Data used for the revision of the guidance

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27 September 2017

efsa
European Food Safety Authority

BACKGROUND: INITIAL DATA SET

	ECPA	BfR
Number of studies	295	162 (316: vivo/vitro)
A.S.	152	114 (122: vivo/vitro)
Formulation types	19	23 (23: vivo/vitro)
Records	762	490 (480 met inclusion criteria)
Exposure time	6-10 h	6-24 h
Observation time	24 h	24 h

ECPA: single study type (human *in vitro*), created collecting data from 295 study reports, covering 152 agrochemical active substances (a.s.), 19 formulation types and large spray concentrations range. Study reports submitted.

BfR: *in vitro* (human and rat) and *in vivo* (rat) studies (in total 316 study types), only human *in vitro* DA extracted from the database to create the BfR dataset of 162 studies, covering 114 a.s., 23 formulation types tested at different concentrations, data collected from original study reports.

QUALITY/PLAUSIBILITY CHECK

- to validate the correctness of data entry in the datasets from sources (study reports) applying a two tiers (I and II) validation protocol
- to verify if new studies conducted according to the current regulatory standards (OECD TG 428, GLP)
- to identify potential deviations from EFSA guidance

for ECPA:

- tier I full **source data verification** (all parameters) for a limited number (17) of studies, randomly selected
- tier II selected key parameters were checked for 28 study reports
- parameters checked: mean and standard deviation (SD) of amount in receptor fluid, skin, tape strips, overall recovery

for BfR:

- tier I full **source data verification** (all parameters) for a limited number (5) of studies, randomly selected
- tier II selected key parameters were checked for 25 study reports
- parameters checked: mean and standard deviation (SD) of amount in receptor fluid, skin, tape strips, overall recovery

- addresses only data handling, not experimental error (minimised by guideline-compliance)

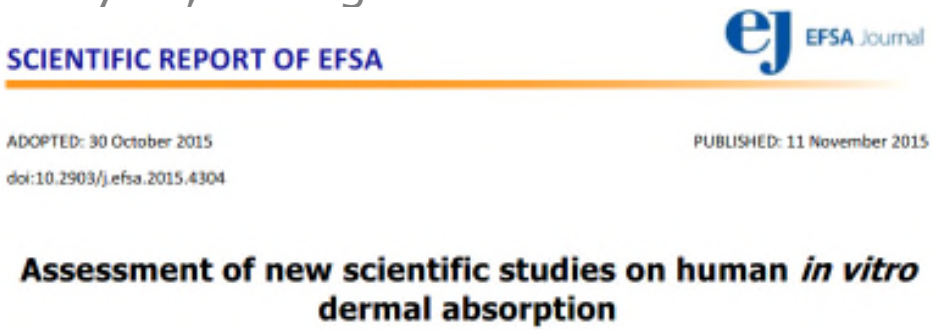
EVALUATION OF THE INITIAL DATA SET

CONCLUSIONS on initially submitted data

- relevant for the revision of the current/development of new guidance on dermal absorption
- acceptable in terms of quality (OECD TG428, GLP) but only means included (partly SD, Max)
- deviations from EFSA guidance (e.g. variability, no. replicates, recovery) noted
- more info may be needed to understand impact of formulation

RECOMMENDATIONS

- to complete the ECPA and BfR datasets by including missing entries and endpoints (t0.5), individual data, removal of duplicates and harmonisation of database structure
- to analyse dermal absorption data including a model-based statistical analysis, taking into account "all" the variables jointly


SCIENTIFIC REPORT OF EFSA

EFSA Journal

ADOPTED: 30 October 2015

PUBLISHED: 11 November 2015

doi:10.2903/j.efsa.2015.4304

Assessment of new scientific studies on human *in vitro* dermal absorption

EXAMPLES FOR TG/GD DEVIATIONS

≥ 95 % Recovery recommended by EFSA GD

- ECPA dataset: in 83.3% of records (every 6th record did not meet recovery criterion of EFSA Guidance)
- BfR dataset: in 68 % of records

< 25 % Relative Standard Deviation recommend by EFSA GD

- ECPA dataset:
  - not reported for 424/762 records (56%)
- BfR dataset:
  - reported for majority=426 records
  - RSD ≥ 25% in 78% of records!

TG428: results for relevant reference chemicals should be available and in agreement with published literature

- not provided in study reports checked

NEW DERMAL ABSORPTION DATA SET

- individual data submitted in 2016 by ECPA and BfR

	ECPA	BfR
Studies (GLP and OECD 428-compliant)	295	125
Active substances	152	94
Formulation types	19	23
Exposure time	6-10 h	6-24 h
Observation time	24 h	24 h
Records*	5,180	2,273

** Record: rows (individual values) with structured dermal absorption data from a.s. concentration tested in the experiment*

No. of studies: reduction from 162 to 125 for BfR resulting from removal of duplications between ECPA and BfR

Records: increase from 762 + 480 (ECPA + BfR) to 5,180 + 2,273 due to inclusion of individual data rather than study group means

QUALITY CONTROL APPROACH

- based on partial source data verification for initial data set
- comparison of means and (if available) SD values from new data set vs. initial data set for all study groups
- TIER I: cut-off = 15 % deviation -> triggering TIER II

for ECPA:

- 8 parameters
- either measured (non-absorbed, directly absorbed, whole skin, stratum corneum, tape strip 1&2, recovery) or calculated (t0.5, absorbed dose)
- = 6,080 data pairs evaluated

for BfR:

- 6 descriptors covering directly or indirectly 8 parameters
- either measured (directly absorbed dose, overall recovery), calculated (absorbed dose; t0.5) or complex (stratum corneum - tape strip 1&2, remaining skin + stratum corneum - tape strip 1&2)
- = 2,131 data pairs evaluated

QUALITY CONTROL RESULTS

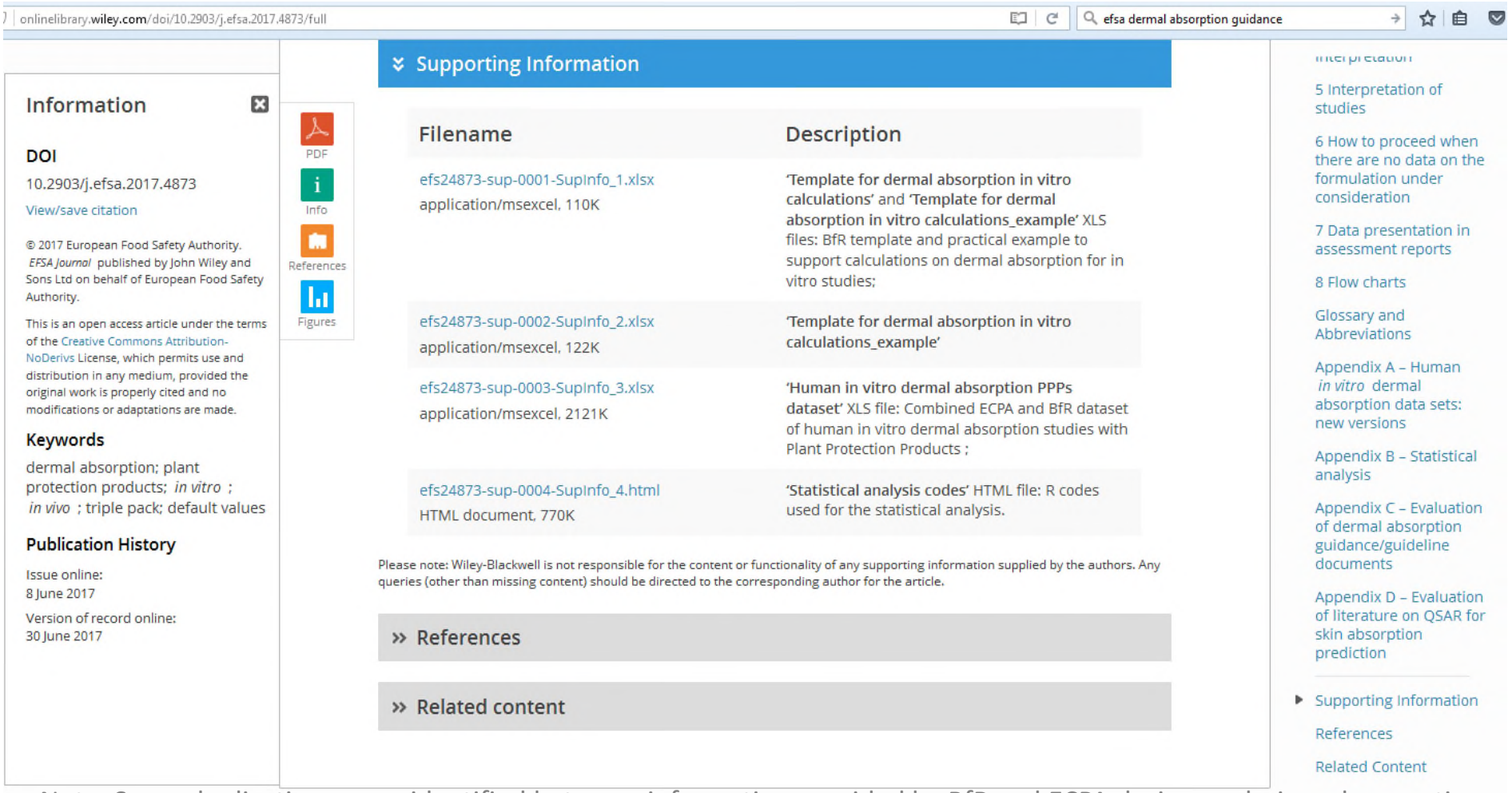
- for ECPA: 4.4 % initial findings (cut-off = 15 % deviation)
  - 1.2 % related to missing data in initial data set or calc. of t0.5
  - 2.3 % related to errors in initial data set
  - 0.9 % remaining findings cured by correcting data set using study report
  - records with recovery outside OECD criteria (90-110%) excluded, reducing record no. from 5,180 to 4,972

- for BfR: 11 % initial findings (cut-off = 15 % deviation)
  - 1.2 % related to rounding
  - 1.3 % related to calculation of t0.5, normalisation, non-detects
  - 6.1 % related to errors in initial data set
  - 2.5 % remaining findings cured by correcting data set
  - records with recovery outside OECD criteria (90-110%) excluded, reducing record no. from 2,273 to 2,258

- Note: mostly low absolute deviations, e.g. 0.03 vs. 0.02 %

CONTENT OF THE FINAL DATABASE

- Published as xls-file of EFSA website
  http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2017.4873/full



Note: Some duplications were identified between information provided by BfR and ECPA during analysis and respective records were removed from the published dataset.

CONTENT OF THE FINAL DATABASE

- The database contains proprietary information.
- The use of proprietary information for registration purposes in the EU should be in line with the data protection rules established under Art. 59 of Regulation (EC) 1107/2009.
- It is recommended that proprietary information included in this database would not be accepted to support any registration outside the EU for which the applicant has not demonstrated that it has regulatory access to the information.

CONTENT OF THE FINAL DATABASE

"Active substance name “

Data provider
Study identifier
Date study performed

Molecular Weight (g/Mol)
Log PO/W
Water solubility (mg/L)
Formulation type
Test preparation (spiking/radioformulation other)

Study design (static/flow-through) (st/fl)
Exposure duration (h)
Skin type (derm skin/epidermal membranes) (derm/epiderm)
Human Skin source (cadaver/surgical) (cad/surg)
Skin region (abdomen/breast/dorsum/leg) used PER CELL
No. of Donors (all donors) per concentration
No. of Donors per concentration after exclusion of cells
…

CONTENT OF THE FINAL DATABASE

…
Cell number (numbered or specific id from study report)
Donor id (numbered or specifc id from study report)
Donor sex (m/f)
Donor age (years)
No. of acceptable replicates per concentration
No. replicates for each donor per concentration
Replicate id (numbered)
Excluded from calculation (x for yes)
No. replicates for each donor per concentration after exclusion of cells
Receptor medium
Concentration Tested (g/L or g/kg)
Type of concentration tested (concentrate, dilution 1-3)
Applied Concentration (µg/cm2) PER CELL
Applied Concentration (µg/cm2) MEAN per tested concentration
…

CONTENT OF THE FINAL DATABASE

…
Non-Absorbed dose (swabs + donor rinse) (% of applied dose) PER CELL
Non-Absorbed dose (swabs + donor rinse) (% of applied dose) MEAN per tested concentration
Directly Absorbed dose (Receptor fluid including receptor rinse) (% of applied dose) PER CELL
Directly Absorbed dose (Receptor fluid including receptor rinse) (% of applied dose) MEAN per tested concentration
Directly Absorbed dose (Receptor fluid including receptor rinse) (% of applied dose) S.D. per tested concentration
Whole Skin dose including stratum corneum (% of applied dose) PER CELL
Whole Skin dose including stratum corneum (% of applied dose) MEAN per tested concentration
"Stratum corneum dose including all tapes (% of applied dose) PER CELL“
Stratum corneum dose including all tapes (% of applied dose) MEAN per tested concentration
Dose Tapes 1-2 (% of applied dose) PER CELL
Dose Tapes 1-2 (% of applied dose) MEAN per tested concentration
…

CONTENT OF THE FINAL DATABASE

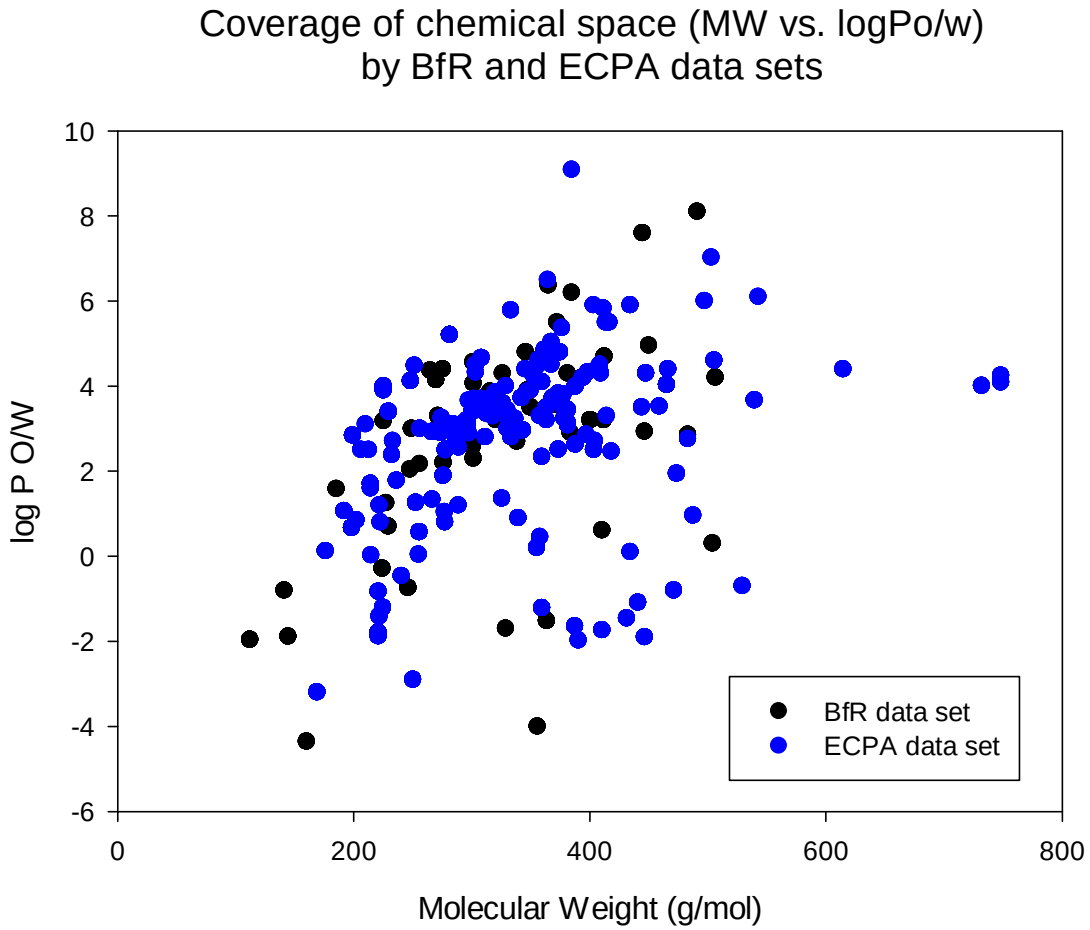
…
Overall Recovery (% of applied dose) PER CELL
Overall recovery (% of applied dose) MEAN per tested concentration
Overall recovery (% of applied dose) S.D. per tested concentration
%Absorption at T0.5 percentage in receptor fluid at 12h relative to 24h PER CELL
%Absorption at T0.5 percentage in receptor fluid at 12h relative to 24h MEAN per tested concentration
%Absorption at T0.5 at sample time point (10 or 12 h)
Remark
Absorbed (directly absorbed+whole skin- TS1/2) PER CELL
"Absorbed (directly absorbed+whole skin- TS1/2) MEAN per tested concentration"

RATIONALE FOR COMBINING DATASETS

- N in data base should be as large as possible
- origin should be as broad as possible but relevant
  - combination what (some) industry measured
  - (one) authority received from various sources (n=37, now partly merged companies)
- extend the chemical space covered
  - with regard to active substance and
  - formulation

-> aim for representativeness (to the largest extent possible)

"CHEMICAL SPACE" COVERED



FORMULATION SPACE

- Group 1: Primarily organic solvent based (158)

code	description	N
EC	Emulsifiable concentrate	90
DC	Dispersible concentrate	1
EW	Emulsion O/W	15
SE	Supso-emulsion	29
OL/OF	Oil-miscible liquid	1
OD	Oil based SC	18
ES	Emulsion for seed treatment	1
ME	microemulsion	3

- for further detail rf. to table B.2 / Annex B chapter 3 of the revised guidance

FORMULATION SPACE

- Group 2: Primarily water-based / dispersed (161)

code	description	N
SL	Soluble concentrate	21
SC	Suspension concentrate	121
FS	FL for seed treatment	18
FL	Flowable	1

- Group 3: Solid (77)

code	description	N
WP	Wettable powder	12
W(D)G	Water-disperible granules	57
SG	Water-soluble granules	5
SP	Water-soluble powder	2
DS	Powder for dry seed treat	1

FORMULATION SPACE

- Group 4: Other (22)

code	description	N
CB	Bait concentrate	1
CS	Capsule suspension	6
GEL	GD, gel for direct application	1
RB	Bait, pellets, wax block, pasta	6
ZC	CS / SC mixture	3
PS	Seed coated with pesticide	1
AI	Actice ingredient exp. solution	4

- XX/NA (6) with no information on formulation were excluded from statistical analysis

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ADDITIONAL SLIDES

RECOVERY IN THE DATASET