in brackets are from single application) assuming Koc = 1000

Time (d)	Step 1		Step 2, North, Oct-Feb		Step 2, South, Oct-Feb	
	Actual	TWA	Actual	TWA	Actual	TWA
0	0.177 (day 1)		0.149 (0.100)		0.127 (0.089)	
1		0164		0.142 (0.096)		0.122 (0.085)

The Applicant also conducted some calculations for three unknown degradation products from the aqueous photolysis study which exceeded 10% AR. These were Deg 10, Deg 11 and Deg 14. Due to the extremely rapid and extensive photolysis of XDE-729 methyl, these degradates were very rapidly formed and degraded and appear to be transient. Step 1 and 2 PECsw values for these degradates were calculated from the maximum Step 1 and 2 PECsw values for parent XDE-729 methyl taking into account the maximum percent formed and the molecular weight difference. The RMS has recalculated the metabolite PECsw values to take into account higher parent Step 2 PECsw values.

Table B.8.190 PECsw values for aqueous photolysis metabolites of XDE-729 methyl

Photoproduct	Molecular weight	Max % in water	Step 1	Step 2 North Oct-Feb	Step 2 South Oct-Feb
XDE-729 methyl	345	-	1.197	0.412	0.332
Deg 10	326	12.6	0.234	0.049	0.039
Deg 11	273	15.7	0.178	0.061	0.049
Deg 14	229	11.5	0.091	0.031	0.025

B.8.6.1.2 Step 3

The RMS has calculated PECsw for spray drift at Step 3 using the FOCUS drift calculator. The highest dose of the formulation "GF-2573" is 1 l/ha. Assuming a relative density of 0.905 (see section B.2.2.13) giving an application dose of 905 g/ha, using standard FOCUS assumptions for a single application (which gives higher spray drift), nominal PECsw values are as follows:

FOCUS ditch = 5.814 µg/l
FOCUS stream = 4.315 µg/l
FOCUS pond = 0.198 µg/l

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The Applicant simulated XDE-729 methyl and X11393729 at Step 3. The following input parameters were used.

Table B.8.191 FOCUSsw Step 3 and 4 input parameters for XDE-729 methyl

Property	Value	Comment
General		
Molar Mass (g/mol):	345	List of End Points
Saturated vapour pressure (Pa at 20ºC):	5.9×10^{-9}	Measured value (List of End Points)
Molar enthalpy vaporisation (J/mol):	95000	FOCUS default
Solubility in water (mg/L at 20ºC):	1.67	Measured value (List of End Points)
Molar enthalpy of dissolution (J/mol):	27000	FOCUS default
Diffusion co-efficient in water (m^2/d):	4.3×10^{-5}	FOCUS default
Diffusion co-efficient in air (m^2/d):	0.43 *	FOCUS default
Sorption		
Koc (mol/g):	987	Average Kfoc value (n = 7)
Freundlich exponent	0.88	Average value (n = 7)
Ref. Conc. in liquid phase (g/m^3):	1	FOCUS default
Uptake and Wash-Off		
Plant root uptake factor:	0.5	FOCUS default for systemic substance
Wash-off factor from crop		
(MACRO, mm^{-1}):	0.05	FOCUS default
(PRZM, cm^{-1}):	0.50	FOCUS default
Transformation		
Half-life water (days, 20ºC):	1.8	Geomean whole system value (n = 2)
Half-life soil (Parent only, days, 20ºC):	20	
Half-life soil (for run with Acid, days, 20ºC):	3.3	
Half-life sediment (days, 20ºC):	1000	Worst case default
Half-life crop (days, 20ºC):	10	FOCUS default
Activation energy (TOXSWA, J/mol):	65400	EFSA recommendation
Exponent (MACRO, K^{-1}):	0.0948	EFSA recommendation
Q_{10} factor (PRZM):	2.58	EFSA recommendation
Formation fraction to XDE-729 Acid	0.45	Arithmetic mean (n = 8)

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Table B.8.192 FOCUSsw Step 3 and 4 input parameters for X11393729

Property	Value	Comment
General		
Molar Mass (g/mol):	331	List of End Points
Sat. vapour pressure (Pa at 20ºC):	2.0×10^{-5}	Measured value (List of End Points)
Molar enthalpy vaporisation (J/mol):	95000	FOCUS default
Solubility in water (mg/L at 20ºC):	3070	Measured value at pH 7 (List of End Points)
Molar enthalpy of dissolution (J/mol):	27000	FOCUS default
Diffusion co-efficient in water (m^2/d):	4.3×10^{-5}	FOCUS default
Diffusion co-efficient in air (m^2/d):	0.43	FOCUS default
Sorption (average inputs)		
Koc (mol/g):	27.5	Average Kfoc from the highest pH soils (n = 2)
Freundlich exponent	0.88	Average 1/n from the highest pH soils (n = 2)
Ref. Conc. in liquid phase (g/m^3):	1	FOCUS default
Uptake and Wash-Off		
Plant root uptake factor:	0	No data. Default worst case
Wash-off factor from crop		
(MACRO, mm^{-1}):	0.05	FOCUS default
(PRZM, cm^{-1}):	0.50	FOCUS default
Transformation		
Half-life water (days, 20ºC):	4.7	Geomean whole system value (n = 2)
Half-life soil (days, 20ºC):	22	Geomean from field sites, normalised (n = 8)
Formation fraction in soil:	0.45	Average from field sites, normalised (n = 8)
Half-life sediment (days, 20ºC):	1000	Worst case default
Half-life crop (days, 20ºC):	10	FOCUS default
Act. energy (TOXSWA, J/mol):	65400	EFSA recommendation
Exponent (MACRO, K^{-1}):	0.0948	EFSA recommendation
Q_{10} factor (PRZM):	2.58	EFSA recommendation

The RMS agrees with the input parameters for XDE-729 methyl with the exception of the use of a plant uptake factor of 0.5. In principle, the RMS considers that it is acceptable to use a plant uptake factor in the modelling, as whilst the soil degradation parameter is derived from field dissipation studies, all the studies were bare soil studies, thus plant uptake should not have been a process contributing to the disappearance of the parent substance and its metabolites. However, the RMS is aware that there is currently much discussion related to the derivation of plant uptake factor. Current EFSA approach is to assume a default plant factor of 0 unless this can be refined by the use of the equations of Briggs *et al* 1983. The RMS has investigated the log Kow values for XDE-729 methyl and X11393729. The parent has log Kow ranging from 3.75 – 3.92, leading to a TSCF predicted by Briggs *et al* 1983 of 0.16 – 0.12. X11393729 has log Kow of 0.42 at pH 5 to -1.01 at pH 9, leading to TSCF values of 0.048 – 0.032. Thus it can be seen that application of the Briggs equation leads to much lower values of TSCF for parent than used by the Applicant. The RMS advocates use of a crop uptake factor of 0.14, the average of 0.12 and 0.16.

It is noted from the assessment of laboratory and field degradation rates that the RMS considers X11393729 to possess pH dependent degradation in soil. The Applicant has used a geometric mean DT50 from all the field data as the soil degradation input parameter for X11393729. In the groundwater modelling, the RMS has advocated use

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of a DT50 of 36.9 days with a formation fraction of 0.34 from the two alkaline field dissipation sites (see section B.8.6.2).

The RMS also notes that as there did not appear to be a relationship between soil organic carbon and Kf that ideally the models should have been run with Kf as the input parameter. However, the need to perform simulations with Kf rather than Kfoc could also be subject to expert discussion.

In setting up the application patterns, the Applicant simulated single applications in winter cereals (1 x 7.82 g a.s./ha around the date of emergence and 6.25 g a.s./ha around 1 January) and spring cereals (6.25 g a.s./ha at 7 days post emergence). In addition, they simulated the double application scenario to winter cereals of 1 application of 7.82 g a.s./ha around the date of emergence in the autumn followed by 6.25 g a.s./ha followed by an application at a minimum of 70 days afterwards and around the beginning of the next calendar year. However, because SWASH will not allow an application scheme with the first application later in the year than the second application, runs were set up using manual correction of input files.

To ensure that application rates were selected that were in line with the GAP, the Applicant ran PAT outside of the SWASH shell to calculate the appropriate application dates. As a starting point, the first possible application date (in autumn) was set to the crop emergence date. The actual application date for each MACRO year was calculated. Then the first possible application date for the second application was selected based on (1) maintaining a minimum 70 day interval between the applications and (2) an earliest application date of 1st January.

To run the MACRO model, the input files were set up in SWASH for two applications per year with a nominal application date in January and one at the end of the year (after crop emergence). These runs were set up as batch files in MACRO. Then the application dates in the inputXXX.par and parenXXX.par files were amended to give the previously defined application dates that are in line with the GAP. Finally, after manually inputting the application dates, MACRO was run from the batch file to produce the m2t files.

The Applicant noted that in the drainage scenarios, the only significant route of entry for parent XDE-729 methyl was via spray drift. They also argued that with a 70 day interval between the applications, there would be no accumulation of residues in water bodies. Therefore, the double application was not simulated for parent, but it was run for X11393729 (as a metabolite of the parent) since drainflow was likely to be a major route of entry for X11393729 and hence there may be a cumulative effect from the double application.

For PRZM, a similar process was followed by the Applicant by preparing a project in SWASH with the first application in the calendar year set to 70 days after the emergence date and an interval that would give the correct application date in autumn. An extra complication with PRZM is that the output (.p2t) files have a time range limited to one year from 1st October to 30th September. Because the autumn application for XDE-729 methyl within a calendar year occurs after 30th September, TOXSWA cannot run the simulation because it requires the 2nd application to be within the one year period specified by the p2t file. Therefore, after running PRZM,

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the p2t files were amended by changing the 2nd application date to 30th September and inserting a nominal application rate of 0.1 g/ha. Similarly, the 2nd application in the .TXW file was amended to 0.1 g/ha and a nominal deposition value of 0.00001 mg/m^2 so that the TOXSWA model could be run. These extra minimal loadings were considered by the Applicant to have no discernible impact on the model outputs but were necessary to allow the models to run. The RMS agrees this is certainly the case for the simulations of X11393729.

For parent, the RMS can confirm from scrutiny of the graphical output that the primary entry route for the substance at drainage scenarios appears to be spray drift, with little drainage entry occurring; with this in mind, it is highly unlikely that a reduction in plant uptake factor would result in a change to the peak concentrations at the drained scenarios. For run-off scenarios, the graphical output indicates that run-off and spray drift are both important; run-off was responsible for the highest concentrations at R1 pond and stream and R4 stream, with drift giving the highest concentration at R3 stream. For this reason, the RMS has re-run the run-off scenarios for the single application in the autumn to check the magnitude of the resulting run-off concentrations from the highest application dose. The simulations were performed using identical input parameters to the Applicant with the exception that the plant uptake factor was reduced to 0.14 from 0.5. Note that the single application also maximises the spray drift input. A similar set of runs has been made for early spring application to check the effect of the lower plant uptake factor when the application is made to a better established crop.

The outcome of the RMS runs for the autumn application was that the peak concentrations from run-off were virtually identical to those in the Applicant modelling. Thus the RMS concludes that there is virtually no effect of plant uptake at the autumn timing.

For the spring timing, the peak concentrations were the same. It was noted that at R1 pond, spray drift and run-off inputs were virtually identical in the RMS simulation. Graphical output from the Applicant was not available for this scenario. In the RMS modelling for R3, the timing of application was earlier than in the Applicant's modelling (RMS simulation had application of 30 January, whereas Applicant modelling gave application on 19 February). Consequently, the concentration in the water body due to run-off was lower than in the Applicant modelling, presumably because whilst the run-off events occurred on the same dates in RMS and Applicant modelling, the RMS simulation gave an earlier application and therefore more degradation occurred reducing the run-off loss in the RMS modelling. The RMS re-ran this scenario changing the earliest application date to 19 February. This resulted in an application on 19th February, and the subsequent run-off concentration appeared to be identical to that from the Applicant's modelling. At R1 stream, the RMS estimates that the run-off concentration was increased to 0.0235 µg/l compared to 0.020 µg/l. At R4 stream, there was no difference in run-off concentrations. Thus it is difficult to discern whether the reduced plant uptake factor influences run-off concentrations from spring applications. However, there does appear to be an influence at the R1 stream scenario with spring application.

The RMS also re-ran the double application GAP for winter cereals to check the impact on X11393729 concentrations by using the lower plant uptake factor for parent

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and incorporating pH dependence of degradation assumptions. The selection of pH dependent degradation parameters for X11393729 is described in section B.8.6.2 for groundwater modelling. The RMS does not have the specific technical knowledge available to be able to manipulate all the input files in order to achieve specific application dates as the Applicant has done. Therefore, application dates were set up initially assuming 295 day interval. The start date of the application window around the beginning of the year was calculated from emergence date + 70 days (assumed by the Applicant as the minimum interval) or 1 January, whichever was the later in order to make sure that the spring application was in the calendar year following the autumn application. The end date of the application window in the autumn was initially calculated by start date + 295 days (i.e. 365 days – 70 days = 295 days) + 31 days (the addition31 days is needed to meet the PAT criteria for min interval with 2 applications). In order to allow TOXSWA to run the water body simulation for run-off scenarios without error, the .p2t and .txw files were amended in line with the Applicant's approach.

An initial run using these settings indicated that in some scenarios, the autumn application was made six to eight weeks after emergence. Therefore changes were made to the application interval and application window end date in some cases to attempt to bring the autumn application closer to the date of emergence. The end date was therefore set to emergence date + 30 days where this had not been the case in the original simulation.

Even after this additional modification, the initial application date was still generally later than that seen in the Applicant modelling. Therefore it is not possible to make direct comparisons between the Applicants results and those of the RMS. However, for the most vulnerable scenarios in this modelling, i.e. D1, D2 and R3, the RMS global maximum concentrations were lower than the Applicants. In less vulnerable scenarios, RMS global maximum concentrations were often slightly higher. Given this, it is difficult to discern whether the combination of lower plant uptake factor for parent plus pH dependent degradation of X11393729 is practically making any difference to the predicted concentrations. With this in mind, the Applicants concentrations are used for risk assessment purposes. However, the comparison of concentrations from the Applicant's simulations and those from the RMS are shown below for completeness.

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Table B.8.193 Comparison of Applicant and RMS concentrations (µg/l) for X11393729 at FOCUSsw Step 3, following a double application of XDE-729 methyl to winter cereals in autumn at 7.82 g/ha followed by spring application at 6.25 g as/ha using field DT50 inputs; RMS results in parentheses

App Dates*	Scenario	Source	Date of Max PEC	Global Max.
29-Sep-81 16-Jan-82 (16 Jan-82) 03-Oct-82 (23 Oct-82)	D1 Ditch D1 Stream	Drainflow Drainflow	24-Nov-82 (10-Apr-82) 24-Nov-82 (10-Apr-82)	**0.210** **(0.200)** **0.132** **(0.125)**
30-Oct-85 12-Jan-86 (12-Jan-86) 03-Nov-86 (03-Nov-86)	D2 Ditch D2 Stream	Drainflow Drainflow	20-Nov-86 (27-Mar-86) 20-Nov-86 (27-Mar-86)	**0.281** **(0.277)** **0.176** **(0.173)**
27-Nov-91 07-Feb-92 (30-Jan-92) 22-Nov-92 (22-Nov-92)	D3 Ditch	Drainflow	09-Feb-93 (09-Feb-93)	**0.000** **(0.001)**
29-Sep-84 16-Jan-85 (16-Jan-85) 28-Sep-85 (09-Oct-85)	D4 Pond D4 Stream	Drainflow Drainflow	23-Dec-85 (23-Dec-85) 07-Dec-85 (07-Dec-85)	**0.024** **(0.034)** **0.042** **(0.056)**
02-Dec-77 10-Feb-78 (10-Feb-78) 27-Nov-78 (10-Dec-78)	D5 Pond D5 Stream	Drainflow Drainflow	13-Feb-79 (13-Feb-79) 24-Jan-78 (23-Jan-78)	**0.027** **(0.031)** **0.044** **(0.046)**
16-Dec-85 27-Feb-86 (27-Feb-86) 06-Dec-86 (30-Dec-86)	D6 Ditch	Drainflow	18-Dec-86 (19-Jan-87)	**0.103** **(0.146)**
14-Nov-78 (28-Nov-78) 24-Feb79 (24-Jan-79)	R1 Pond R1 Stream	Runoff Runoff	31-Dec-78 (31-Dec-78) 25-Nov-78 (9-Mar-79)	**0.001** **(0.001)** **0.059** **(0.022)**
06-Dec-80 (21-Dec-80) 19-Feb-81 (19-Feb-81)	R3 Stream	Runoff	16-Dec-80 (03-Mar-81)	**0.061** **(0.035)**
10-Nov-79 (10-Dec-79) 21-Jan-80 (21-Jan-80)	R4 Stream	Runoff	21-Dec-79 (21-Dec-79)	**0.032** **(0.044)**

* 1st application for drainage scenarios is in autumn before the TOXSWA simulation period which runs from 1st January to 31st December

The results of the Applicants simulations are shown below.

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Applicant results for XDE-729 methyl

Table B.8.194 FOCUS Step 3 PECsw values (µg/l) for XDE-729 methyl following autumn application to winter cereals at 7.82 g as/ha using field DT50 inputs (earliest application at emergence of crop)

Scenario	App Date	Source	Date of Max PEC	Global Max.
D1 Ditch	03-Oct-82	Drift	03-Oct-82	0.050
D1 Stream	03-Oct-82	Drift	03-Oct-82	0.044
D2 Ditch	03-Nov-86	Drift	03-Nov-86	0.050
D2 Stream	03-Nov-86	Drift	03-Nov-86	0.043
D3 Ditch	22-Nov-92	Drift	22-Nov-92	0.049
D4 Pond	28-Sep-85	Drift	28-Sep-85	0.002
D4 Stream	28-Sep-85	Drift	28-Sep-85	0.043
D5 Pond	27-Nov-78	Drift	27-Nov-78	0.002
D5 Stream	27-Nov-78	Drift	27-Nov-78	0.046
D6 Ditch	06-Dec-86	Drift	06-Dec-86	0.050
R1 Pond	14-Nov-78	Runoff	31-Dec-78	0.003
R1 Stream	14-Nov-78	Runoff	25-Nov-78	0.035
R3 Stream	05-Dec-80	Drift	05-Dec-80	0.046
R4 Stream	10-Nov-79	Runoff	21-Dec-79	0.041

Table B.8.195 FOCUS Step 3 PECsw values (µg/l) for XDE-729 methyl following spring application to winter cereals at 6.25 g as/ha using field DT50 inputs (earliest application at emergence of crop); application window start 1st January

Scenario	**App Date**	**Source**	**Date of Max PEC**	**Global Max.**
D1 Ditch	16-Jan-82	Drift	16-Jan-82	**0.040**
D1 Stream	16-Jan-82	Drift	16-Jan-82	**0.035**
D2 Ditch	12-Jan-86	Drift	12-Jan-86	**0.039**
D2 Stream	12-Jan-86	Drift	12-Jan-86	**0.030**
D3 Ditch	30-Jan-92	Drift	30-Jan-92	**0.039**
D4 Pond	16-Jan-85	Drift	16-Jan-85	**0.001**
D4 Stream	16-Jan-85	Drift	16-Jan-85	**0.031**
D5 Pond	02-Jan-78	Drift	02-Jan-78	**0.001**
D5 Stream	02-Jan-78	Drift	02-Jan-78	**0.029**
D6 Ditch	14-Jan-86	Drift	14-Jan-86	**0.040**
R1 Pond	01-Jan-79	Drift	01-Jan-79	**0.001**
R1 Stream	01-Jan-79	Drift	01-Jan-79	**0.026**
R3 Stream	19-Feb-81	Drift	19-Feb-81	**0.037**
R4 Stream	04-Jan-80	Drift	04-Jan-80	**0.026**

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Table B.8.196 FOCUS Step 3 PECsw values (µg/l) for XDE-729 methyl following a double application of XDE-729 methyl to winter cereals in autumn at 7.82 g/ha followed by spring application at 6.25 g as/ha using field DT50 inputs; run-off scenarios only

Scenario	App Dates (Aut+Spring)	Source	Date of Max PEC	Global Max.
R1 Pond	14-Nov-78	Runoff	31-Dec-78	**0.003**
R1 Stream	24-Feb-79	Runoff	25-Nov-78	**0.035**
R3 Stream	06-Dec-80 19-Feb-81	Runoff	16-Dec-80	**0.041**
R4 Stream	10-Nov-79 21-Jan-80	Runoff	21-Dec-79	**0.041**

Table B.8.197 FOCUS Step 3 PECsw values (µg/l) for XDE-729 methyl following spring application to spring cereals at 6.25 g as/ha using field DT50 inputs (earliest application 7 days post emergence of crop)

Scenario	App Date	Source	Date of Max PEC	Global Max.
D1 Ditch	14-May-82	Drift	14-May-82	**0.039**
D1 Stream	14-May-82	Drift	14-May-82	**0.031**
D3 Ditch	07-Apr-92	Drift	07-Apr-92	**0.039**
D4 Pond	30-May-85	Drift	30-May-85	**0.001**
D4 Stream	30-May-85	Drift	30-May-85	**0.033**
D5 Pond	08-Apr-78	Drift	08-Apr-78	**0.001**
D5 Stream	08-Apr-78	Drift	08-Apr-78	**0.031**
R4 Stream	22-Mar-84	Drift	22-Mar-84	**0.026**

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Applicant results for X11393729

Note that this metabolite is also a significant metabolite formed in the water/sediment study at a maximum of 20% AR. The maximum PECsw at Step 3 for parent was 0.05 µg/l. If this concentration were to degrade forming X11393729, based on 20% formation and a molecular weight correction of 0.959, this would result in a PECsw of 0.0096 µg/l for X11393729. This is a relatively minor concentration in relation to concentrations from drainage and run-off.

Table B.8.198 FOCUS Step 3 PECsw values (µg/l) for X11393729 following XDE-729 methyl autumn application to winter cereals at 7.82 g as/ha using field DT50 inputs (earliest application at emergence of crop)

Scenario	App Date	Source	Date of Max PEC	Global Max.
D1 Ditch	03-Oct-82	Drainflow	25-Nov-82	**0.217**
D1 Stream	03-Oct-82	Drainflow	24-Nov-82	**0.136**
D2 Ditch	03-Nov-86	Drainflow	20-Nov-86	**0.293**
D2 Stream	03-Nov-86	Drainflow	20-Nov-86	**0.184**
D3 Ditch	22-Nov-92	Drainflow	09-Feb-93	**0.000**
D4 Pond	28-Sep-85	Drainflow	23-Dec-85	**0.024**
D4 Stream	28-Sep-85	Drainflow	07-Dec-85	**0.043**
D5 Pond	27-Nov-78	Drainflow	13-Feb-79	**0.028**
D5 Stream	27-Nov-78	Drainflow	24-Jan-78	**0.045**
D6 Ditch	06-Dec-86	Drainflow	18-Dec-86	**0.112**
R1 Pond	14-Nov-78	Runoff	31-Dec-78	**0.001**
R1 Stream	14-Nov-78	Runoff	25-Nov-78	**0.059**
R3 Stream	05-Dec-80	Runoff	16-Dec-80	**0.061**
R4 Stream	10-Nov-79	Runoff	21-Dec-79	**0.032**

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Table B.8.199 FOCUS Step 3 PECsw values (µg/l) for X11393729 following XDE-729 methyl spring application to winter cereals at 6.25 g as/ha using field DT50 inputs (earliest application on 1st January)

Scenario	App Date	Source	Date of Max PEC	Global Max.
D1 Ditch	16-Jan-82	Drainflow	10-Apr-82	**0.109**
D1 Stream	16-Jan-82	Drainflow	10-Apr-82	**0.068**
D2 Ditch	12-Jan-86	Drainflow	27-Mar-86	**0.212**
D2 Stream	12-Jan-86	Drainflow	27-Mar-86	**0.132**
D3 Ditch	30-Jan-92	Drainflow	25-Apr-92	**0.000**
D4 Pond	16-Jan-85	Drainflow	24-Dec-85	**0.001**
D4 Stream	16-Jan-85	Drainflow	02-Feb-85	**0.002**
D5 Pond	02-Jan-78	Drainflow	29-Jan-78	**0.024**
D5 Stream	02-Jan-78	Drainflow	24-Jan-78	**0.055**
D6 Ditch	14-Jan-86	Drainflow	09-Feb-86	**0.097**
R1 Pond	01-Jan-79	Runoff	02-Feb-79	**0.001**
R1 Stream	01-Jan-79	Runoff	02-Feb-79	**0.018**
R3 Stream	19-Feb-81	Runoff	03-Mar-81	**0.019**
R4 Stream	04-Jan-80	Runoff	19-Mar-80	**0.006**

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Table B.8.200 FOCUS Step 3 PECsw values (µg/l) for X11393729 following a double application of XDE-729 methyl to winter cereals in autumn at 7.82 g/ha followed by spring application at 6.25 g as/ha using field DT50 inputs

App Dates*	Scenario	Source	Date of Max PEC	Global Max.
29-Sep-81 16-Jan-82 03-Oct-82	D1 Ditch	Drainflow	24-Nov-82	**0.210**
	D1 Stream	Drainflow	24-Nov-82	**0.132**
30-Oct-85 12-Jan-86 03-Nov-86	D2 Ditch	Drainflow	20-Nov-86	**0.281**
	D2 Stream	Drainflow	20-Nov-86	**0.176**
27-Nov-91 07-Feb-92 22-Nov-92	D3 Ditch	Drainflow	09-Feb-93	**0.000**
29-Sep-84 16-Jan-85 28-Sep-85	D4 Pond	Drainflow	23-Dec-85	**0.024**
	D4 Stream	Drainflow	07-Dec-85	**0.042**
02-Dec-77 10-Feb-78 27-Nov-78	D5 Pond	Drainflow	13-Feb-79	**0.027**
	D5 Stream	Drainflow	24-Jan-78	**0.044**
16-Dec-85 27-Feb-86 06-Dec-86	D6 Ditch	Drainflow	18-Dec-86	**0.103**
14-Nov-78 24-Feb79	R1 Pond	Runoff	31-Dec-78	**0.001**
	R1 Stream	Runoff	25-Nov-78	**0.059**
06-Dec-80 19-Feb-81	R3 Stream	Runoff	16-Dec-80	**0.061**
10-Nov-79 21-Jan-80	R4 Stream	Runoff	21-Dec-79	**0.032**

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Table B.8.201 FOCUS Step 3 PECsw values (µg/l) for X11393729 following XDE-729 methyl spring application to spring cereals at 6.25 g as/ha using field DT50 inputs (earliest application 7 days post emergence of crop)

Scenario	App Date	Source	Date of Max PEC	Global Max.
D1 Ditch	14-May-82	Drainflow	22-Sep-82	**0.015**
D1 Stream	14-May-82	Drainflow	21-Sep-82	**0.017**
D3 Ditch	07-Apr-92	Drainflow	10-Feb-93	**0.000**
D4 Pond	30-May-85	Drainflow	23-Dec-85	**0.001**
D4 Stream	30-May-85	Drainflow	09-Dec-85	**0.001**
D5 Pond	08-Apr-78	Drainflow	31-Jan-78	**0.000**
D5 Stream	08-Apr-78	Drainflow	03-Jan-78	**0.000**
R4 Stream	22-Mar-84	Runoff	15-May-84	**0.027**

B.8.6.1.3 Step 4

The RMS has calculated PECsw for the formulation for spray drift at Step 4 using the FOCUS drift calculator. The highest dose of the formulation "GF-2573" is 1 l/ha. Assuming a relative density of 0.905 (see section B.2.2.13) giving an application dose of 905 g/ha, using standard FOCUS assumptions for a single application (which gives higher spray drift) with a 5m mitigation distance, nominal PECsw values are as follows:

FOCUS ditch = 1.576 µg/l
FOCUS stream = 1.576 µg/l
FOCUS pond = 0.172 µg/l

The Applicant also took the exposure assessments for XDE-729 methyl and X11393729 to Step 4. SWAN v 1.1.4 was used to aid this process by implementing spray drift buffer zones from 5m to 20m as necessary. Run-off mitigation equivalent to 10m or 20m was also included as necessary. FOCUS Landscape and Mitigation recommended reductions for run-off were used. For a 10m buffer strip, a reduction of 60% for run-off water and pesticide transported in the aqueous phase and 85% reduction for eroded solids and pesticide transported in the sediment phase was used. For a 20m buffer strip, a reduction of 80% for the aqueous phase and 95% for the sediment phase was used.

The results of the Step 4 simulations for XDE-729 methyl at drainflow scenarios can be accepted as there was little if any contribution to water body concentrations from drainflow.

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For XDE-729 methyl at run-off scenarios, the results of the Step 3 simulations at the most vulnerable run-off scenario (R3 stream) by the RMS did not suggest an increase in concentration from the changes in input parameters suggested by the RMS. However, differences in application date and date on which the maximum concentration were noted will have also affected the results of the RMS simulations compared with those from the Applicant. With this in mind, as with Step 3, the Applicants results are shown below.

For X11393729, there will be no influence of spray drift mitigation on calculated concentrations as TOXSWA cannot simulate formation of metabolites from a precursor in the water body. Therefore Step 4 calculations can only influence the simulated entry of X11393729 via run-off. The Applicants step 4 calculations are also shown below.

Applicant results for XDE-729 methyl

Table B.8.202 FOCUS Step 4 PECsw values (µg/l) for XDE-729 methyl following autumn application to winter cereals at 7.82 g as/ha using field DT50 inputs (earliest application at emergence of crop); 5m buffer zone for spray drift only

Scenario	App Date	Source	Date of Max PEC	Global Max.
Step 4 – 5m Drift Only				
D1 Ditch	03-Oct-82	Drift	03-Oct-82	0.014
D1 Stream	03-Oct-82	Drift	03-Oct-82	0.016
D2 Ditch	03-Nov-86	Drift	03-Nov-86	0.014
D2 Stream	03-Nov-86	Drift	03-Nov-86	0.016
D3 Ditch	22-Nov-92	Drift	22-Nov-92	0.013
D4 Pond	28-Sep-85	Drift	28-Sep-85	0.001
D4 Stream	28-Sep-85	Drift	28-Sep-85	0.016
D5 Pond	27-Nov-78	Drift	27-Nov-78	0.001
D5 Stream	27-Nov-78	Drift	27-Nov-78	0.017
D6 Ditch	06-Dec-86	Drift	06-Dec-86	0.014
R1 Pond	14-Nov-78	Runoff	31-Dec-78	0.003
R1 Stream	14-Nov-78	Runoff	25-Nov-78	0.035
R3 Stream	05-Dec-80	Runoff	16-Dec-80	0.041
R4 Stream	10-Nov-79	Runoff	21-Dec-79	0.041

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Table B.8.203 FOCUS Step 4 PECsw values (µg/l) for XDE-729 methyl following autumn application to winter cereals at 7.82 g as/ha using field DT50 inputs (earliest application at emergence of crop); 10 and 20 m buffer zone for spray drift and run-off

Scenario	App Date	Source	Date of Max PEC	Global Max.
10m Drift + Runoff				
D1 Ditch	03-Oct-82	Drift	03-Oct-82	**0.007**
D1 Stream	03-Oct-82	Drift	03-Oct-82	**0.008**
D2 Ditch	03-Nov-86	Drift	03-Nov-86	**0.007**
D2 Stream	03-Nov-86	Drift	03-Nov-86	**0.008**
D3 Ditch	22-Nov-92	Drift	22-Nov-92	**0.007**
D4 Pond	28-Sep-85	Drift	28-Sep-85	**0.001**
D4 Stream	28-Sep-85	Drift	28-Sep-85	**0.008**
D5 Pond	27-Nov-78	Drift	27-Nov-78	**0.001**
D5 Stream	27-Nov-78	Drift	27-Nov-78	**0.009**
D6 Ditch	06-Dec-86	Drainflow	19-Jan-87	**0.009**
R1 Pond	14-Nov-78	Runoff	31-Dec-78	**0.001**
R1 Stream	14-Nov-78	Runoff	25-Nov-78	**0.016**
R3 Stream	05-Dec-80	Runoff	16-Dec-80	**0.019**
R4 Stream	10-Nov-79	Runoff	21-Dec-79	**0.018**
20m Drift + Runoff				
R1 Pond	14-Nov-78	Runoff	31-Dec-78	**0.001**
R1 Stream	14-Nov-78	Runoff	25-Nov-78	**0.008**
R3 Stream	05-Dec-80	Runoff	16-Dec-80	**0.010**
R4 Stream	10-Nov-79	Runoff	21-Dec-79	**0.010**

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Table B.8.204 FOCUS Step 4 PECsw values (µg/l) for XDE-729 methyl following spring application to winter cereals at 6.25 g as/ha using field DT50 inputs (earliest application at emergence of crop); application window start 1st January. 5m buffer (spray drift only) and 10 m buffer zone (spray drift and run-off)

Scenario	App Date	Source	Date of Max PEC	Global Max.
5 m Drift Only				
D1 Ditch	16-Jan-82	Drift	16-Jan-82	**0.011**
D1 Stream	16-Jan-82	Drift	16-Jan-82	**0.013**
D2 Ditch	12-Jan-86	Drift	12-Jan-86	**0.011**
D2 Stream	12-Jan-86	Drift	12-Jan-86	**0.011**
D3 Ditch	30-Jan-92	Drift	30-Jan-92	**0.010**
D4 Pond	16-Jan-85	Drift	16-Jan-85	**0.001**
D4 Stream	16-Jan-85	Drift	16-Jan-85	**0.011**
D5 Pond	02-Jan-78	Drift	02-Jan-78	**0.001**
D5 Stream	02-Jan-78	Drift	02-Jan-78	**0.010**
D6 Ditch	14-Jan-86	Drift	14-Jan-86	**0.011**
R1 Pond	01-Jan-79	Drift	01-Jan-79	**0.001**
R1 Stream	01-Jan-79	Runoff	02-Feb-79	**0.020**
R3 Stream	19-Feb-81	Runoff	03-Mar-81	**0.018**
R4 Stream	04-Jan-80	Runoff	19-Mar-80	**0.016**
10 m Drift + Runoff Reduction				
R1 Pond	01-Jan-79	Drift	01-Jan-79	**0.001**
R1 Stream	01-Jan-79	Runoff	02-Feb-79	**0.009**
R3 Stream	19-Feb-81	Runoff	03-Mar-81	**0.008**
R4 Stream	04-Jan-80	Runoff	19-Mar-80	**0.007**

Table B.8.205 FOCUS Step 4 PECsw values (µg/l) for XDE-729 methyl following spring application to spring cereals at 6.25 g as/ha using field DT50 inputs (earliest application 7 days post emergence of crop)

Scenario	App Date	Source	Date of Max PEC	Global Max.
Step 4 – 5m Drift Only				
D1 Ditch	14-May-82	Drift	14-May-82	**0.011**
D1 Stream	14-May-82	Drift	14-May-82	**0.011**
D3 Ditch	07-Apr-92	Drift	07-Apr-92	**0.011**
D4 Pond	30-May-85	Drift	30-May-85	**0.001**
D4 Stream	30-May-85	Drift	30-May-85	**0.012**
D5 Pond	08-Apr-78	Drift	08-Apr-78	**0.001**
D5 Stream	08-Apr-78	Drift	08-Apr-78	**0.011**
R4 Stream	22-Mar-84	Drift	22-Mar-84	**0.018**
Step 4 – 10m Drift + Runoff				
R4 Stream	22-Mar-84	Runoff	15-May-84	**0.008**

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Applicant values for X11393729

Table B.8.206 FOCUS Step 4 PECsw values (µg/l) for X11393729 following XDE-729 methyl autumn application to winter cereals at 7.82 g as/ha using field DT50 inputs (earliest application at emergence of crop)

Scenario	App Date	Source	Date of Max PEC	Global Max.
Step 4 (10m Drift and Runoff)				
R1 Pond	14-Nov-78	Runoff	31-Dec-78	**0.000**
R1 Stream	14-Nov-78	Runoff	25-Nov-78	**0.027**
R3 Stream	05-Dec-80	Runoff	16-Dec-80	**0.028**
R4 Stream	10-Nov-79	Runoff	21-Dec-79	**0.014**

B.8.6.2 Groundwater

The Applicant undertook PECgw modelling using FOCUS PELMO 4.4.3 and FOCUS PEARL 4.4.4. In line with the proposed GAP, the Applicant provided simulations of the following use patterns:

Winter cereals in the autumn at 7.82 g as/ha at crop growth stage BBCH 10-29 (25% interception) followed by a second application in the spring at 6.25 g as/ha at growth stage BBCH 13-45 (25% interception) with a minimum 70 day interval. First application set to date of emergence, second application set to 70 days after emergence.

Winter cereals in the autumn at 7.82 g as/ha at crop growth stage BBCH 10-29 (25% interception). Application set to date of emergence.

Winter cereals in the spring at 6.25 g as/ha at growth stage BBCH 13-45 (25% interception). Application set to 1st January.

Spring cereals in the spring at 6.25 g as/ha at growth stage BBCH 13-45 (25% interception). Application set to 7 days post-emergence.

Each GAP was simulated to be applied annually with the models run for 26 years.

The RMS considers this to be a reasonable representation of the GAP for Annex I listing purposes. For national registrations, MSs using FOCUSgw modelling should satisfy themselves that the application timings based on default crop timings such as dates of emergence and the dates chosen by the Applicant are appropriate for their locality.

For each of the above use patterns, the Applicant conducted three sets of simulations, one for parent XDE-729 methyl, one for X11393729 and one for X11449757. This was because of the application of EFSA guidance on derivation of DegT50 from field dissipation studies and the Applicants interpretation of the guidance resulted in differences in degradation rates for parent dependent on whether parent only would be simulated or whether metabolites were included in a simulation taking into account

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metabolite formation from parent. This is described in section B.8.1.5 b). Aside from a concern whether metabolite X11393729 may exhibit pH dependent degradation which probably needs further expert discussion, the RMS can agree with approach used and the selection of input parameters.

With respect to soil adsorption values for parent, the Applicant used an arithmetic mean Kfoc value of 987 ml/g and 1/n of 0.88 from the complete data set from the second study submitted. The RMS agrees to use of the second study and not the first study. However, as one of the seven tested soils was an organic soil with 33% organic carbon content, the RMS considered that result from this soil should be excluded from consideration of modelling input parameters. It is noted that if the results from the organic soil are excluded, the arithmetic mean Kfoc increases to 995 ml/g and 1/n falls to 0.87. Therefore, the effect of including the results from organic soil is to make the leaching properties slightly worse. Thus the RMS can agree to use of the Applicant's chosen soil adsorption properties for the parent in this modelling.

A plant uptake factor of 0.5 was chosen for the parent as the Applicant argued that information in the biological dossier indicates that the parent and/or X11393729 is taken up into plants via the roots and translocated. In principle, the RMS considers that it is acceptable to use a plant uptake factor in the modelling, as whilst the soil degradation parameter is derived from field dissipation studies, all the studies were bare soil studies, thus plant uptake should not have been a process contributing to the disappearance of the parent substance and its metabolites. However, the RMS is aware that there is currently much discussion related to the derivation of plant uptake factor. Current EFSA approach is to assume a default plant factor of 0 unless this can be refined by the use of the equations of Briggs *et al* 1983. The RMS has investigated the log Kow values for XDE-729 methyl and X11393729. The parent has log Kow ranging from 3.75 – 3.92, leading to a TSCF predicted by Briggs *et al* 1983 of 0.16 – 0.12. X11393729 has log Kow of 0.42 at pH 5 to -1.01 at pH 9, leading to TSCF values of 0.048 – 0.032. Thus it can be seen that application of the Briggs equation leads to much lower value of TSCF for parent than used by the Applicant.

The RMS has also considered the results of a confined rotational crops metabolism study as it is known that such results have been used in considering plant uptake factors. Details of this study can be found at section B.7.1.3 of the DAR. In this study, 10 g XDE-729 methyl/ha labelled in either Ph or Py positions was applied to bare soil and left for periods of 14 days, 90 days and 270 days before planting lettuce, radish and wheat. As the GAP is for cereals, only the results in this study on wheat are considered here. After planting wheat, the forage was harvested at GS 25 (interval between planting and harvest not specified) and analysed for total radioactive residue (TRR). Hay was harvested at GS 61-85 and grain and straw harvested at GS 89. There was no analysis of soil residues either in terms of concentrations or characterisation of radioactivity either immediately after treatment or at the time of planting. The LOQ for the analytical method for plant material was 0.00055 mg/kg for Ph labelled material and 0.00082 mg/kg for Py labelled material. At the time of harvest after the 14 day plant back time, the forage had TRR residues <LOQ. TRR residues in hay grain and straw were either <LOQ or 0.001 mg/kg. For information, very similar findings were achieved at the other plant back times and with the other crops. Discussing with the RMS residues evaluator, all that could be concluded from this study was that the TRR residues were very low. However, the information in the

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study was insufficient to be able to relate the residues found to the amount applied or the residue remaining at the time of planting. Therefore this study is of very limited use in terms of attempting to quantify a plant uptake factor.

Reference to the Biological Assessment Dossier (BAD) provided by the Applicant to the RMS indicates that a study was performed in which a formulated product containing XDE-729 methyl was incorporated into soil and pre-germinated seedlings of a range of crop species planted in the treated soil. The range of crops was wheat (*Triticum aestivum)*, pea (*Pisum sativum)*, oil seed rape (*Brassica napus)*, sugar beet (*Beta vulgaris)*, sunflower (*Helianthus annuus)*, maize (*Zea mays)*, oat (*Avena sativa)* and white mustard (*Sinapis alba)*. Plants were visually assessed for injury. The presence of injury was taken by the Applicant as evidence that XDE-729 methyl can be taken up by from soil by roots and then translocated. The BAD supplied no further details, only stating that peas were identified as a species sensitive to XDE-729 methyl. The information provided here can only be treated as qualitative, there being no quantitative measurement of the extent of plant uptake. Certainly it is unlikely that significant effects would have been seen in wheat as this is a crop on which this herbicide is being registered for use.

The RMS considers that there is no robust evidence to support the use of a plant uptake factor of 0.5 for XDE-729 methyl. At best, the RMS considers that plant uptake could be set at a value of 0.14 (average of 0.12 and 0.16) from the Briggs equation using logKow.

It was noted in the soil adsorption studies that X11393729 and X11449757 both showed evidence of reduced soil adsorption at higher pH. For both substances, lowest adsorption was seen on the two highest pH soils tested (pH 7.2 and 7.5). The Applicant proposed that for each of these metabolites, the lowest two Kfoc values should be averaged. In addition, the 1/n values associated with these Kfocs were also averaged. Thus for X11393729, sorption parameters proposed were Kfoc 28 ml/g with 1/n 0.88. For X11449757, sorption parameters proposed were Kfoc 17 ml/g with 1/n 0.93. The RMS can agree with these values as the two individual values for each substance are close to each other suggesting that there might not be expected to be that much additional change if pH were to further increase. This is certainly the case for X11393729 which has a single pKa of 5.11. The RMS notes that X11449757 has two pKa values (5.6 for the carboxylic acid group and 7.1 for the phenolic group) however, as the Kfoc values at pH 7.2 and 7.5 are close to each other, this gives some reassurance that there is unlikely to be further significant change at higher pH.

The RMS also notes that as there did not appear to be a relationship between soil adsorption and Kf for parent and metabolites that ideally the models should have been run with Kf as the input parameter. However, the need to perform simulations with Kf rather than Kfoc could also be subject to expert discussion.

The RMS notes that the Applicant chose water solubilities from pH 7. For the two metabolites, water solubility changes with pH, increasing with increasing pH. However, as the main use of water solubility data is in conjunction with vapour pressure to simulate volatilisation, the combination of values are likely to lead to very low or no losses by volatilisation, increasing the residue available for leaching, and this is therefore acceptably conservative. However, in principle, as degradation

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parameters from field dissipation studies have been used, volatilisation ought to have been disabled, but this is unlikely to make a significant difference to the calculations.

A summary of the substance input parameters used is given below. Temperature correction in all simulations was set to a Q10 of 2.58 and moisture correction B value set to 0.7.

Table B.8.207 FOCUS PELMO inputs for XDE-729 methyl (simulating parent only)

Parameter	**Value**	**Comments**
Molecular mass:	345	
Plant uptake factor:	0.5	FOCUS recommendation for systemic substance
<u>Volatilisation and photolysis data</u>		
Vapour pressure (Pa, 20ºC):	5.9×10^{-9}	Measured value (List of End Points)
Aqueous solubility (mg/L, 20ºC):	1.7	Measured value (List of End Points)
Soil photolysis rate (d^{-1}) :	0	Photolysis not considered
Diffusion coeff. air (cm^2/s) :	0.05	FOCUS recommendation
Volatilisation depth (cm):	0.1	FOCUS recommendation
<u>Sorption data</u>		
Koc (mol/g)	987	Average Kfoc value (n = 7)
Freundlich exponent (1/n)	0.88	Average value (n = 7)
pKa	20	Default to disable pH dependence
Increase for air-dried soil:	1	FOCUS recommendation
Kinetic sorption parameters:	0	Kinetic sorption not implemented
Depth dependent data	Standard (Tier 1)	FOCUS recommendation
<u>Degradation data:</u>		
DT50 (days, 20°C, pF2):	20	Geomean (n = 8) SFO after 10mmm rain from normalised field dissipation studies
Rate correction in soil option:	Recommended	FOCUS recommendation
Rel. deg at neq sites:	0	FOCUS recommendation

Note: FOCUS default values were used for any other input parameters not shown

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Table B.8.208 FOCUS PEARL inputs for XDE-729 methyl (simulating parent only)

Parameter	Value	Comments
General data		
Molar mass (g/mole):	345	-
Sat. vap. pressure (Pa, 20ºC):	5.9×10^{-9}	Measured value (List of End Points)
Sol in water (mg/L, 20ºC):	1.7	Measured value (List of End Points)
Enthalpy of vaporisation (kJ/mole):	95	FOCUS recommendation
Enthalpy of dissolution (kJ/mole):	27	FOCUS recommendation
Sorption data		
Option:	Kom, pH independent	
Kom, (mol/g at 20 ºC)[+]:	573	Average Kfom value (n=7)
Enthalpy of sorption (kJ/mole):	0	Not implemented
Equilibrium sorption:		
Ref. conc. in liq. phase (mg/L):	1	FOCUS recommendation
Freundlich exponent (1/n):	0.88	Average value (n = 7)
Non-equilibrium sorption:		
Desorption rate coeff. (d^{-1}):	0	Non-equilibrium sorption not implemented
Factor Kf,neq/Kf,eq:	0	Non-equilibrium sorption not implemented
Transformation data		
Half-life (days at 20ºC):	20	Geomean (n = 8) SFO after 10mmm rain from normalised field dissipation studies
Optimum moisture conditions	Yes	Relevant for pF 2
Exponent for effect of liquid:	0.7	FOCUS recommendation
Molar act. energy (kJ/mole):	65.4	EFSA recommendation
Diffusion data		
Ref temperature (ºC):	20	FOCUS recommendation
Ref diff. coeff. in water (m^2/d):	4.3×10^{-5}	FOCUS recommendation
Ref diff. coeff. in air (m^2/d) :	0.43	FOCUS recommendation
Crop data		
Wash-off factor (m^{-1}):	0.0001	FOCUS recommendation
Canopy process option:	Lumped	FOCUS recommendation
Half-life at crop surface (d):	1000000	FOCUS recommendation
Coeff. for uptake by plant	0.5	FOCUS recommendation for systemic substance

[+] Kom = Koc/1.724

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Table B.8.209 FOCUS PELMO and PEARL Inputs for X11393729 (formed from parent)

Parameter	**Value**	**Comments**
General data		
Molecular mass:	331	-
Plant uptake factor:	0	Worst-case value
Sat. vap. pressure (Pa, 20ºC):	2×10^{-5}	Measured value
Sol in water (mg/L, 20ºC):	3070	Measured value at pH 7
Sorption data		
Kfoc (mol/g):	28	Average Kfoc from the highest pH soils (n = 2)
Kfom (mol/g):	16.0	From Kfoc/1.724
Freundlich exponent:	0.88	Average 1/n from the highest pH soils (n = 2)
Transformation data		
DT50 Parent (days, 20°C/pF2):	3.3	From sequential modelling of parent and X11393729, normalised field data
Rate constant, k (d^{-1}):	0.210	From ln2/DT50
DT50 Acid (days, 20°C/pF2):	22	From sequential modelling of parent + X11393729, normalised field data
Formation fraction:	0.45	From sequential modelling of parent + X11393729, normalised field data
Rate constant, k (d^{-1}):		
Parent > Acid (d^{-1})	0.0945	Based on FF = 0.45
Parent > CO_2/NER (d^{-1})	0.1155	Based on FF = (1 – 0.45)

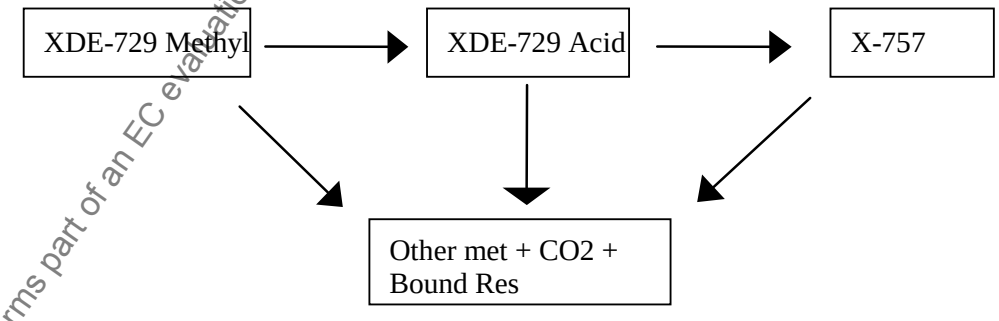
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Table B.8.210 FOCUS PELMO and PEARL Inputs for X11449757 (formed in sequence from parent and X11393729)

Parameter	Value	Comments
General data		
Molecular mass:	317	-
Plant uptake factor:	0	Worst-case value
Sat. vap. pressure (Pa, 20ºC):	5×10^{-5}	Measured value (List of End Points)
Sol in water (mg/L, 20ºC):	265	Measured value at pH 7 (List of End Points)
Sorption data		
Kfoc (mol/g):	17	Average Kfoc from the highest pH soils (n = 2)
Kfom (mol/g):	9.9	From Kfoc/1.724
Freundlich exponent:	0.93	Average Kfoc from the highest pH soils (n = 2)
Transformation data		
DT50 Parent (days, 20°C/pF2):	1.7	From sequential modelling of parent + X11393729 + X11449757, normalised field data
Rate constant, k (d^{-1}):	0.408	From ln2/DT50
Parent > Acid (d^{-1})	0.2162	Based on FF = 0.53
Parent > CO_2/NER (d^{-1})	0.1918	Based on FF = (1 – 0.53)
DT50 Acid (days, 20°C/pF2):	14	From sequential modelling of parent + X11393729 + X11449757, normalised field data
Formation fraction (from parent):	0.53	From sequential modelling of parent + X11393729 + X11449757, normalised field data
Rate constant, k total (d^{-1}):	0.0495	From ln2/DT50
Acid > X-757 (d^{-1})	0.0297	Based on FF = 0.60
Acid > CO_2/NER (d^{-1})	0.0198	Based on FF = (1 – 0.60)
DT50 X-757 (days, 20°C/pF2):	19	From sequential modelling of parent + X11393729 + X11449757, normalised field data
Formation fraction (from X11393729):	0.60	From sequential modelling of parent + X11393729 + X11449757, normalised field data

The following degradation scheme was used in both PELMO and PEARL.

Figure B.8.230 Degradation scheme for modelling groundwater concentrations of XDE-729 methyl, X11393729 and X11449757



The following results were obtained from the Applicant's modelling. In the following tables, X11393729 is denoted by "XDE 729 acid" and X11449757 by "X-757".

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Table B.8.211 80th percentile PECgw Values (µg/l) for XDE-729 methyl following application to winter cereals

Scenario	Crop emerg. date (dd/mm)	Autumn, 7.82 g/ha at emergence, 25% int		Spring, 6.25 g/ha on 1st Jan, 25% int		*Double app, autumn + spring with 70 d interval	
		PELMO	PEARL	PELMO	PEARL	PELMO	PEARL
Chateaudun	26/10	0.000	0.000	0.000	0.000	0.000	0.000
Hamburg	01/11	0.000	0.000	0.000	0.000	0.000	0.000
Jokioinen	20/09	0.000	0.000	0.000	0.000	0.000	0.000
Kremsmünster	05/11	0.000	0.000	0.000	0.000	0.000	0.000
Okehampton	17/10	0.000	0.000	0.000	0.000	0.000	0.000
Piacenza	01/12	0.000	0.000	0.000	0.000	0.000	0.000
Porto	30/11	0.000	0.000	0.000	0.000	0.000	0.000
Sevilla	30/11	0.000	0.000	0.000	0.000	0.000	0.000
Thiva	30/11	0.000	0.000	0.000	0.000	0.000	0.000

* Application scheme is 7.82 g as/ha at emergence with 25% intercept (5.865 g/ha to soil) followed by 6.25 g as/ha at 70 days post-emergence with 25% intercept (4.688 g/ha to soil)

Table B.8.212 80th percentile PECgw values (µg/l) for X11393729 following application of XDE-729 methyl to winter cereals

Scenario	Crop emerg. date (dd/mm)	Autumn, 7.82 g/ha at emergence, 25% int		Spring, 6.25 g/ha on 1st Jan, 25% int		*Double app, autumn + spring with 70 d interval	
		PELMO	PEARL	PELMO	PEARL	PELMO	PEARL
Chateaudun	26/10	0.001	0.001	0.000	0.000	0.001	0.001
Hamburg	01/11	0.010	0.008	0.003	0.002	0.016	0.012
Jokioinen	20/09	0.003	0.002	0.001	0.000	0.005	0.004
Kremsmünster	05/11	0.004	0.003	0.002	0.001	0.007	0.006
Okehampton	17/10	0.012	0.011	0.005	0.003	0.019	0.015
Piacenza	01/12	0.005	0.003	0.002	0.002	0.008	0.006
Porto	30/11	0.010	0.006	0.006	0.002	0.012	0.007
Sevilla	30/11	0.000	0.000	0.000	0.000	0.000	0.000
Thiva	30/11	0.000	0.000	0.000	0.000	0.000	0.000

* Application scheme is 7.82 g as/ha at emergence with 25% intercept (5.865 g/ha to soil) followed by 6.25 g as/ha at 70 days post-emergence with 25% intercept (4.688 g/ha to soil)

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Table B.8.213 80th percentile PECgw values (µg/l) for X11449757 following application of XDE-729 methyl to winter cereals

Scenario	Crop emerg. date (dd/mm)	Autumn, 7.82 g/ha at emergence, 25% int		Spring, 6.25 g/ha on 1st Jan, 25% int		*Double app, autumn + spring with 70 d interval	
		PELMO	PEARL	PELMO	PEARL	PELMO	PEARL
Chateaudun	26/10	0.007	0.009	0.003	0.004	0.011	0.016
Hamburg	01/11	0.048	0.040	0.019	0.017	0.068	0.059
Jokioinen	20/09	0.037	0.027	0.013	0.010	0.053	0.042
Kremsmünster	05/11	0.024	0.019	0.013	0.010	0.040	0.032
Okehampton	17/10	0.049	0.043	0.020	0.017	0.073	0.059
Piacenza	01/12	0.018	0.013	0.008	0.009	0.024	0.023
Porto	30/11	0.041	0.029	0.016	0.010	0.047	0.034
Sevilla	30/11	0.001	0.000	0.000	0.000	0.001	0.000
Thiva	30/11	0.003	0.002	0.001	0.001	0.003	0.004

* Application scheme is 7.82 g as/ha at emergence with 25% intercept (5.865 g/ha to soil) followed by 6.25 g as/ha at 70 days post-emergence with 25% intercept (4.688 g/ha to soil)

Table B.8.214 80th percentile PECgw values (µg/l) for XDE-729 methyl and metabolites (XDE-729 Acid = X11393729, X-757 = X11449757) following a single application to spring cereals

Scenario	Application Date (dd/mm)	XDE-729 methyl		XDE-729 Acid		X-757	
		PELMO	PEARL	PELMO	PEARL	PELMO	PEARL
Chateaudun	17/03	0.000	0.000	0.000	0.000	0.001	0.002
Hamburg	08/04	0.000	0.000	0.001	0.002	0.013	0.019
Jokioinen	25/05	0.000	0.000	0.001	0.000	0.015	0.013
Kremsmünster	08/04	0.000	0.000	0.001	0.001	0.011	0.011
Okehampton	08/04	0.000	0.000	0.002	0.002	0.014	0.014
Porto	17/03	0.000	0.000	0.001	0.000	0.006	0.003

Application scheme is one application of 6.25 g as/ha at 7 days post-emergence with 25% intercept (4.688 g/ha to soil)

The areas of contention around the input parameters are the use of a plant uptake factor of 0.5 for the parent and lack of accounting for pH dependence of degradation of X11393729. From the results above, it is unlikely that the use of a lower plant uptake factor for parent will influence parent results in terms of regulatory decision making. However, it is possible that the use of a lower plant uptake factor would lead to higher concentrations of metabolites being simulated. To check this, the RMS has re-run the metabolite simulations with the Applicant's preferred parameters but with plant uptake factors for parent of 0 and 0.14 and these changes in parameters make no difference to metabolite concentrations.

With regard to pH dependence of degradation of X11393729, it is noted that faster degradation of this metabolite occurs at low pH, with slower degradation at high pH. As there was a decrease in strength of adsorption at higher pH, it is possible that taking account slower degradation at higher pH could influence leaching concentrations of X11393729 and X11449757.

With this in mind, the RMS has repeated the modelling for two applications to winter cereals with PELMO for both X11393729 and X11449757. PELMO was used because it gave consistently higher results than PEARL. Separate simulations were

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run for each substance as the Applicant had done. Parent plant uptake factor was changed to 0.14.

For the run to predict concentrations of X11393729, a geometric mean DT50 from the two highest pH field sites (Spain Spring and Spain Autumn) and arithmetic mean formation fraction from these two sites was used. The DT50 used was 36.9 days and the formation fraction from the parent was 0.34. The parent DT50 used in the simulation was 3.3 days, equivalent to a rate constant of 0.2100 day^{-1}. Dividing the parent rate constant by the formation fraction gave a rate constant for formation of X11393729 of 0.0714 day^{-1} with rate constant to CO2/NER of 0.1386 day^{-1}. All other parameters were kept the same as used by the Applicant.

For the run to predict concentrations of X11449757, ideally a formation fraction for X11393729 to X11449757 derived from the two Spanish sites is required. However, it was noted that it was not possible to obtain robust kinetic parameters for the substances from these sites once X11449757 had been added to the kinetic modelling. Therefore the RMS modelling for X11449757 was undertaken using the parent DT50 of 1.7 days from the Applicants X11449757 groundwater modelling with the DT50 and formation fraction for X11393729 from the two Spanish alkaline sites. Therefore, dividing the parent rate constant of 0.4077 day^{-1} by the formation fraction of 0.34 gave a rate constant for formation of X11393729 of 0.1386 day^{-1} with rate constant to CO_2/NER of 0.2691 day^{-1}. The X11449757 kinetic parameters were the mean parameters used in the Applicants groundwater modelling for this metabolite. Therefore the X11393729 rate constant of 0.0188 (equivalent to a DT50 of 36.9 days) was divided by the X11449757 formation fraction of 0.60 to give a rate constant for formation of X11449757 of 0.0113 day^{-1} and with rate constant to CO_2/NER of 0.0075 day^{-1}.

A comparison of the 80th percentile annual averages from Applicant and RMS modelling is presented below.

Table B.8.215 Comparison of Applicant and RMS groundwater simulations of X11393729 and X11449757, RMS simulations taking account of pH dependent degradation on alkaline soils.

Scenario	Crop emerg. date (dd/mm)	X11393729		X11449757	
		Applicant	RMS	Applicant	RMS
Chateaudun	26/10	0.001	0.009	0.011	0.018
Hamburg	01/11	0.016	0.052	0.068	0.064
Jokioinen	20/09	0.005	0.026	0.053	0.055
Kremsmünster	05/11	0.007	0.032	0.040	0.043
Okehampton	17/10	0.019	0.055	0.073	0.059
Piacenza	01/12	0.008	0.028	0.024	0.028
Porto	30/11	0.012	0.035	0.047	0.038
Sevilla	30/11	0.000	0.000	0.001	0.003
Thiva	30/11	0.000	0.002	0.003	0.007

As can be seen from the above simulation, X11393729 concentrations are increased but do not exceed 0.1 µg/l. The effect on X11449757 is variable, but as with X11393729, did not exceed 0.1 µg/l. The lack of suitable formation fractions from

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X11393729 to X11449757 at the alkaline sites is not ideal, but the results give a possible indication of the effect of pH. As suggested previously, the possible pH dependence of X11393729 (and X11449757) could be subject to expert discussion.

B.8.7 Fate and behaviour in air (IIA 7.2.2, IIIA 9.3)

A theoretical calculation of the potential for oxidative photo-oxidation of XDE-729 methyl in the atmosphere was submitted, using the method of Atkinson (1988) with the US EPA AopWin v 1.92 software. A rate constant of 4.9622×10^{-12} cm³/molecule/s was calculated for reaction with OH radicals. This corresponded to a first order DT_{50} of 2.155 days assuming a hydroxyl radical concentration of 1.5×10^{6} radicals/cm^3 and a 12 hour daylight period.

(Wendelburg and Boulton 2011)

B.8.7.1 Summary & assessment – fate in air

XDE-729 methyl has a vapour pressure of 5.9×10^{-9} Pa at 20ºC (section B.2.1.5), water solubility of 1.66 – 1.69 mg/l at pH 5 – 9 (section B.2.1.11) and calculated Henry's Law constant of $1.20 – 1.23 \times 10^{-6}$ Pa m^3/mol at pH 5 – 9 (section B.2.1.6). This would suggest that volatility of XDE-729 methyl from water or moist soil and leaf surfaces will be limited. The vapour pressure suggests that dry deposits will be unlikely to dissipate significantly via volatilisation.

The 'Atkinson' half life of 2.2 days suggests that there may be a possibility for long-range transport were XDE-729 methyl to enter the atmosphere. However, the low relative values of vapour pressure and Henry's Law constant suggest that volatilisation is unlikely from soil and leaf surfaces, and thus it is considered that the risk of long range transport of this active substance is very low. The RMS notes that recent EFSA conclusions have highlighted potential for long range transport of substances with an Atkinson half life >2 days as a result of aerosol formation during spraying operations. This possibility has not been addressed in this assessment. However, it is likely that any subsequent exposure of the environment as a result of long range transport will be well within that already considered by the existing environmental exposure and risk assessment.

An 'Atkinson' calculation was not presented for the main soil metabolite, X11393729, but vapour pressure (2×10^{-5} Pa at 20ºC) and solubility data (0.1 – 46.1 g/l at pH 5 – 9) suggest that this metabolite is unlikely to volatilise.

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Direct photolysis in air ‡	Not studied - no data requested
Quantum yield of direct phototransformation	active substance: 5.6
Photochemical oxidative degradation in air ‡	DT_{50} of 2.2 days derived by the Atkinson model (AopWin version 1.92). OH (12 h) concentration assumed = 1.5×10^6 radicals/cm^3
Volatilisation ‡	Not submitted, not required
Metabolites	X11393729 unlikely to be volatile

B.8.8 Predicted environmental concentrations in air (PECa) (IIIA 9.3)

Method of calculation	Expert judgement, based on vapour pressure, dimensionless Henry's Law Constant and information on volatilisation from plants and soil.

$PEC_{(a)}$

Maximum concentration	Expected to be negligible

B.8.9 Definition of the residue (IIA 7.3)

The residue definition for further risk assessment is defined as follows:

In soil, parent XDE-729 methyl, X11393729 and X11449757

In surface water, parent XDE-729 methyl, X11393729, X11406790, X11449757, and aqueous photolysis metabolites Deg 10, Deg11 and Deg 14

In sediment, parent XDE-729 methyl, X11393729, X11406790 and X11449757, and aqueous photolysis metabolites Deg 10, Deg11 and Deg 14

In groundwater, parent XDE-729 methyl, X11393729 and X11449757

In air, parent XDE-729 methyl

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B.8.10 References relied on

Annex II

Annex Point/ Reference Number	Author(s)	Year	Title Source (where different from the Company), Company, Report Number, GLP or GEP status (where relevant), Published or not	Data Protection claimed (Y/N)	Owner
KIIA 7.1.1/01	Yoder, R.N., K. A. Guenthensperger, Boulton, J.P., Adelfinskaya, Y.A.	2011 (Amended 2012)	Soil Degradation of XDE-729 ME under Aerobic Conditions on Four Global Soils AMENDED REPORT Dow AgroSciences LLC DAS Report No.: 090121 (Accession Number): 2009175 GLP/GEP (Y/N): Y Published (Y/N): N	Y	DAS
KIIA 7.1.1/02	Yoder, R.N., Boulton, J.P	2011	Soil Degradation of XDE-729 ME under Anaerobic, Low Temperature and Sterile Conditions Dow AgroSciences LLC DAS Report No.: 101654 (Accession Number): 2009566 GLP/GEP (Y/N): Y Published (Y/N): N	Y	DAS
KIIA 7.1.1/03 (submitted under KIIA 8.9.2/11	Liu, D. And Croffie, J.	2012	Determination of Non-Extractable Residues of XDE-729 Methyl in Soil under Aerobic Conditions Dow AgroSciences LLC DAS Report No.: 110767, 110767 (Accession Number) 2012111 GLP/GEP (Y/N): Y Published (Y/N): N	Y	DAS
KIIA 7.1.2/01 (See KIIA 7.1.1/02)	Yoder, R.N., Boulton, J.P	2011	Soil Degradation of XDE-729 ME under Anaerobic, Low Temperature and Sterile Conditions Dow AgroSciences LLC DAS Report No.: 101654 (Accession Number): 2009566 GLP/GEP (Y/N): Y Published (Y/N): N	Y	DAS

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KIIA 7.1.3/01	Ma, M., Adelfinskaya, Y.A.	2011	Photodegradation of XDE-729 Methyl on Soil Dow AgroSciences LLC DAS Report No.: 110382 (Accession Number): 2009360 GLP/GEP (Y/N): Y Published (Y/N): N	Y	DAS
KIIA 7.2.1/01 (See KIIA 7.1.1/01)	Yoder, R.N., Guenthensperger, K. A., Boulton, J.P., Adelfinskaya, Y.A.	2011 (Amended 2012)	Soil Degradation of XDE-729 ME under Aerobic Conditions on Four Global Soils Dow AgroSciences LLC DAS Report No.: 090121 (Accession Number): 2009175 GLP/GEP (Y/N): Y Published (Y/N): N	Y	DAS
KIIA 7.2.1/02	Jackson, R.	2012a	Derivation of the Soil Degradation Kinetics Inputs for Modelling the Fate of XDE-729 Methyl and its Metabolites in the EU. Dow AgroSciences DAS Report No.: GHE-P-12651 (Accession Number): 2009591 GLP/GEP (Y/N): N Published (Y/N): N	Y	DAS
KIIA 7.2.1/03	Jackson, R.	2013	Recalculation of the Field Dissipation Rates for XDE-729 methyl and its Metabolites for Model Inputs Dow AgroSciences DAS Report No.: GHE-P-12971 (Accession Number): 2019338 GLP/GEP (Y/N): N Published (Y/N): N	Y	DAS

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KIIA 7.2.2/01 (See KIIA 7.1.1/02)	Yoder, R.N., Boulton, J.P	2011	Soil Degradation of XDE-729 ME under Anaerobic, Low Temperature and Sterile Conditions Dow AgroSciences LLC DAS Report No.: 101654 (Accession Number): 2009566 GLP/GEP (Y/N): Y Published (Y/N): N	Y	DAS
IIA 7.2.3/01 (See IIA 7.1.1/01)	Yoder, R.N., K. A. Guenthensperger, Boulton, J.P., Adelfinskaya, Y.A.	2011 (Amended 2012)	Soil Degradation of XDE-729 ME under Aerobic Conditions on Four Global Soils AMENDEd REPORT Dow AgroSciences LLC DAS Report No.: 090121 (Accession Number): 2009175 GLP/GEP (Y/N): Y Published (Y/N): N	Y	DAS
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KIIA 7.3.1/02	Kellner, T.	2012b	Soil dissipation study with one autumn application of XDE-729 as GF-2573 at four sites in Northern and Southern Europe in 2010-2012 Eurofins Agroscience Services GmbH DAS Report No.: S10-00921 (Accession Number): 2013670 GLP/GEP (Y/N): Y Published (Y/N): N	Y	DAS
KIIA 7.3.1/03	Jackson, R.	2012b	Calculation of the Dissipation Rates for XDE-729 methyl and Its Acid Metabolite from European Field Studies Dow AgroSciences DAS Report No.: GHE-P-12805 (Accession Number): 2014369 GLP/GEP (Y/N): N Published (Y/N): N	Y	DAS
KIIA 7.3.3/01	Jackson, R.	2012c	Modelling the Potential Accumulation of Non-extractable Residues of XDE-729 methyl in Soil Dow AgroSciences DAS Report No.: GHE-P-12808 (Accession Number): 2014398 GLP/GEP (Y/N): N Published (Y/N): N	Y	DAS

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KIIA 7.4.1/01	Yoder, R.N., Smith, K.P., Adusumilli, H.	2011(Amended 2012)	Batch Equilibrium Adsorption/Desorption of XDE-729 Methyl and Adsorption of its X11393729 and X11449757 Metabolites Amended Report Dow AgroSciences LLC DAS Report No.: 101864 (Accession Number): 2009568 GLP/GEP (Y/N): Y Published (Y/N): N	Y	DAS
KIIA 7.4.1/02	Yoder, R.N., Brackman, R., Jonas, N.	2012	Freundlich Isotherm Calculations for XDE-729 methyl Dow AgroSciences LLC DAS Report No.: 120834 (Accession Number): 2014025 GLP/GEP (Y/N): Y Published (Y/N): N	Y	DAS
KIIA 7.4.2/01 (KIIA 7.4.1/01)	Yoder, R.N., Smith, K.P., Adusumilli, H.	2011(Amended 2012)	,Batch Equilibrium Adsorption/Desorption of XDE-729 Methyl and Adsorption of its X11393729 and X11449757 Metabolites Amended Report Dow AgroSciences LLC DAS Report No.: 101864 (Accession Number): 2009568 GLP/GEP (Y/N): Y Published (Y/N): N	Y	DAS
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KIIA 7.6/01	Blakeslee, B.A., Balcer, J.L., Laughlin, L.A.	2011	Aqueous Photolysis of XDE-729 ME in pH 7 Buffer and Natural Water Under Xenon Light Dow AgroSciences LLC DAS Report No.: 101793 (Accession Number): 2009567 GLP/GEP (Y/N): Y Published (Y/N): N	Y	DAS
KIIA 7.6/01 (submitted under KIIA 8.6/09)	Hellstern, J.	2012	Determination of Photolysis Reaction of XDE 729 Methyl under Test Conditions used in a *Myriophyllum* Eurofins Agroscience Services EcoChem GmbH DAS Report No.: 120547, S12-01352 (Accession Number) 2014337 GLP/GEP (Y/N): Y Published (Y/N): N	Y	DAS
KIIA 7.7/01	Feil, N.	2011	Ready Biodegradability of X11393729 in an CO2 Headspace Test INSTITUT FUR Biologische Analytik und Consulting IBACON GmbH, DAS Report No.: 64421082 (Accession Number): 2009570 GLP/GEP (Y/N): Y Published (Y/N): N	Y	DAS
KIIA 7.8.3/01	Laughlin, L.A., Balcer, J. L	2011 (Amended report 2012)	Aerobic Transformation of XDE-729 Methyl in Two Aquatic Sediment Systems Amended Report Dow AgroSciences LLC DAS Report No.: 101741 (Accession Number): 2009206 GLP/GEP (Y/N): Y Published (Y/N): N	Y	DAS

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KIIA 7.8.3/02	Laughlin, L. A., Boulton, J., Jonas, N.	2012	Aerobic Transformation of XDE-729 Methyl in Two Aquatic Sediment Systems – Supplemental 30 Day Study Dow AgroSciences LLC DAS Report No.: 120872 (Accession Number): 2014428 GLP/GEP (Y/N): Y Published (Y/N): N	Y	DAS
KIIA 7.10/01	Wendelburg, B.M., Boulton, J.P.	2011	Estimation of the Photochemical Oxidation Rate of XDE-729 Dow AgroSciences LLC DAS Report No.: 101450 (Accession Number): 2008281 GLP/GEP (Y/N): Y Published (Y/N): N	Y	DAS

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KIIIA 9.2.3/01 (See KIIA 7.3.3/01)	Jackson, R.	2012a	Modelling the Potential Accumulation of Non-Extractable Residues of XDE-729 Methyl in Soil Dow AgroSciences DAS Report No.: GHE-P-12808 (Accession Number) 2014398 GLP/GEP (Y/N): N Published (Y/N): N	Y	DAS

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KIIIA 9.7/01	Jackson, R.	2012c	FOCUS Surface Water Modelling for XDE-729 Methyl and its Metabolites Following Use in Cereals Dow AgroSciences DAS Report No.: GHE-P-12807 (Accession Number) 2014429 GLP/GEP (Y/N): N Published (Y/N): N	Y	DAS
KIIIA 9.6/02	Jackson, R.	2013	FOCUS Ground Water Modelling for XDE-729 methyl and Its Acid Metabolite Using Soil Degradation Inputs from Filed Studies Dow AgroSciences DAS Report No.: GHE-P-12985 (Accession Number) 2019709 GLP/GEP (Y/N): N Published (Y/N): N	Y	DAS
KIIIA 9.7/02	Jackson, R.	2013	FOCUS Surface Water Modelling for XDE-729 methyl and Its Acid Metabolite Using Soil Degradation Inputs from Filed Studies Dow AgroSciences DAS Report No.: GHE-P-12984 (Accession Number) 2019708 GLP/GEP (Y/N): N Published (Y/N): N	Y	DAS

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