Renewal Assessment Report

Dimethenamid-P

BAS 656 12 H

Volume 3 – B.6 Toxicology and metabolism data and assessment of risks for humans

Rev. 0 - 10 August 2016

Rapporteur Member State: Germany

Co-Rapporteur Member State: Bulgaria

Version history

When	What
10 August 2016	First version submitted to EFSA

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B Summary, evaluation and assessment of the data and information

B.6 Toxicology and metabolism data and assessment of risks for humans

This document reviews the toxicological studies and human exposure for the plant protection product BAS 656 12 H containing the active substance dimethenamid-P (720 g/L) formulated as an emulsifiable concentrate.
BAS 656 12 H was not the representative formulation during the first EU peer review of dimethenamid-P, where a similar product (BAS 656 07 H) was evaluated instead.

B.6.1 Acute toxicity of plant protection product

The studies on acute oral and acute dermal toxicity as well as on irritation and skin sensitisation were conducted with BAS 656 08 H; the study on acute inhalation toxicity was conducted with BAS 656 07 H and was already evaluated for Annex I inclusion of dimethenamid-P. The tested formulations contain the same amount of dimethenamid-P (720 g/L) and the same/similar co-formulants like BAS 656 12 H (see Vol. 4 for a comparison of the formulations); thus, the study results are considered to be applicable to BAS 656 12 H as well. A summary of the toxicological evaluation for BAS 656 12 H is given in Table B.6.1-1. The individual studies are presented under B.6.1.1 to B.6.1.6.

Table B.6.1-1: Summary of evaluation of the studies on acute toxicity including irritancy and skin sensitisation for BAS 656 12 H

Type of test, model system (Guideline)	Result	Acceptability	Classification (acc. to the criteria in Dir. 67/548/EEC)	Classification (acc. to the criteria in Reg. 1272/2008)	Reference
LD_{50} oral, rat (OECD 423)	>500 mg/kg bw and <2000 mg/kg bw	Yes	R22	H302	[redacted]., 2006a, ASB2008-8109
LD_{50} dermal, rat (OECD 402)	>5000 mg/kg bw	Yes	None	None	[redacted], 2006b, ASB2008-8110
LC_{50} inhalation, rat (OECD 403)	>5.6 mg/L air	Yes	R37	H335	[redacted], 1998, TOX1999-472
Skin irritation, rabbit (OECD 404)	Irritant	Yes	R38	H315	[redacted], 2006, ASB2008-8111
Eye irritation, rabbit (OECD 405)	Irritant	Yes	R36	H319	[redacted], 2000, TOX2003-84, ASB2003-84
Skin sensitisation, guinea pig (OECD 406, 9 x Buehler)	Sensitising	Yes	R43	H317	[redacted]., 2006c, ASB2008-8114

Based on the results for BAS 656 08 H and BAS 656 07 H, BAS 656 12 H is considered to be of moderate acute oral toxicity (Xn, R22; Cat. 4, H302) and of very low acute dermal and inhalation toxicity. The formulation is a skin irritant (Xi, R38; Cat. 2, H315), eye irritant (Xi, R36; Cat. 2, H319) and, with respect to observations in the acute inhalation toxicity study, also a respiratory irritant (Xi; R37; Cat. 3, H335). Classification of BAS 656 12 H as skin sensitiser (Xi, R43; Cat. 1, H317) is warranted.

B.6.1.1 Oral toxicity

Reference: 7.1.1
Report: BAS 656 08 H: Acute oral toxicity study in rats, [redacted] 2006a, 2006/1026825, ASB2008-8109
Guideline(s): OECD 423 (2001), 2004/73/EEC B.1, EPA OPPTS 870.1100
Deviations: No
GLP: Yes
Acceptability: Yes

Materials and methods

Test material (Lot/Batch No.)	BAS 656 08 H (Batch No.2014)
Species	Rat, Wistar, HanRcc:WIST(SPF)
No. of animals (group size)	3 x 3 females (nulliparous and non-pregnant)
Dose(s)	500 and 2000 mg/kg bw
Exposure	Once by gavage
Vehicle/Dilution	Double-distilled water
Post exposure observation period	14 days
Remarks	None

Results and discussions

Table B.6.1-2: Results of acute oral toxicity study in rats of BAS 656 08 H

Dose [mg/kg bw]	Toxicological results[1)]	Duration of signs	Time of death	LD_{50} [mg/kg bw] (14 days)
Female rats				
500	0/3/3	day 1	--	>500
500	0/3/3	day 1	--	>500
2000	3/3/3	day 1	day 1	<2000

1) Number of animals which died/number of animals with clinical signs/number of animals used

Table B.6.1-3: Summary of findings of acute oral toxicity study in rats of BAS 656 08 H

Mortality:	All animals of the 2000 mg/kg bw administration group were found dead on hour 4 or on study day 1.
Clinical signs:	Clinical observation in the 2000 mg/kg bw administration group revealed impaired and poor general state, dyspnoea, staggering, tremor, twitching, piloerection and salivation and were observed from hour 0 through to hour 5 after administration. In the 500 mg/kg administration groups impaired general state, dyspnoea, staggering, piloerection, salivation and lacrimation were observed from hour 0 through to hour 4 after administration.
Body weight:	The mean body weight of the first 500 mg/kg bw administration group increased throughout the study period. The mean body weight of the second 500 mg/kg bw administration group increased during the first post-exposure observation week but did not adequately increase during the second week.
Macroscopic examination:	The necropsies performed at the end of the study revealed no apparent findings.

Conclusion

Under the experimental conditions, the oral LD_{50} of BAS 656 08 H is >500 and <2000 mg/kg bw in rats. Thus, classification is required as Xn; R22 according to the classification criteria of Council Directive 67/548/EEC and subsequent regulations and as Cat. 4; H302 according to Regulation (EC) No. 1272/2008.

B.6.1.2 Dermal toxicity

Reference: 7.1.2
Report: BAS 656 08 H: Acute dermal toxicity study in rats, [redacted], 2006b, 2006/1026826, ASB2008-8110
Guideline(s): OECD 402, 92/69/EEC B.3, EPA OPPTS 870.1200
Deviations: No
GLP: Yes
Acceptability: Yes

Materials and methods

Test material (Lot/Batch No.)	BAS 656 08 H (Batch No. 2014)
Species	Rat, Wistar HanRcc:WIST(SPF)
No. of animals (group size)	5 males and 5 females (nulliparous and non-pregnant)
Dose(s)	5000 mg/kg bw
Exposure	24 hours (dermal, semi-occlusive)
Vehicle/Dilution	None
Post exposure observation period	14 days
Remarks	None

Results and discussions

Table B.6.1-4: Results of acute dermal toxicity study in rats of BAS 656 08 H

Dose [mg/kg bw]	Toxicological results[1)]	Duration of signs	Time of death	LD_{50} [mg/kg bw] (14 days)
Male rats				
5000	0/0/5	--	--	>5000
Female rats				
5000	0/0/5	--	--	>5000

[1)] Number of animals which died/number of animals with clinical signs/number of animals used

Table B.6.1-5: Summary of findings of acute dermal toxicity study in rats of BAS 656 08 H

Mortality:	No mortality occurred.
Clinical signs:	No clinical signs of toxicity were observed.
Body weight:	The mean body weights of the male animals increased throughout the study period. The mean body weight of the females did not adequately increase during the first post-exposure observation week, probably due to the bandage procedure, but increased during the second week.
Macroscopic examination:	The necropsies performed at the end of the study revealed no apparent findings.

Conclusion

Under the experimental conditions, the dermal LD_{50} of BAS 656 08 H is higher than 5000 mg/kg bw in rats. Thus, no classification is required according to the classification criteria of Council Directive 67/548/EEC and subsequent regulations as well as according to Regulation (EC) No. 1272/2008.

B.6.1.3 Inhalation toxicity

Reference: 7.1.3
Report: BAS 656 07 H – Acute inhalation toxicity study in Wistar rats, [redacted]., 1998, 33/10838, TOX1999-472
Guideline(s): OECD 403, 92/69/EEC and 93/21/EEC, EPA/FIFRA 81-3
Deviations: No
GLP: Yes
Acceptability: Yes

Materials and methods

Test material (Lot/Batch No.)	BAS 656 07 H (Batch No. 98001)
Species	Rat, SPF Wistar / Chbb:THOM
No. of animals (group size)	5 rats/sex/dose (females: nulliparous, non-pregnant)
Concentration(s)	5.6 mg/L
Exposure	4 hours (nose only)
Vehicle/Dilution	None
Post exposure observation period	14 days
Remarks	None

Results and discussions

Table B.6.1-6: Concentration(s) and exposure conditions

Nominal conc. [mg/L air]	Actual conc. [mg/L air]	MMAD[1)] [µm]	GSD[2)] [µm]
25.7	5.6	0.93-0.94	3.9-3.8

1) MMAD = Mass Median Aerodynamic Diameter
2) GSD = Geometric Standard Deviation

Table B.6.1-7: Results of acute inhalation toxicity study in rats of BAS 656 07 H

Concentration [mg/L air]	Toxicological results [1)]	Duration of signs	Time of death	LC_{50} [mg/L air] (14 days)
Male rats				
5.6	0/5/5	day 0 - day 7	-	>5.6 mg/L
Female rats				
5.6	0/5/5	day 0 - day 7	-	>5.6 mg/L

1) Number of animals which died/number of animals with clinical signs/number of animals used

Table B.6.1-8: Summary of findings of acute inhalation toxicity study in rats of BAS 656 07 H

Mortality:	No mortality occurred.
Clinical signs:	Clinical examination revealed attempts to escape, irregular and accelerated respiration, respiratory sounds as well as squatting posture, smeared fur and piloerection. No clinical signs could be detected from post exposure day 7 onward.
Body weight:	Body weight development was depressed in the first post exposure week but recovered in the second.
Macroscopic examination:	During necropsy grey red discoloration of the lungs was found in the animals. Histopathological examination was performed on the lungs of 2 animals, which revealed acute congestion, slight alveolar edema, slight diffuse alveolar histiocytosis and slight multifocal perivascular infiltration of eosinophils (one animal only).

Conclusion

Under the experimental conditions, the inhalation LC_{50} of BAS 656 07 H is higher than 5.6 mg/L air in rats. Thus, regarding acute inhalation toxicity no classification is required for BAS 656 08 H according to the classification criteria of Council Directive 67/548/EEC and subsequent regulations as well as according to Regulation (EC) No. 1272/2008. However, the histopathological findings indicate that BAS 656 07 H and BAS 656 08 H are irritating to the respiratory system (R37; H335) which is supported by the classification of BAS 656 08 H as skin and eye irritant (see B.6.1.4 and B.6.1.5).

B.6.1.4 Skin irritation

Reference: 7.1.4
Report: BAS 656 08 H: Acute dermal irritation/corrosion in rabbits, [redacted]., 2006, 2006/1026827, ASB2008-8111
Guideline(s): OECD 404 (2002), 2004/73/EEC B.4, EPA OPPTS 870.2500 (1998), JMAFF (2000)
Deviations: No
GLP: Yes
Acceptability: Yes

Materials and methods

Test material (Lot/Batch No.)	BAS 656 08 H (Batch No. 2014)
Species	Rabbit, New Zealand White A1007 INRA (SPF)
No. of animals (group size)	2 males and 1 female
Initial test using one animal	No
Exposure	0.5 mL (4 hours, semi-occlusive)
Vehicle/Dilution	None
Post exposure observation period	14 days
Remarks	None

Results and discussions

Table B.6.1-9: Skin irritation of BAS 656 08 H

Animal No.		Scores after treatment[1)]				Mean scores (24-72 h)	Reversible [day]
		1 h	24 h	48 h	72 h		
1 (male)	Erythema Oedema	2 0	2 1	2 0	2 0	2.0 0.3	>14 2
2 (female)	Erythema Oedema	2 0	2 0	2 0	2 0	2.0 0.0	>14 -
3 (male)	Erythema Oedema	2 0	2 0	1 0	1 0	1.3 0.0	7 -

[1)] scores in the range of 0 to 4

Clinical signs:	None

Conclusion

Under the experimental conditions, BAS 656 08 H is a skin irritant with respect to the persistency of the inflammation. Thus, classification is required as Xi; R38 according to the classification criteria of Council Directive 67/548/EEC and subsequent regulations and as Cat. 2; H315 according to Regulation (EC) No. 1272/2008.

B.6.1.5 Eye irritation

Reference: 7.1.5
Report: BAS 656 08 H: Acute eye irritation in rabbits, [redacted] 2000, 2000/1012350, TOX2003-84
Guideline(s): OECD 405 (1987), 92/69/EEC B 5, EPA OPPTS 870.2400
Deviations: No
GLP: Yes
Acceptability: Yes

Materials and methods

Test material (Lot/Batch No.)	BAS 656 08 H (Batch No. AF 461-57)
Species	Rabbit, New Zealand White , Hsdlf: NZW
No. of animals (group size)	3 females
Initial test using one animal	Yes
Exposure	0.1 mL (single instillation into conjunctival sac)
Irrigation (time point)	Yes (after 24 hours with tap water)
Vehicle/Dilution	None
Post exposure observation period	21 days
Remarks	None

Results and discussions

Table B.6.1-10: Eye irritation of BAS 656 08 H

Animal No.		Scores after treatment[1)]				Mean scores (24-72 h)	Reversible [day]
		1 h	24 h	48 h	72 h		
1	Corneal opacity	0	0	1	1	0.7	14
	Iritis	0	1	1	1	1.0	7
	Redness conjunctivae	2	3	3	3	3.0	14
	Chemosis conjunctivae	2	2	2	1	1.7	7
2	Corneal opacity	0	0	0	0	0.0	-
	Iritis	0	0	0	0	0.0	-
	Redness conjunctivae	2	3	3	2	2.7	14
	Chemosis conjunctivae	2	2	1	1	1.3	7
3	Corneal opacity	0	1	1	1	1.0	14
	Iritis	0	0	0	0	0.0	-
	Redness conjunctivae	2	3	3	3	3.0	21
	Chemosis conjunctivae	2	2	2	2	2.0	14

[1)] scores in the range of 0 to 4 for cornea opacity and chemosis, 0 to 3 for redness of conjunctivae and 0 to 3 for iritis

Clinical signs:	None

Conclusion

Under the experimental conditions, BAS 656 08 H is an eye irritant. Thus, classification is required as Xi; R36 according to the classification criteria of Council Directive 67/548/EEC and subsequent regulations and as Cat. 2; H319 according to Regulation (EC) No. 1272/2008.

B.6.1.6 Skin sensitisation

Reference: 7.1.6
Report: BAS 656 08 H: Modified BUEHLER test (9 inductions) in guinea pigs, [redacted], 2006c, 2006/1026828, ASB2008-8114
Guideline(s): OECD 406 (1992), 96/54/ EEC B.6, EPA OPPTS 870.2600, JMAFF
Deviations: No
GLP: Yes
Acceptability: Yes

Materials and methods

Test material (Lot/Batch No.)	BAS 656 08 H (Batch No. 2014)
Species	Guinea pig, Hartley albino, HsdPoc: DH
No. of animals (group size)	Test substance group: 20 female guinea pigs Vehicle control goup: 10 female guinea pigs
Range finding:	Yes
Exposure (concentration(s), no. of applications)	Topical induction: Undiluted (9 x) Challenge: Undiluted
Vehicle	None
Pretreatment prior to topical application	No
Reliability check	Alpha-hexylcinnamaldehyde (5 % intradermal induction, 10 % topical induction and 5 % challenge)
Remarks	Due to cumulative skin irritation, the test patch was moved to the middle of the flank in some animals for the eighth and ninth induction.

Results and discussions

Table B.6.1-11: Skin sensitisation of BAS 656 08 H

	24 hours	**48 hours**
	After challenge	
BAS 656 08 H	11[1]/20	4[1]/20
Test Vehicle Control Group	0[1]/10	0[1]/10
Positive control	10[1]/10	9[1]/10

1) Number of animals with positive dermal response (scores of 1-3)/number of animals in dose group

Clinical signs:	None

Conclusion

Under the experimental conditions, BAS 656 08 H is a skin sensitiser. Thus, classification is required as Xi; R43 according to the classification criteria of Council Directive 67/548/EEC and subsequent regulations and as Cat. 1; H317 according to Regulation (EC) No. 1272/2008.

B.6.1.7 Supplementary studies on the plant protection product

No supplementary studies on the plant protection product were conducted.

B.6.1.8 Supplementary studies for combinations of plant protection products

No studies for combinations of BAS 656 12 H with other plant protection products were conducted.

B.6.2 Dermal absorption

Studies submitted with the dossier for the Renewal Assessment Report:

Data point:	IIA 5.4.1
Report:	Fabian E., Landsiedel R., 2013a (ASB2014-3668) ^{14}C-BAS 656 PH in BAS 656 12 H - Study of penetration through human skin *in vitro* 2013/1184803 BASF SE, Experimental Toxicology and Ecology, 67056 Ludwigshafen, Germany (Experimental work from February 2013 – 15 March 2013)
Guideline(s):	OECD Guideline for testing of chemicals No. 428 (Skin absorption: *In vitro* method (2004)), OECD Guidance Document No. 28 for the conduct of skin absorption studies (March 2004)
Deviations:	No relevant deviations
GLP:	Yes (certified by Landesamt fuer Umwelt, Wasserwirtschaft und Gewerbeaufsicht, Mainz, Germany)
Acceptability:	The study is considered to be acceptable.

Materials and methods:

Test Material:	a) ^{14}C-BAS 656 PH b) BAS 656 12 H (formulated BAS 656-PH) c) BAS 656-PH (dimethenamid-P)
Lot/Batch #:	a) 824-7023 b) 0004701751 c) L74-120
Purity:	a) radiochemical purity: >98 %; specific activity: 7.64 MBq/mg b) Content: 707.8 g dimethenamid-p per litre c) 96.5 %
Stability of test compound:	a) The stability of the test article was confirmed by HPLC analysis prior to and after the study. b) The test article is stable in the formulation; the expiry date of the formulation was Feb 2014. c) Stability guaranteed until July 01, 2016.
Vehicle:	Tap water
Skin preparations:	
Source:	BIOPREDIC International, Saint-Grégoire, France.
Preparation:	Dermatomed human skin membranes with a thickness of 250 - 400 µm were supplied frozen.
Storage of skin samples:	On receipt dermatomed skin samples were vacuum-wrapped, labelled appropriately and stored frozen at –20 °C until use.
Reagents:	
Receptor fluid:	Ultrapure water with about 5 % bovine serum albumin
Extraction media:	Soluene®-350, ethanol, 90 % ethanol solution in tap water
Washing solution:	Texapon® N 70 (sodium-laurylsulfate), 1:140 w/w in bi-distilled water

Study design and methods
The study was conducted at BASF Aktiengesellschaft, Experimental Toxicology and Ecology, 67056 Ludwigshafen, Germany
Test dates: 05-Feb-2013 – 15-Mar-2013

Study design:
Radiolabelled dimethenamid-P (^{14}C-BAS 656 PH (Batch 824-7023, Radiochemical purity >98 %, Specific activity 7.64 MBq/mg)) and the organic solvent based EC formulation BAS 656 12 H (Batch 0004701751; dimethenamid-P content: 707.8.1 g/L) were used to prepare a homogenously radiolabelled BAS 656 12 H formulation concentrate by spiking appropriate amounts of radioactive dimethenamid-P to the non-radioactive formulation. The 1:200 (3.6 g/L) and 1:1000 (0.72 g/L) spray dilutions were prepared accordingly, however tap water was added to obtain the 1:200 and 1:100 dilutions, respectively.
The penetration of dimethenamid-P formulated as BAS 656 12 H through human skin was determined using a modified Franz cell under static conditions equipped with dermatomed human skin at a thickness of 250 - 400 µm. Skin from 6 donors was used in this study. Eight cells each for the formulation concentrate, the 1:200 dilution and 1:1000 dilution were used. For the high and low dose, one cell each was not included in statistics due to invalid recovery and another cell each was not included in statistics due to aberrant first skin wash. For the mid dose, one cell was not included in statistics due to invalid recovery. Each cell was loaded with 10 µL of dosing solutions. Target and actual application rates are given in Table B.6.2-1. The test was performed under semi-occlusive conditions. In order to guarantee sufficient solubility of dimethenamid-P in the receptor fluid, ultrapure water with about 5 % bovine serum albumin was used as the receptor fluid for all dose groups. After 8 hours the skin surface was washed twice using approximately 250 µL Texapon® N70 diluted 1:140 (w/w) in tap water and once about 250 µL tap water. The skin was then wiped dry using cotton swabs. Thereafter the semi-occlusive cover of the cells was renewed and the penetration experiment continued for another 16 hours. Samples of the receptor fluid were withdrawn 1, 2, 4, 6, 8, 12 and 24 hours after application. The removed volume was replaced by fresh receptor fluid. After the last sampling of receptor fluid, the contents of the individual receptor compartments was sampled and - like the receptor fluid samples taken during the course of the experiment - retained for analysis. The total volume of receptor medium was 8.2 mL (4 mL receptor chamber + 4.2 mL sampled and subsequently replaced volume). The diffusion cells were dismantled and all parts were extracted. The skin was removed and washed a second time. As before, the cotton swabs and the washing solutions were retained for analysis. After the skin surface had dried, the stratum corneum was removed by tape stripping using Scotch Crystal Clear Tape 600. The tapes were pooled into two samples (first 2 tapes and the remaining 4 tapes) for analysis. The remaining skin and the tape strips were analysed separately.

Results and discussions:

The stability, homogeneity and content of dimethenamid-P in the application medium were confirmed by analysis. Details are available in the raw-data.
The applied doses and the number of usable human skin samples per dose group are given in Table B.6.2-1 together with the mean recoveries, which were 103.30 %, 96.71 % and 96.27 % for the high, mid and low dose level, respectively.

Table B.6.2-1: *In-vitro* dermal penetration of dimethenamid-P formulated as BAS 656 12 H through human skin - Recovery data

Dose group		High dose (Formulation concentrate)		Mid dose (Spray dilution 1:200)		Low dose (Spray dilution 1:1000)	
Target concentration	[mg/mL]	720		3.6		0.72	
Target dose	[µg/cm²]	7200		36		7.2	
Mean actual applied dose	[µg/cm²]	6496		34		7.8	
Number of cells used/Valid cells		8/6		8/7		8/7	
		Recovery [%]		Recovery [%]		Recovery [%]	
		Mean	S.D.	Mean	S.D.	Mean	S.D.
Unabsorbed dose							
Skin washing after 8 hours		103.08	5.84	71.54	19.26	70.61	9.38
Skin washing after 24 hours		0.02	0.04	0.58	0.54	0.84	0.46
Donor chamber		0.03	0.06	1.05	1.11	2.96	1.60
Dose associated to skin							
Tape strips: 1st sample, strips 1 + 2		0.00	0.00	0.06	0.10	0.02	0.04
Tape strips: 2nd sample; strips 3 - 6		0.00	0.00	0.09	0.13	0.00	0.00
Skin preparation		0.01	0.02	0.78	0.78	0.33	0.26
Absorbed dose							
Sum receptor samples incl. wash out		0.06	0.07	9.36	5.99	9.04	3.36
Receptor fluid		0.10	0.08	5.77	3.68	5.27	1.94
Receptor chamber wash		0.02	0.02	7.48	5.64	7.21	3.49
Total recovery#		103.30	5.82	96.71	3.98	96.27	3.18
Absorption essentially complete at end of study (>75 % absorption within half the study duration)		Yes		Yes		Yes	
Absorption estimates when absorption not essentially completed (= absorbed dose + dose associated to skin + tape strips sample 2)[a]		NA		NA		NA	
Absorption estimates when absorption essentially completed (= absorbed dose + dose associated to skin)		0.18	0.18	23.40	15.84	21.85	8.80
Absorption estimate normalised[b]		NA		NA		NA	
Dermal absorption rate[c]		0.4		39		31	

values may not calculate exactly due to rounding of figures

a Grouping is different than in the report: In accordance with the EFSA Guidance on Dermal Absorption (EFSA Journal 2012;10(4):2665) the radioactivity in the second tape-strip pool (3rd to 6th tape strip) is considered potentially absorbable if less than 75 % of the absorption occurred in the first half of the study (see Table B.7.6.2-1). Finally, the skin preparation is also considered potentially absorbable.

b Cells with insufficient recovery (<95 %) were corrected by normalisation of absorption estimate to 100 % recovery

c In accordance with the EFSA Guidance on Dermal Absorption (EFSA Journal 2012;10(4):2665) one standard deviation was added to the mean % dermal penetration in cases where the standard deviation was ≥25 % of the mean value. This value was then rounded to the required number of significant figures.

NA: not applicable

The mean total recovery was 103.3, 96.71 and 97.27 % for the high (720 g/L), mid (3.6 g/L) and low dose (0.72 g/L), respectively (see Table B.6.2-1). Accordingly, as group mean total recovery for all dose groups was >95 %, no adjustment of the dermal penetration values was necessary. The individual recovery was in the range of 90.26 - 109.86 %. In detail, the individual recovery at the high dose was mostly above 100 % with no cell below 95 %. In the mid and low dose each one cell was below 95 % (90.54 and 90.26 %, respectively). As the dermal penetration estimates of the cells with less than 95 % recovery were well within the range of the cells with greater than 95 % recovery (mid dose: 36.10 % vs. 3.89 - 42.75 %, low dose: 21.17 % vs. 15.07 - 39.34 %), no adjustment of individual cell values was considered to be justified.

A large inter-membrane variability which was partly attributed to inter-donor variability was noted in particular in the mid and low dose. Skin preparations of donor TRA2842 that were used in the mid and the low dose group resulted consistently in the highest absorption values although the integrity tests for these preparations passed the validity criteria and were comparable to the data of skin preparations of other donors. For all dose groups the standard deviations of the absorption estimates were >25 % of the means. Accordingly, one standard deviation was added to the mean absorption estimate. When rounded to the requested number of significant digits, dermal absorption estimates of 0.4, 39 and 31 % were determined for the formulation concentrate, the 1:200 and 1:1000 spray dilutions, respectively.

The total amount of dimethenamid-P recovered in the receptor media after 24 hours was 11.31, 7.78 and 1.68 µg for the formulation concentrate, the 1:200 and 1:1000 spray dilutions, respectively. When compared to the maximum solubilisation capacity 1400 µg/mL i.e. 11480 µg in the total receptor medium volume of 8.2 mL the solubility in the receptor media was 1015, 1476 and 6833 fold higher than actually needed for the formulation concentrate, the 1:200 and 1:1000 spray dilutions, respectively. Even if the receptor chamber volume of 4 mL is considered only, the solubility was at least 495-fold higher than actually needed.

The absorbed dose after 24 hours was determined to be 0.17 % ± 0.17, 22.61 % ± 15.30 and 21.53 % ± 8.7 for the formulation concentrate and the 1:200 and 1:1000 aqueous spray dilutions, respectively. There was no dose-response relationship for absorption from the spray-dilutes. The differences noted were due to inter-membrane variability only. For the mid and the low dose group, about 70 % of the absorbed dose were recovered in the receptor fluid. This limited recovery of the absorbed dose in the receptor fluid is based on relatively high amounts of the test substance that were associated with the receptor chamber. Binding to surfaces of e.g. vessels is a property of dimethenamid-P that is linked to its physical/chemical properties. This test substance behaviour was aimed to be minimised by adding BSA to the receptor fluid. However it was not possible to avoid the binding of dimethenamid-P to the receptor chamber completely.

In all three dose groups absorption was essentially complete as already after 12 hours 84, 99 or 98 % of the total penetrated radioactivity, respectively, was recovered in the receptor media (see Table B.6.2-2). Accordingly, neither the first two nor the following four tape strips were added to the absorption estimate.

Table B.6.2-2: *In-vitro* dermal penetration of dimethenamid-P formulated as BAS 656 12 H through human skin - Penetration kinetics

Dose group	**High dose**		**Mid dose**		**Low dose**	
	(Formulation concentrate)		**(Spray dilution 1:200)**		**(Spray dilution 1:1000)**	
Target concentration [mg/mL]	720		3.6		0.72	
Target dose [µg/cm²]	7200		36		7.2	
Mean actual applied dose [µg/cm²]	6496		34		7.8	
Number of cells used/Valid cells	8/6		8/7		8/7	
	Mean cumulative absorption		Mean cumulative absorption		Mean cumulative absorption	
	[µg]	[%]	[µg]	[%]	[µg]	[%]
Sample time [h]						
1	0.00	0.00	1.01	2.93	0.28	3.58
2	0.00	0.00	3.39	9.83	0.79	10.16
4	0.30	0.00	4.40	12.79	0.97	12.48
6	1.81	0.03	4.66	13.54	1.04	13.34
8	3.78	0.06	4.96	14.43	1.08	13.89
12	5.47	0.08	5.22	15.16	1.11	14.21
24	6.45	0.10	5.28	15.34	1.13	14.50
Kp [*10^{-5} cm/h]	0.29		67.30		64.19	
Absorption rate [µg/cm^2·h]	2.03		2.37		0.51	
Lag time [h]	4.61		0.63		0.50	
% absorbed within 12 hours	84 %		99 %		98 %	

Evaluation according to Guidance on Dermal Absorption (EFSA Journal 2012;10(4):2665), Consideration of stratum corneum and application site residues *in vitro*:

- Is study duration up to 24 hours? Yes
- Did >=75 % of the absorption occur in the first half of the study?
  Concentrate: Yes
  Spray dilution 1: Yes
  Spray dilution 2: Yes

→ Exclude all tape strips from absorption calculation →
Dermal absorption =
% in receptor fluid + % in receptor chamber wash + % in skin sample (excluding all tape strips)

→ Concentrate: 0.18 + 0.18 SD % = 0.36 %
→ Spray dilution 1: 23.40 + 15.84 SD % = 39.24 %
→ Spray dilution 2: 21.85 + 8.80 SD % = 30.65 %

Conclusion:

A slow to moderate penetration of dimethenamid-P formulated as BAS 656 12 H through human

dermatomed skin was observed *in vitro*. The estimated dermal absorption within 24 hours was determined to be 0.18 ± 0.18 %, 23.40 ± 15.84 % and 21.85 ± 8.80 % for the formulation concentrate and the 1:200 and 1:1000 aqueous spray dilutions, respectively. The dermal penetration rates were calculated to be 0.4, 39 and 31 % for the formulation concentrate (720 g/L) and the 3.6 g/L and 0.72 g/L aqueous spray dilutions, respectively.

Data point:	IIA 5.4.1
Report:	[redacted] 1999 (TOX1999-411) ^{14}C-R,S-Dimethenamid and ^{14}C-S-Dimethenamid - Study of the dermal Absorption in Rats BASF Doc ID 1999/10283 [redacted]
Guideline(s):	See below
Deviations:	See below
GLP:	No
Acceptability:	The study is considered to be not acceptable.

Materials and methods:

Test Material:	^{14}C-R,S-dimethenamid and ^{14}C-S-dimethenamid BAS 656 07 H
Lot/Batch #:	Not reported
Purity:	Not reported
Stability of test compound:	Not reported

Study design and methods:
The study investigated the absorption, distribution and excretion of radiolabelled products after single dermal administration of ^{14}C-R,S-dimethenamid and ^{14}C-S-dimethenamid diluted in the neat solvent of a commercial formulation.
Groups of four male Wistar rats were dermally treated with ^{14}C-R,S-dimethenamid at dose levels of 0.004, 0.04 and 0.4 mg/cm^2. The treated skin area was 10 cm^2. The dose regimen was as follows:

Table B.6.2-3: Dose regimen – sacrifice time and number of animals

Duration of exposure [h]	**4**	**8**		
Sacrifice after [h]	4	8	24	72
Number of animals	4	4	4	4

For ^{14}C-S-dimethenamid, the dose regimen was as follows:

Table B.6.2-4: Dose regimen – dose, duration of exposure, sacrifice time and number of animals

Dose [mg/cm^2]	**Duration of exposure [h]**	**Sacrifice after [h]**	**Number of animals**
0.004	8	72	4
0.04	8	72	4
0.4	8	72	4

After dosing, animals were placed in metabolism cages in order to collect excreta up to 72 hours. After the respective exposure period, the protective cover was removed and the exposed skin was washed with a mild soap solution. At the end of the various collection periods, animals were sacrificed and the following specimens/tissues checked for radioactivity:

> excreta, bloodcells, plasma, liver, kidneys, carcass, skin [treated (= application site) and surrounding skin)], cage wash, skin wash, protective cover.

The total amount of test compound that was absorbed by each animal is the sum of the quantity found in the excreta, organs/tissues, carcass and cage wash.

Results and discussions:

The results of the dermal absorption of ^{14}C-R,S-dimethenamid dissolved in the respective blank formulation are given in the table below:

Table B.6.2-5: Dermal absorption of ^{14}C-R,S-dimethenamid in rats

Percentage of applied radioactivity absorbed				
Exposure time [h]	Sacrifice time [h]	0.004 mg/cm^2	0.04 mg/cm^2	0.4 mg/cm^2
4	4	10.98	0.96	4.74
8	8	11.35	2.47	4.89
8	24	14.34	6.25	7.38
8	72	18.18	8.41	9.09

Note: These are non-audited data

As can be seen in the table, about 18 % of the radioactivity applied was absorbed at maximum.
After an 8 h-exposure of ^{14}C-R,S-dimethenamid in BAS 656 07 H at a dose level of 0.4 mg/cm^2, 25.8 % were absorbed after 72 hours.
The results of the dermal absorption with ^{14}C-S-dimethenamid in the respective blank formulation are as follows:

Table B.6.2-6: Dermal absorption of ^{14}C-S-dimethenamid in rats

Percentage of applied radioactivity absorbed				
Exposure time [h]	Sacrifice time [h]	0.004mg/cm^2	0.04 mg/cm^2	0.4 mg/cm^2
8	72	15.17	27.32	23.29

Note: These are non-audited data

In the experiments with ^{14}C-S-dimethenamid in the respective blank formulation, about 27 % of the radioactivity was absorbed at maximum.

Conclusion:

The study is considered to be not acceptable.
No guideline is reported. The study was not conducted according to GLP. Results were reported as “Preliminary information”. There is no complete study report. Individual data were not given. The results should not be used for risk assessment.

Data point:	IIA 5.4.1
Report:	[redacted].; 1993 (TOX1999-412) [^{14}C]-Dimethenamid Technical: Rates of permeation through human and rat epidermis using an *in vitro* assay Reg. Doc. #BASF 93 / 11759; Study No.: 494-S Performing laboratory: [redacted] (Experimental work: 13 April - 5 November, 1993)
Guideline(s):	None
Deviations:	Not applicable
GLP:	It is reported that the study was performed in accordance with Swiss GLP Guidelines (March 1986) that comply with US EPA, Japanese and OECD principles of GLP
Acceptability:	The study is considered to be not acceptable.

Materials and methods:

Test Material:
Non-radiolabelled test article:
Dimethenamid technical (batch no. 5835-15), a brown-red viscoid with a purity of 96.6 % (w/w) of a.i..

Manufacturer:	[redacted]
Storage:	at 4 °C, in the dark
Solubility:	Water: 1.174 mg/L; good in corn oil or PEG 200; Ethanol: greater than 50 %
Stability:	stable for at least two years at 4 °C.
Tracer(s):	
Common name:	[^{14}C]-dimethenamid (designated as substance 10; S.10)
Batch number:	RA 683, 901101
Radiochemical purity:	98.4 %
Specific activity:	183.3 µCi/mg (= 4.07 x 10^8 dpm/mg)
Vehicle:	MeOH abs.
Concentration:	113.73 pCi/500 pl
Manufacturer:	[redacted]
Storage:	at -20 °C, in the dark
Common name:	[^{14}C]-dimethenamid (designated as substance 9; S.9)
Batch number:	RA 683, 901101
Radiochemical purity:	98.4%
Specific activity:	183.3 pCi/mg (= 4.07 x 10^8 dpm/mg)
Vehicle:	MeOH abs.
Concentration:	123.1 µCi/500 p1
Manufacturer:	[redacted]
Storage:	at -20 °C, in the dark

Study design:
Route of administration: Dermally at a nominal dose volume of 400 pl.
Frequency of administration: The test article is administered as a single application on three epidermal preparations per dose concentration and by evaluating three dose concentrations.
Stability and homogeneity is determined.

Test system (epidermal tissue):
Rat

Strain	Albino Hanlbm: WIST (SPF) rats

Sex	Males
Age	born 5 May 1992 (F1C off-springs of C mating) Untreated control animals of study no 461R
Animal numbers	10 to 12, and 20 to 23 (tail marked)
Supplier (parents)	BRL, Biological Research Laboratories, Ltd. Wölferstrasse 4, CH-4414 Füllinsdorf, Switzerland
Pre-experimental husbandry	
Identification of test system	Uniquely numbered using tail marking. The numbers will be allocated randomly Cages by colour coded card showing study number, animal numbers and sex.
Environment	
Housing	room no. 620
Temperature	19 - 25 °C, recorded daily
Rel. humidity	40 – 70 %, recorded daily
Lighting	Fluorescent - 12 h light/12 h dark per day
Caging	individually, in Macrolon size 4 plastic cages with solid bottoms and sifted granular wood provided as bedding
Diet and drinking water	
Diet	KLIBA pelleted standard diet no. 32-343-4, from Klingentalmühle AG. Basel, CH-4303 Kaiseraugst, Switzerland, *ad libitum*, offered freshly weekly.
Water	Municipal supply of CH-4132 Muttenz, *ad libitum* from polyethylene bottles, offered freshly each week.
Animal health procedures	A clinical inspection for external signs of ill-health was performed on 5 February 1993. No findings were noted.
Acclimatisation period	The animals were assigned to this study at 5 February, 1993. They represent untreated control animals derived from the reproduction study 461-R.

The aim of this study was to measure the permeability of dimethenamid technical over a 24 hour period after a single administration to post-mortem, dermatomed human skin membrane and to rat full skin using static glass diffusion cells. Tracing of [^{14}C]-dimethenamid in a radiochemical assay served as the method for these permeation measurements.
It is reported that the study plan was designed by taking into account the dermal penetration protocols carried out by the British Agrochemical Association (BAA) as referenced in "Methods for Measuring Dermal Penetration of Pesticides" by R. C. Scott et al., Food and Chemical Toxicology, 31, (7) 523-529 (1993) and the recommendations made in ECETOC Monograph No. 20 "Percutaneous Absorption", Brussels, August 1993.
Fresh post mortem excised human skin from the abdominal region of 3 white women was obtained from the Institute of Pathology of the University of Basle, Switzerland. Skin from male Albino Hanlbm : Wistar rats was used.
The integrity of the skin sample was checked by measurement of the electrical properties of the tissues.

Table B.6.2-7: Study design

Group epidermal designation	Species	Dose levels		Number of cells used per preparation
		mg/mL	µCi/cell	
A	Rat	80	2.275 (S.10)	3
B	Rat	20	2.275 (S.10)	3
C	Rat	5	2.275 (S.10)	3
D	Human	80	2.462 (S.9)	3
E	Human	20	2.462 (S.9)	3
F	Human	5	2.462 (S.9)	3

Three concentrations of active substance were evaluated that correspond approximately to the application rate in the field, namely 80 mg/mL, 20 mg/mL and 5 mg/mL.

Dose application:
The test concentrations were applied with an Eppendorf pipette at a volume of 400 µL per cell. The experiments were conducted in triplicates, i.e. with three cells running in parallel for each dose concentration.
All donor cells were covered with a double-layer of parafilm™ during the entire 24-hour running period.

Receptor fluid:
The penetrating molecule has to have a high solubility in the receptor fluid, and the receptor fluid should not alter the permeability properties of the skin. Therefore, 50 % EtOH/PBS was used as the receptor fluid. The receptor fluid was continuously stirred and maintained at 32 °C ± 1 °C throughout the experimental phase.

Sampling:
Samples of 250 µL were taken at the following timepoints after application: 0, 2, 4, 6, 8, 20, 22 and 24 hours. Samples were replaced with an equal volume of fresh receptor fluid using a Hamilton syringe. The syringe was washed with methanol abs. and then quickly rinsed with receptor fluid between each loading step.

Termination of the experiment:
After completion of the experiment the donor chamber was removed and rinsed with methanol abs.. The parafilm sheet on top of the donor chamber was also rinsed with abs. methanol. The residue on top of the epidermis was collected with a pipette. The epidermis was rinsed with receptor fluid. These washings were collected in one vial that was labelled as "residue on top". The epidermal disk was removed from the diffusion cell and put in a vial for further treatment. The remaining receptor fluid was collected and transferred into a vial. The acceptor chamber was rinsed with methanol abs. and the washings collected in a separate vial.

Post-treatment of the skin:
The skin samples were combusted in a PACKARD Sample Oxidiser (model 307) at our Analytics Department. For that purpose the central part of the epidermal disk was punched with a puncher (covering a circle of 10 mm in diameter) and the remaining tissue was cut in 4 pieces. Thereafter, the tissue was transferred onto filter paper boats and combusted in a stream of oxygen in the oxidiser. To the remaining liquid in the vial 10 mL scintillation cocktail was added and measured. The result of this skin vial rinse has been added to the recovery vial designated "top". The liberated $^{14}CO_2$ was absorbed in 10 mL of reagent (CARBO-SORB, Packard Instrument Company) and was automatically mixed

with 10 mL of scintillation mixture.

Measurement of radioactivity:
Radioactivity was determined in a Packard liquid scintillation counter Tri-carb 2500 TR equipped with multi-parameter MCA technology that corrects for common counting interferences caused by luminescence, colour quenching and background, uniquench dpm and other options. All measurements were performed in duplicate for a counting time allowing a counting error below 5 % or for a maximum counting time of 10 minutes. All measurements were corrected for the respective scintillation back-ground. Unless stated otherwise, 10 mL of the scintillation cocktail Ultima Gold ™, Canberra Packard Ltd.) were added. Radioactivity was determined in the receptor fluid, application site washings (residues on top of the skin membrane and on the parafilm), receptor cell washings and in the skin membrane by liquid scintillation counting at the testing facility.
A quench curve for [^{14}C]-isotopes is installed in this counter. It has been generated by counting a series of standard samples, each containing the same amount of nuclide and varying amounts of the quenching agent. The efficiency for each sample was calculated and the quench curve was plotted as % efficiency versus amount-of-quench.
When counting a sample, the value of the quench indicator was calculated for the sample. Then this value was used to interpolate the counting efficiency for the sample from the [^{14}C]-quench curve.

Data processing:
- At each time point the total amount that had passed through the membrane was summed up according to the formula:

$t_1 = c_1V$
$t_2 = c_2V + clv$
$t_3 = c_3V + c_2v + c_1v$
(etc.)

or

$$tn = V.cn + V \sum_{i=1}^{n-1} ci$$

where c_1 = concentration in sample 1 at sample time t_l, V = receptor volume, v = added volume (= sampled volume).
- These amounts were divided by the application surface, in cm^2.
- The results were plotted as amount/cm^2 vs. time.

Absorption rate (J):

Definition: Absorption rate expresses the amount that passes through the membrane per cm^2 and time unit.
Calculation: The absorption rate was calculated from the slope of the curve by taking into account amount/cm^2 vs. time.

Percutaneous permeability constant (Kp):

Definition: The permeability constant is a measure of the speed or facility of a compound to permeate through a skin membrane and it is constant for a given permeant under a given set of experimental conditions.
Calculations:
- Kp was calculated as follows:

$Kp\ (cm\ h^{-1}) = J / C_d$

where J = absorption rate and C_d is the concentration in the donor chamber.

Other terms used:

- Test material left in the lower chamber (acceptor chamber)
  The amount (dpm) of the test material recovered in the rinses of the acceptor chamber.
- Residue (dpm) left on top of the skin membrane
  The amount of the compound that remained on top of the skin or skin membrane after the completion of the experiment.
- Test article bound in the skin.
  The amount (dpm) of the test article bound to the skin after completion of the experiment.
- Glassware wash:
  The amount (dpm) of the test article which was associated with the inner surface of the glassware.
- Recovery:
  All of the above mentioned amounts were summed up to calculate the original amount of the amount applied to the static diffusion cells.

  Note: Mean values were used since three identical runs have been done.

Results and discussions:

Human skin experiments:
Three doses each were evaluated in triplicates in three independent experiments with human dermatomed epidermal slices.

Mean permeation in percentage over 8 hours:
The mean permeations (± sem) in the time period from 0 to 8 hours were 0.59 % ± 0.04 % (n=9), i.e. 0.56 % ± 0.22 % at the low dose, 0.64 % ± 0.32 % at the medium dose, and 0.58 % ± 0.26 % at the high dose (n=3 each).

Table B.6.2-8: Mean permeation in percentage (± sem) over 8 hours (n = 6 diffusion cells)

Skin experiment	80 mg/mL	20 mg/mL	5 mg/mL	Total mean ± sem (n=9)
Human 1	0.71 %	0.62 %	0.73 %	
Human 2	0.28 %	0.33 %	0.32 %	
Human 3	0.75 %	0.50 %	0.64 %	
Mean	0.58 % ± 0.26	0.64 % ± 0.32	0.56 % ± 0.22	0.59 % ± 0.04
Rat 1	0.02 %	0.095 %	0.12 %	
Rat 2	0.14 %	0.17 %	0.19 %	
Rat 3	0.005 %	0.12 %	0.07 %	
Mean	0.07 % ± 0.06	0.13 % ± 0.04	0.13 % ± 0.06	0.11 % ± 0.03

Mean permeation in percentage over 24 hours:
The mean permeations were:
2.9 % ± 0.4 % (n=9), namely 2.69 % ± 1.05 % at the low dose, 2.67 % ± 0.99 % at the medium dose, and 3.41 % ± 1.46 % at the high dose (n=3 each).

Percutaneous absorption rate (J):
For each concentration tested, the absorption rate was calculated from the linear part of the curve by fitting. In the first human skin experiment the percutaneous absorption rates (J) were determined as follows: 4.49 µg/cm^2 h^{-1} at the low dose concentration (5 mg/mL), 16.04 µg/cm^2 h^{-1} at the medium dose (20 mg/mL), and 80.70 µg/cm^2 h^{-1} at the high dose concentration (80 mg per mL). In the second human skin experiment the following absorption rates were determined: 1.80 µg/cm^2 h^{-1} at 5 mg/mL,

7.18 µg/cm^2 h^{-1} at 20 mg/mL and 34.93 µg/cm^2 h^{-1} at 80 mg/mL. In the third experiment the corresponding values are: 3.35 µg/cm^2 h^{-1}, 12.07 µg/cm^2 h^{-1} and 85.35 µg/cm^2 h^{-1}, respectively. The related mean percutaneous absorption rates are 3.21 ± 1.35 µg/cm^2 h^{-1}, 11.76 ± 4.44 µg/cm^2 h^{-1} and 66.99 ± 27.87 µg/cm^2/h, respectively.
The results obtained confirm the expected dose-response relationship.

Rat skin experiments:
Three doses each were tested in triplicates in three independent experiments.

Mean permeation in percentage over 8 hours:
The mean permeations (± sem) in the time period from 0 to 8 hours were determined as 0.11 % ± 0.03 % (n=9), i.e. 0.13 % ± 0.06 % for the low dose, 0.13 % ± 0.04 % for the medium dose and 0.07 % ± 0.06 % for the high dose concentration (n=3 each).

Mean permeation in percentage over 24 hours:
The mean permeations over the 24 hour period were determined as 2.4 % ± 0.7 (n=9), namely 2.71 % ± 0.76 % for the low dose, 2.94 % ± 0.61 % for the medium dose, and 1.61 % ± 1.15 % for the high dose (n=3 each).

Table B.6.2-9: Mean permeation in percentage (± sem) over 24 hours (n = 6 diffusion cells)

Skin experiment	80 mg/mL	20 mg/mL	5 mg/mL	Total mean ± sem (n=9)
Human 1	4.15 %	3.58 %	3.67 %	
Human 2	1.73 %	1.60 %	1.59 %	
Human 3	4.34 %	2.82 %	2.83 %	
Mean	3.41 % ± 1.46	2.67 % ± 0.99	2.69 % ± 1.05	2.9 % ± 0.4
Rat 1	1.11 %	2.38 %	2.56 %	
Rat 2	2.93 %	3.58 %	3.53 %	
Rat 3	0.80 %	2.85 %	2.04 %	
Mean	1.61 % ± 1.15	2.94 % ± 0.61	2.71 % ± 0.76	2.4 % ± 0.7

Percutaneous absorption rate (J):
For each concentration tested, the absorption rate was calculated from the linear curve fitting. In the first rat experiment the absorption rates calculated were 3.13 µg/cm^2 h^{-1} for the low dose concentration (5 mg/mL), 10.64 µg/cm^2 h^{-1} for the medium dose (20 mg/mL) and 20.54 µg/cm^2 h^{-1} for the high dose concentration (80 mg/mL).
In the second rat experiment the corresponding absorption rates were determined as 4.20 µg/cm^2 h^{-1} at 5 mg/mL, 16.25 µg/cm^2 h^{-1} at 20 mg/mL and 59.13 µg/cm^2 h^{-1} at 80 mg/mL. The corresponding percutaneous absorption rates in the third experiments were 2.46 µg/ cm^2 h^{-1}, 12.72 µg/cm^2 h^{-1} and 12.78 µg/cm^2 h^{-1}, respectively. The related mean absorption rates therefore are: 3.26 ± 0.88 µg/cm^2 h^{-1}, 13.20 ± 2.84 µg/cm^2 h^{-1} and 30.82 ± 24.82 µg/cm^2 h^{-1}, respectively. As has been already observed in the human experiment, the results obtained with rat skin confirm the expected dose-response relationship.

Permeability constant (Kp):
For the three concentrations tested the following mean permeability constants (Kp) were calculated:
A Kp value of 16.20 (± 4.38) x 10^{-4} cm h^{-1} was calculated for the low dose, a kp of 16.50 (± 3.54) x 10^{-4} cm h^{-1} was obtained for the medium dose concentration, and a kp value of 9.63 (± 7.76) x 10^{-4} cm h^{-1} was determined for the high dose concentration.

Summary:
In an *in vitro* skin permeation experiment the permeation characteristic of dimethenamid was evaluated using human dermatomed skin and whole back skin from male Wistar rats. Permeation of the test article during the first 8 hours after application to the static Franz diffusion cell was well below 1 %: in skin from both species reflecting the highly effective barrier properties of the stratum corneum and the relatively prolonged lag time of 4 to 8 hours for the human skin membranes and 10 to 13 hours for the rat skin.
The mean permeation over 24 hours was determined as 2.9 % ± 0.4 % in the dermatomed human skin and 2.4 % ± 0.7 % in the whole rat skin.

Conclusion:

The study is considered to be not acceptable.
It is reported that the study was conducted for investigative purposes only. No guideline is reported. Dimethenamid was not tested in a commercial formulation. The study does not comply to the requirements of the Guidance on Dermal Absorption (EFSA Journal 2012;10(4):2665).

B.6.3 Available toxicological data relating to co-formulants

Toxicological information on the co-formulants is presented in Vol. 4. No additional labelling of the product with respect to the toxicological properties of the co-formulants is required.

B.6.4 Exposure data

The representative Plant Protection Product BAS 656 12 H containing 720 g/L dimethenamid-P is intended to be used as an herbicide on maize, soybean, sunflower and sugar beet. A summary of the critical uses and the overall conclusion regarding exposure for operators, workers, bystanders and residents is presented in B.6.5.
The calculations for dimethenamid-P are based on the parameters and endpoints given in Table B.6.4-1.

Table B.6.4-1: Product information and toxicological reference values used for exposure assessment

Product name and code	BAS 656 12 H
Formulation type	Emulsifiable concentate (EC)
Category	Herbicide
Container size(s), short description	0.15 to 1 L container (42 mm opening), 1 to 10 L container (54 mm opening)
Active substance(s) (incl. content)	Dimethenamid-P 720 g/L
AOEL systemic	0.04 mg/kg bw/d
Inhalative absorption	100 %
Oral absorption	100 %
Dermal absorption	Concentrate: 0.4 % Dilution 1: 39 % (3.6 g/L)) Dilution 2: 31 % (0.72 g/L) based on BAS 656 12 H

B.6.4.1 Operator exposure

B.6.4.1.1 Estimation of operator exposure

A summary of the exposure models used for estimation of operator exposure to dimethenamid-P during application of BAS 656 12 H according to the critical uses is presented in Table B.6.4-2. Outcome of the estimation is presented in Table B.6.4-3. Detailed calculations are given in Appendix 1.

Table B.6.4-2: Exposure models for intended uses

Critical use(s)	Maize, soybean, sunflower, sugar beet (max. 1.2 L product/ha)
Model(s)	German model [Uniform Principles for Safeguarding the Health of Applicators of Plant Protection Products (Uniform Principles for Operator Protection), Mitteilungen aus der Biologischen Bundesanstalt für Land-und Forstwirtschaft, Berlin-Dahlem, Heft 277, 1992]
	UK POEM (revised) [Estimation of Exposure and Absorption of Pesticides by Spray Operators, Scientific subcommittee on Pesticides and British Agrochemical association Joint Medical Panel Report (UK MAFF), 1986 and the Predictive Operator Exposure Model (POEM) V 1.0, (UK MAFF), 1992. ("UK model")]
	AOEM (not yet implemented in the EU, proposed by the applicant for a refinement of the UK POEM) [Joint development of a new Agricultural Operator Exposure Model – Project Report, BfR Wissenschaft 07/2013, Berlin 2013 (http://www.bfr.bund.de/cm/350/joint-development-of-a-new-agricultural-operator-exposure-model.pdf)]

Table B.6.4-3: Estimated operator exposure

		Dimethenamid-P	
Model data	**Level of PPE**	**Total absorbed dose (mg/kg bw/day)**	**% of systemic AOEL**
Tractor mounted boom spray application outdoors to low crops Application rate: 0.864 kg as/ha			
German Model Body weight: 70 kg	no PPE[1)]	0.1992	497.9
	+ gloves during mixing/loading and gloves, coverall and sturdy footwear during appl.	0.0143	35.7
UK POEM Application volume: 100 L/ha Container: 10 L, 63 mm closure[3)] Body weight: 60 kg	no PPE[2)]	1.8778	4694.6
	+ gloves during mixing/loading and appl.	0.2980	745.0
AOEM Body weight: 60 kg	with workwear	0.0757	189.3
	+ gloves during mixing/loading and appl.	0.0044	11.0

1) no PPE: Operator wearing T-shirt and shorts
2) no PPE: Operator wearing long sleeved shirt, long trousers ("permeable") but no gloves
3) realistic worst-case for the treatment of 50 ha

B.6.4.1.2 Measurement of operator exposure

Since the operator exposure estimations carried out according to the German model (and the AOEM) indicated that the acceptable operator exposure level (AOEL) will not be exceeded under conditions of intended uses, a study to provide measurements of operator exposure was not necessary and was therefore not performed.

B.6.4.2 Bystander and resident exposure

B.6.4.2.1 Estimation of bystander and resident exposure

Table B.6.4-4 shows the exposure model used for estimation of bystander and resident exposure to dimethenamid-P. Outcome of the estimation is presented in Table B.6.4-5. Detailed calculations are shown in Appendix 1.

Table B.6.4-4: Exposure models for intended uses

Critical use(s)	Maize, soybean, sunflower, sugar beet (max. 1 x 1.2 L product/ha)
Model	Martin, S. et al. (2008) [Guidance for Exposure and Risk Evaluation for Bystanders and Residents Exposed to Plant Protection Products During and After Application; J. Verbr. Lebensm. 3 (2008): 272-281 Birkhäuser Verlag Basel] and Bundesanzeiger (BAnz), 06 January 2012, Issue No. 4, pp. 75-76

Table B.6.4-5: Estimated bystander and resident exposure

	Dimethenamid-P	
Model data	**Total absorbed dose (mg/kg bw/day)**	**% of systemic AOEL**
Tractor mounted boom spray application outdoors to low crops Application rate: 1 x 0.864 kg as/ha		
Bystanders (adult) Drift rate: 2.77 % (1 m) Body weight: 60 kg	0.0156	38.9
Bystanders (children) Drift rate: 2.77 % (1 m) Body weight: 16.15 kg	0.0121	30.4
Residents (adult) Drift rate: 2.77 % (1 m) Body weight: 60 kg	0.0011	2.8
Residents (children) Drift rate: 2.77 % (1 m) Body weight: 16.15 kg	0.0019	4.7

B.6.4.2.2 Measurement of bystander and/or resident exposure

Since the bystander and/or resident exposure estimations carried out indicated that the acceptable operator exposure level (AOEL) for dimethenamid-P will not be exceeded under conditions of intended uses, a study to provide measurements of bystander/resident exposure was not necessary and was therefore not performed.

B.6.4.3 Worker exposure

B.6.4.3.1 Estimation of worker exposure

Table B.6.4-6 shows the exposure model used for estimation of worker exposure after entry into a previously treated area or handling a crop treated with BAS 656 12 H according to the critical use(s). Outcome of the estimation is presented in Table B.6.4-7. Detailed calculations are shown in Appendix 1.

Table B.6.4-6: Exposure models for intended uses

Critical use(s)	Maize, soybean, sunflower, sugar beet (max. 1 x 1.2 L product/ha)
Model	German re-entry model, Krebs et al. (2000) [Uniform Principles for Safeguarding the Health of Workers Re-entering Crop Growing Areas after Application of Plant Protection Products, Nachrichtenbl. Deut. Pflanzenschutzdienst., 52(1), p. 5-9]

Table B.6.4-7: Estimated worker exposure

		Dimethenamid-P	
Model data	**Level of PPE**	**Total absorbed dose (mg/kg/day)**	**% of systemic AOEL**
Number of applications and application rate: 1 x 0.864 kg as/ha			
2 h/day[1)], DFR: 1 µg/cm²/kg as TC: 2500 cm²/person/h[2)] Body weight: 60 kg	no PPE[3)]	0.0281[4)]	70.2[4)]

1) 2 h/day for professional applications for maintenance, inspection or irrigation activities etc.
2) US-EPA policy paper [EPA, Science Advisory Council for Exposure; 2000; Agricultural Default Transfer Coefficients, Policy # 003.1, May 7 1998 revised 7 August 2000]
3) no PPE: Worker wearing long sleeved shirt, long trousers ("permeable") but no gloves
4) for a DFR of 3 µg/cm²/kg as the estimated worker exposure would amount to 0.0842 mg/kg bw/day or 210.6 % of the systemic AOEL without PPE and to 0.0042 mg/kg bw/day or 10.5 % of the systemic AOEL with protective gloves and workwear

B.6.4.3.2 Measurement of worker exposure

Since the worker exposure estimations carried out indicated that the acceptable operator exposure level (AOEL) will not be exceeded under conditions of intended uses, a study to provide measurements of worker exposure was not necessary and was therefore not performed.

B.6.5 Exposure and risk assessment

The risk assessment according to the German model and the AOEM has shown that the estimated exposure towards dimethenamid-P in BAS 656 12 H will not exceed the systemic AOEL for operators if PPE is used. According to the German model the PPE comprises gloves during mixing/loading and coverall, sturdy footwear and gloves during application. No safe use could be demonstrated according to the UK POEM even if the use of gloves was considered.
For workers, bystanders and residents no unacceptable risk was identified when the product is used as intended.
A summary of the critical uses and the overall conclusion regarding exposure for operators, workers and bystanders/residents is presented in Table B.6.5-1.

Table B.6.5-1: Critical uses and overall conclusion of exposure assessment

Crops[1] and situation (e.g. growth stage of crop)	F/G or I[2]	Application		Application rate		Remarks: (e.g. surfactant (L/ha)) critical gap for operator, worker, bystander or resident exposure based on [*Exposure model*]	Acceptability of exposure assessment			
		Method/Kind (incl. application technique[3])	Max. number (min. interval between applications) a) per use b) per crop/season	kg as/ha a) max. rate per appl. b) max. total rate per crop/season	Water L/ha min/max		Operator	Worker	Bystander	Residents
Maize, soybean, sunflower, sugar beet	F	Foliar spray, tractor-mounted boom sprayers	a) 1 b) 1	a) 0.864 b) 0.864	100-400	German model				
						UK POEM				
						(AOEM)				

	Exposure acceptable without PPE / risk mitigation measures
	Further refinement and/or risk mitigation measures required
	Exposure not acceptable/ Evaluation not possible

[1] Pooled critical GAPS with the same max. application rate per application and using the same application technique
[2] F: field or outdoor application, G: greenhouse application, I: indoor application

B.6.6 References relied on

Data Point EU as of 2014	Author(s)	Year	Title Company Report No. Source (where different from company) GLP or GEP status Published or not	Vertebrate study Y/N	Data Protection Claimed Y/N	Justification if data protection is claimed	Owner	Previously submitted Y/N If yes, old data point
KCP 7.1.1	[redacted]	2006	BAS 656 08 H - Acute oral toxicity study in rats 2006/1026825 [redacted] GLP, unpublished BVL-2630572 ASB2008-8109	Y	Y	New data for AIR3 renewal	BASF	III A 7.1.1
KCP 7.1.2	[redacted]	2006	BAS 656 08 H - Acute dermal toxicity study in rats 2006/1026826 [redacted] GLP, unpublished BVL-2630574 ASB2008-8110	Y	Y	New data for AIR3 renewal	BASF	III A 7.1.2
KCP 7.1.4	[redacted]	2006	BAS 656 08 H - Acute dermal irritation/corrosion in rabbits 2006/1026827 [redacted] GLP, unpublished BVL2630577 ASB2008-8111	Y	Y	New data for AIR3 renewal	BASF	III A 7.1.4
KCP 7.1.5	[redacted]	2000	BAS 656 08 H - Acute eye irritation in rabbits 2000/1012350 [redacted] GLP, unpublished BVL-2630579 ASB2003-84	Y	Y	New data for AIR3 renewal	BASF	III A 7.1.5
KCP 7.1.5	[redacted]	2000	Amendment No. 1: BAS 656 08 H - Acute eye irritation in rabbits 2000/1018471 [redacted] GLP, unpublished BVL-2630580	Y	Y	New data for AIR3 renewal	BASF	III A 7.1.5
KCP 7.1.5	[redacted]	2007	Amendment No. 2 to the report - BAS 656 08 H - Acute eye irritation in rabbits 2007/1037727 [redacted] GLP, unpublished BVL-2630581	Y	Y	New data for AIR3 renewal	BASF	N III A 7.1.5

Data Point EU as of 2014	Author(s)	Year	Title Company Report No. Source (where different from company) GLP or GEP status Published or not	Vertebrate study Y/N	Data Protection Claimed Y/N	Justification if data protection is claimed	Owner	Previously submitted Y/N If yes, old data point
KCP 7.1.6	[redacted]	2006	BAS 656 08 H - Modified BUEHLER test (9 inductions) in guinea pigs 2006/1026828 [redacted] GLP, unpublished BVL-2630583 ASB2008-8114	Y	Y	New data for AIR3 renewal	BASF	N III A 7.1.6
KCP 7.3	Fabian E., Landsiedel R.	2013	14C-BAS 656 PH in BAS 656 12 H - Study of penetration through human skin in vitro 2013/1184803 BASF SE, Ludwigshafen/Rhein, Germany Fed.Rep. GLP, unpublished BVL-2630585 ASB2014-3668	N	Y	New data for AIR3 renewal	BASF	N III A 7.3

Appendix 1 Exposure calculations

A 1.1 Operator exposure

Table A 1: Input parameters considered for the estimation of operator exposure with the German model

Formulation type:	EC		**Application technique:**	Field Crop Tractor Mounted (FCTM)	
Application rate (AR):	0.864	kg as/ha			
Area treated per day (A):	20	ha	**Dermal hands m/L ($D_{M(H)}$):**	2.4	mg/person/kg as
Dermal absorption (DA):	0.4	% (concentr.)	**Dermal hands appl. ($D_{A(H)}$):**	0.38	mg/person/kg as
	39	% (dilution)	**Dermal body appl. ($D_{A(B)}$):**	1.6	mg/person/kg as
Inhalation absorption (IA):	100	%	**Dermal head appl. ($D_{A(C)}$):**	0.06	mg/person/kg as
Body weight (BW):	70	kg/person	**Inhalation m/L (I_M):**	0.0006	mg/person/kg as
AOEL	0.04	mg/kg bw/d	**Inhalation appl. (I_A):**	0.001	mg/person/kg as

Table A 2: Estimation of operator exposure towards dimethenamid-P using the German model

Without PPE			**With PPE**		
Operators: Systemic dermal exposure after application in maize, sugar beet, soybean, sunflower					
Dermal exposure during mixing/loading					
Hands			Hands		
$SDE_{OM(H)} = (D_{M(H)} \times AR \times A \times DA) / BW$			$SDE_{OM(H)} = (D_{M(H)} \times AR \times A \times PPE$ [1)] $\times DA) / BW$		
(2.4 x 0.864 x 20 x 0.4 %) / 70			(2.4 x 0.864 x 20 x 0.01 x 0.4 %) / 70		
External dermal exposure	41.472	mg/person	External dermal exposure	0.41472	mg/person
External dermal exposure	0.592457	mg/kg bw/d	External dermal exposure	0.005925	mg/kg bw/d
Systemic dermal exposure	**0.00237**	**mg/kg bw/d**	**Systemic dermal exposure**	**0.000024**	**mg/kg bw/d**
Dermal exposure during application					
Hands			Hands		
$SDE_{OA(H)} = (D_{A(H)} \times AR \times A \times DA) / BW$			$SDE_{OA(H)} = (D_{A(H)} \times AR \times A \times PPE$ [1)] $\times DA) / BW$		
(0.38 x 0.864 x 20 x 39 %) / 70			(0.38 x 0.864 x 20 x 0.01 x 39 %) / 70		
External dermal exposure	6.5664	mg/person	External dermal exposure	0.065664	mg/person
External dermal exposure	0.093806	mg/kg bw/d	External dermal exposure	0.000938	mg/kg bw/d
Systemic dermal exposure	**0.036584**	**mg/kg bw/d**	**Systemic dermal exposure**	**0.000366**	**mg/kg bw/d**
Body			Body		
$SDE_{OA(B)} = (D_{A(B)} \times AR \times A \times DA) / BW$			$SDE_{OA(B)} = (D_{A(B)} \times AR \times A \times PPE$ [2)] $\times DA) / BW$		
(1.6 x 0.864 x 20 x 39 %) / 70			(1.6 x 0.864 x 20 x 0.05 x 39 %) / 70		
External dermal exposure	27.648	mg/person	External dermal exposure	1.3824	mg/person
External dermal exposure	0.394971	mg/kg bw/d	External dermal exposure	0.019749	mg/kg bw/d
Systemic dermal exposure	**0.154039**	**mg/kg bw/d**	**Systemic dermal exposure**	**0.007702**	**mg/kg bw/d**
Head			Head		
$SDE_{OA(C)} = (D_{A(C)} \times AR \times A \times DA) / BW$			$SDE_{OA(C)} = (D_{A(C)} \times AR \times A \times DA) / BW$		
(0.06 x 0.864 x 20 x 39 %) / 70			(0.06 x 0.864 x 20 x 39 %) / 70		
External dermal exposure	1.0368	mg/person	External dermal exposure	1.0368	mg/person
External dermal exposure	0.014811	mg/kg bw/d	External dermal exposure	0.014811	mg/kg bw/d
Systemic dermal exposure	**0.005776**	**mg/kg bw/d**	**Systemic dermal exposure**	**0.005776**	**mg/kg bw/d**
Total systemic dermal exposure: $SDE_O = SDE_{OM(H)} + SDE_{OA(H)} + SDE_{OA(B)} + SDE_{OA(C)}$			Total systemic dermal exposure: $SDE_O = SDE_{OM(H)} + SDE_{OA(H)} + SDE_{OA(B)} + SDE_{OA(C)}$		
Total external dermal exposure	76.7232	mg/person	Total external dermal exposure	2.899584	mg/person
Total external dermal exposure	1.096046	mg/kg bw/d	Total external dermal exposure	0.041423	mg/kg bw/d
Total systemic dermal exposure	**0.198769**	**mg/kg bw/d**	**Total systemic dermal exposure**	**0.013868**	**mg/kg bw/d**
Operators: Systemic inhalation exposure after application in maize, sugar beet, soybean, sunflower					
Inhalation exposure during mixing/loading					
$SIE_{OM} = (I_M \times AR \times A \times IA) / BW$			$SIE_{OM} = (I_M \times AR \times A \times IA) / BW$		
(0.0006 x 0.864 x 20 x 100 %) / 70			(0.0006 x 0.864 x 20 x 100 %) / 70		
External inhalation exposure	0.010368	mg/person	External inhalation exposure	0.010368	mg/person

External inhalation exposure	0.000148	mg/kg bw/d	External inhalation exposure	0.000148	mg/kg bw/d
Systemic inhalation exposure	**0.000148**	**mg/kg bw/d**	**Systemic inhalation exposure**	**0.000148**	**mg/kg bw/d**
Inhalation exposure during application					
$SIE_{OA} = (I_A$ x AR x A x IA) / BW			$SIE_{OA} = (I_A$ x AR x A x IA) / BW		
(0.001 x 0.864 x 20 x 100 %) / 70			(0.001 x 0.864 x 20 x 100 %) / 70		
External inhalation exposure	0.01728	mg/person	External inhalation exposure	0.01728	mg/person
External inhalation exposure	0.000247	mg/kg bw/d	External inhalation exposure	0.000247	mg/kg bw/d
Systemic inhalation exposure	**0.000247**	**mg/kg bw/d**	**Systemic inhalation exposure**	**0.000247**	**mg/kg bw/d**
Total systemic inhalation exposure: $SIE_O = SIE_{OM} + SIE_{OA}$			Total systemic inhalation exposure: $SIE_O = SIE_{OM} + SIE_{OA}$		
Total external inhalation exposure	0.027648	mg/person	Total external inhalation exposure	0.027648	mg/person
Total external inhalation exposure	0.000395	mg/kg bw/d	Total external inhalation exposure	0.000395	mg/kg bw/d
Total systemic inhalation exposure	**0.000395**	**mg/kg bw/d**	**Total systemic inhalation exposure**	**0.000395**	**mg/kg bw/d**
Total systemic exposure: $SE_O = SDE_O + SIE_O$			Total systemic exposure: $SE_O = SDE_O + SIE_O$		
Total systemic exposure	13.941504	mg/person	Total systemic exposure	0.998404	mg/person
Total systemic exposure	**0.199164**	**mg/kg bw/d**	**Total systemic exposure**	**0.014263**	**mg/kg bw/d**
% of AOEL	**497.9**	**%**	**% of AOEL**	**35.7**	**%**

[1] reduction factor for gloves is 0.01 (professional appl.)

[2] reduction factor for protective garment is 0.05 (professional appl.)

Table A 3: Estimation of operator exposure towards dimethenamid-P using the UK-POEM (without PPE)

Active substance	**dimethenamid-P**			
Product	BAS 656 12 H			
Formulation type	organic solvent-based			
Concentration of a.s.	720	mg/mL		
Dose	1.2	L preparation/ha (0.864 kg as/ha)		
Application volume	100	L/ha		
Application method	Tractor-mounted/trailed boom sprayer: hydraulic nozzles			
Container	10 litres 63 mm closure			
Work rate/day	50	ha		
Duration of spraying	6	h		
PPE during mix./loading	None			
PPE during application	None			
Dermal absorption from product	0.4	%		
Dermal absorption from spray	31	% (‘worst case‘ for the application volume of 100 L/ha)%		
EXPOSURE DURING MIXING AND LOADING				
Container size	10	Litres		
Hand contamination/operation	0,05	mL		
Application dose	1.2	Litres product/ha		
Work rate	50	ha/day		
Number of operations	6	/day		
Hand contamination	0.3	mL/day		
Protective clothing	None			
Transmission to skin	100	%		
Dermal exposure to formulation	0.3	mL/day		
DERMAL EXPOSURE DURING SPRAY APPLICATION				
Application technique	Tractor-mounted/trailed boom sprayer: hydraulic nozzles			
Application volume	100	spray/ha		
Volume of surface contamination	10	mL/h		
Distribution	Hands	Trunk	Legs	
	65 %	10 %	25 %	
Clothing	None	Permeable	Permeable	
Penetration	100 %	5 %	15 %	
Dermal exposure	6.5	0.05	0.375	mL/h
Duration of exposure	6	h		
Total dermal exposure to spray	41.55	mL/day		
ABSORBED DERMAL DOSE				

	Mix/load		Application	
Dermal exposure	0.3	mL/day	41.55	mL/day
Concen. of a.s. product or spray	720	mg/mL	8.64	mg/mL
Dermal exposure to a.s.	216	mg/day	358.992	mg/day
Percent absorbed	0.4	%	31	%
Absorbed dose	0.864	mg/day	111.288	mg/day
INHALATION EXPOSURE DURING SPRAYING				
Inhalation exposure	0.01	mL/h		
Duration of exposure	6	h		
Concentration of a.s. in spray	8.64	mg/mL		
Inhalation exposure to a.s.	0.518	mg/day		
Percent absorbed	100	%		
Absorbed dose	0.518	mg/day		
PREDICTED EXPOSURE				
Total absorbed dose	112.67	mg/day		
Operator body weight	60	kg		
Operator exposure	1.878	mg/kg bw/day		
Amount of AOEL	**4694.6**	**%**		

Table A 4: Estimation of operator exposure towards dimethenamid-P using the UK-POEM (with gloves during mixing/loading and application)

Active substance	**dimethenamid-P**			
Product	BAS 656 12 H			
Formulation type	organic solvent-based			
Concentration of a.s.	720	mg/mL		
Dose	1.2	L preparation/ha (0.864 kg as/ha)		
Application volume	100	L/ha		
Application method	Tractor-mounted/trailed boom sprayer: hydraulic nozzles			
Container	10 litres 63 mm closure			
Work rate/day	50	ha		
Duration of spraying	6	h		
PPE during mix./loading	Gloves			
PPE during application	Gloves			
Dermal absorption from product	0.4	%		
Dermal absorption from spray	31	% (‘worst case‘ for the application volume of 100 L/ha)		
EXPOSURE DURING MIXING AND LOADING				
Container size	10	Litres		
Hand contamination/operation	0,05	mL		
Application dose	1.2	Litres product/ha		
Work rate	50	ha/day		
Number of operations	6	/day		
Hand contamination	0.3	mL/day		
Protective clothing	Gloves			
Transmission to skin	10	%		
Dermal exposure to formulation	0.03	mL/day		
DERMAL EXPOSURE DURING SPRAY APPLICATION				
Application technique	Tractor-mounted/trailed boom sprayer: hydraulic nozzles			
Application volume	100	spray/ha		
Volume of surface contamination	10	mL/h		
Distribution	Hands	Trunk	Legs	
	65 %	10 %	25 %	
Clothing	Gloves	Permeable	Permeable	
Penetration	10 %	5 %	15 %	
Dermal exposure	0.65	0.05	0.375	mL/h
Duration of exposure	6	h		
Total dermal exposure to spray	6.45	mL/day		
ABSORBED DERMAL DOSE				
	Mix/load		Application	

Dermal exposure	0.03	mL/day	6.45	mL/day
Concen. of a.s. product or spray	720	mg/mL	8.64	mg/mL
Dermal exposure to a.s.	21.6	mg/day	55.728	mg/day
Percent absorbed	0.4	%	31	%
Absorbed dose	0.086	mg/day	17.276	mg/day
INHALATION EXPOSURE DURING SPRAYING				
Inhalation exposure	0.01	mL/h		
Duration of exposure	6	h		
Concentration of a.s. in spray	8.64	mg/mL		
Inhalation exposure to a.s.	0.518	mg/day		
Percent absorbed	100	%		
Absorbed dose	0.518	mg/day		
PREDICTED EXPOSURE				
Total absorbed dose	17.88	mg/day		
Operator body weight	60	kg		
Operator exposure	0.298	mg/kg bw/day		
Amount of AOEL	**745.0**	**%**		

Table A 5: Input parameters considered for the estimation of operator exposure towards dimethenamid-P with the AOEM

Active substance:	dimethenamid-P		**Dermal hands m/L ($D_{M(H)}$):**	88187	µg/person
Product:	BAS 656 12 H		**Dermal hands prot. m/L ($D_{M(Hp)}$):**	399	µg/person
Application technique:	Low Crop Tractor Mounted (LCTM)		**Dermal body m/L ($D_{M(B)}$):**	50345	µg/person
			Dermal body prot. m/L ($D_{M(Bp)}$):	669	µg/person
Crop type:	maize, sugar beet, soybean, sunflower		**Dermal head m/L ($D_{M(C)}$):**	2241	µg/person
Formulation type:	Liquid		**Dermal head prot. m/L ($D_{M(Cp)}$):**	36	µg/person
Application rate (AR):	0.864	kg as/ha	**Dermal hands appl. ($D_{A(H)}$):**	6408	µg/person
Area treated per day (A):	50	ha	**Dermal hands prot. appl. ($D_{A(Hp)}$):**	328	µg/person
Dermal absorption (DA):	0.4	% (concen.)	**Dermal body appl. ($D_{A(B)}$):**	3583	µg/person
	39	% (dilution)	**Dermal body prot. appl. ($D_{A(Bp)}$):**	98	µg/person
Inhalation absorption (IA):	100	%	**Dermal head appl. ($D_{A(C)}$):**	169	µg/person
Body weight (BW):	60	kg/person	**Inhalation m/L (I_M):**	11	µg/person
AOEL	0.04	mg/kg bw/d	**Inhalation appl. (I_A):**	7	µg/person

Table A 6: Estimation of operator exposure towards dimethenamid-P using the AOEM

Potential exposure			**With workwear and PPE (gloves m/L, gloves appl.)**		
Systemic exposure dermal route					
Dermal exposure during mixing/Loading					
$SDE_{OM(H)} = (D_{M(H)} \times DA) / BW$			$SDE_{OM(H(p))} = (D_{M(H(p))} \times DA) / BW$		
(88187 x 0.4 %) / 60			(399 x 0.4 %) / 60		
Systemic hands exposure	**5.87913**	**µg/kg bw/d**	**Systemic hands exposure**	**0.0266288**	**µg/kg bw/d**
$SDE_{OM(B)} = (D_{M(B)} \times DA) / BW$			$SDE_{OM(B(p))} = (D_{M(B(p))} \times DA) / BW$		
(50345 x 0.4 %) / 60			(669 x 0,4 %) / 60		
Systemic body exposure	**3.35637**	**µg/kg bw/d**	**Systemic body exposure**	**0.0446213**	**µg/kg bw/d**
$SDE_{OM(C)} = (D_{M(C)} \times DA) / BW$			$SDE_{OM(C(p))} = (D_{M(C(p))} \times DA) / BW$		
(2241 x 0.4 %) / 60			(2241 x 0.4 %) / 60		
Systemic head exposure	**0.14942**	**µg/kg bw/d**	**Systemic head exposure**	**0.1494247**	**µg/kg bw/d**
Dermal exposure during application					
$SDE_{OA(H)} = (D_{A(H)} \times DA) / BW$			$SDE_{OA(H(p))} = (D_{A(H(p))} \times DA) / BW$		
(6408 x 39 %) / 60			(328 x 39 %) / 60		
Systemic hands exposure	**41.6494**	**µg/kg bw/d**	**Systemic hands exposure**	**2.1289938**	**µg/kg bw/d**
$SDE_{OA(B)} = (D_{A(B)} \times DA) / BW$			$SDE_{OA(B(p))} = (D_{A(B(p))} \times DA) / BW$		
(3583 x 39 %) / 60			(98 x 39 %) / 60		
Systemic body exposure	**23.2877**	**µg/kg bw/d**	**Systemic body exposure**	**0.63882**	**µg/kg bw/d**
$SDE_{OA(C)} = (D_{A(C)} \times DA) / BW$			$SDE_{OA(C(p))} = (D_{A(C(p))} \times (PPE) \times DA) / BW$		

(169 x 39 %) / 60			(169 x 39 %) / 60		
Systemic head exposure	**1.10065**	**µg/kg bw/d**	**Systemic head exposure**	**1.1006452**	**µg/kg bw/d**
Total systemic dermal exposure: $SDE_O = SDE_{OM(H)} + SDEOM_{(B)} + SDEOM_{(C)} + SDE_{OA(H)} + SDE_{OA(B)} + SDE_{OA(C)}$			Total systemic dermal exposure: $SDE_O = SDE_{OM(H(p))} + SDEOM_{(Bp)} + SDEOM_{(C(p))} + SDE_{OA(H(p))} + SDE_{OA(Bp)} + SDE_{OA(C(p))}$		
Total systemic dermal exposure	**75.4227**	**µg/kg bw/d**	**Total systemic dermal exposure**	**4.0891338**	**µg/kg bw/d**
Systemic exposure inhalation route					
Inhalation exposure during mixing/loading					
$SIE_{OM} = (I_M \times IA) / BW$			$SIE_{OM} = (I_M \times (PPE) \times IA) / BW$		
(11 x 100 %) / 60			(11 x 100 %) / 60		
Systemic inhalation exposure	**0.18922**	**µg/kg bw/d**	**Systemic inhalation exposure**	**0.1892207**	**µg/kg bw/d**
Inhalation exposure during application					
$SIE_{OA} = (I_A \times IA) / BW$			$SIE_{OA} = (I_A \times (PPE) \times IA) / BW$		
(7 x 100 %) / 60			(7 x 100 %) / 60		
Systemic inhalation exposure	**0.11387**	**µg/kg bw/d**	**Systemic inhalation exposure**	**0.1138712**	**µg/kg bw/d**
Total systemic inhalation exposure: $SIE_O = SIE_{OM} + SIE_{OA}$			Total systemic inhalation exposure: $SIE_O = SIE_{OM} + SIE_{OA}$		
Total systemic inhalation exposure	**0.30309**	**µg/kg bw/d**	**Total systemic inhalation exposure**	**0.3030919**	**µg/kg bw/d**
Total systemic exposure: $SE_O = SDE_O + SIE_O$			**Total systemic exposure: $SE_O = SDE_O + SIE_O$**		
Total systemic exposure	**4.54355**	**mg/person**	**Total systemic exposure**	**0.2635335**	**mg/person**
Total systemic exposure	**0.07573**	**mg/kg bw/d**	**Total systemic exposure**	**0.0043922**	**mg/kg bw/d**
% of AOEL	**189.3**	**%**	**% of AOEL**	**11.0**	**%**

A 1.2 Bystander and resident exposure

Table A 7: Input parameters considered for the estimation of bystander exposure

Intended use(s):	maize, sugar beet, soybean, sunflower		**Drift (D):**	2.77	% (FC, 1 m)
Application rate (AR):	0.864	kg as/ha	**Exposed body surface area (BSA):**	1	m² (adults)
	86.4	mg/m²		0.21	m² (children)
Body weight (BW):	60	kg/person (adults)	**Specific Inhalation Exposure (I^*_A):**	0.001	mg/kg as (6 hours, adults)
	16.15	kg/person (children)		0.000575	mg/kg as (6 hours, children)
Dermal absorption (DA):	39	% ('worst case')	**Area Treated (A):**	20	ha/d (based on FCTM)
Inhalation absorption (IA):	100	%			
AOEL:	0.04	mg/kg bw/d	**Exposure duration (T):**	5	min

Table A 8: Estimation of bystander exposure towards dimethenamid-P

Adults			**Children**		
Bystander: Systemic dermal exposure during/after application (via spray drift)					
$SDE_B = (AR \times D \times BSA \times DA) / BW$			$SDE_B = (AR \times D \times BSA \times DA) / BW$		
(86.4 x 2.77 % x 1 x 39 %) / 60			(86.4 x 2.77 % x 0.21 x 39 %) / 16.15		
External dermal exposure	2.39328	mg/person	External dermal exposure	0.502589	mg/person
External dermal exposure	0.039888	mg/kg bw/d	External dermal exposure	0.03112	mg/kg bw/d
Systemic dermal exposure	**0.015556**	**mg/kg bw/d**	**Systemic dermal exposure**	**0.012137**	**mg/kg bw/d**
Bystander: Systemic inhalation exposure during/after application (via spray drift)					
$SIE_B = (I^*_A \times AR \times A \times T \times IA) / BW$			$SIE_B = (I^*_A \times AR \times A \times T \times IA) / BW$		
(0.001 / 360 x 0.864 x 20 x 5 x 100 %) / 60			(0.000575 / 360 x 0.864 x 20 x 5 x 100 %) / 16.15		
External inhalation exposure	0.00024	mg/person	External inhalation exposure	0.000138	mg/person
External inhalation exposure	0.000004	mg/kg bw/d	External inhalation exposure	0.000009	mg/kg bw/d
Systemic inhalation exposure	**0.000004**	**mg/kg bw/d**	**Systemic inhalation exposure**	**0.000009**	**mg/kg bw/d**
Total systemic exposure: $SE_B = SDE_B + SIE_B$			Total systemic exposure: $SE_B = SDE_B + SIE_B$		
Total systemic exposure	0.933619	mg/person	Total systemic exposure	0.196148	mg/person
Total systemic exposure	**0.01556**	**mg/kg bw/d**	**Total systemic exposure**	**0.012145**	**mg/kg bw/d**
% of AOEL	**38.9**	**%**	**% of AOEL**	**30.4**	**%**

Table A 9: Input parameters considered for the estimation of resident exposure

Intended use(s):	maize, sugar beet, soybean, sunflower		**Drift (D):**	2.77	% (FC, 1 m)
Application rate (AR):	0.864	kg as/ha	**Transfer coefficient (TC):**	7300	cm^2/h (adults)
	0.00864	mg/cm^2		2600	cm^2/h (children)
Number of applications (NA):	1		**Turf Transferable Residues (TTR):**	5	%
Body weight (BW):	60	kg/person (adults)	**Exposure Duration (H):**	2	h
	16.15	kg/person (children)	**Airborne Concentration of Vapour (ACV):**	0	mg/m^3
Dermal absorption (DA):	39	% ('worst case')	**Inhalation Rate (IR):**	16.57	m^3/d (adults)
Inhalation absorption (IA):	100	%		8.31	m^3/d (children)
Oral absorption (OA):	100	%	**Saliva Extraction Factor (SE):**	50	%
AOEL:	0.04	mg/kg bw/d	**Surface Area of Hands (SA):**	20	cm^2
			Frequency of Hand to Mouth (Freq):	20	events/h
			Dislodgeable foliar residues (DFR):	20	%
			Ingestion Rate for Mouthing of Grass/Day (IgR):	25	cm^2/d

Table A 10: Estimation of resident exposure towards dimethenamid-P

Adults			**Children**		
Residents: Systemic dermal exposure after application (via deposits caused by spray drift)					
SDE_R = (AR x NA x D x TTR x TC x H x DA) / BW			SDE_R = (AR x NA x D x TTR x TC x H x DA) / BW		
(0.00864 x 1 x 2.77 % x 5 % x 7300 x 2 x 39 %) / 60			(0.00864 x 1 x 2.77 % x 5 % x 2600 x 2 x 39 %) / 16.15		
External dermal exposure	0.174709	mg/person	External dermal exposure	0.062225	mg/person
External dermal exposure	0.002912	mg/kg bw/d	External dermal exposure	0.003853	mg/kg bw/d
Systemic dermal exposure	**0.001136**	**mg/kg bw/d**	**Systemic dermal exposure**	**0.001503**	**mg/kg bw/d**
Residents: Systemic inhalation exposure after application (via vapour)					
SIE_R = (AC_V x IR x IA) / BW			SIE_R = (AC_V x IR x IA) / BW		
(0 x 16.57 x 100 %) / 60			(0 x 8.31 x 100 %) / 16.15		
External inhalation exposure		none	External inhalation exposure		none
Systemic inhalation exposure		**none**	**Systemic inhalation exposure**		**none**
			Residents: Systemic oral exposure (hand-to-mouth transfer)		
			$SOE_{R(H)}$ = (AR x NA x D x TTR x SE x SA x Freq x H x OA) / BW		
			(0.00864 x 1 x % x 5 % x 50 % x 20 x 20 x 2 x 100 %) / 16.15		
			External oral exposure	0.004787	mg/person
			External oral exposure	0.000296	mg/kg bw/d
			Systemic oral exposure	**0.000296**	**mg/kg bw/d**
			Residents: Systemic oral exposure (object-to-mouth transfer)		
			$SOE_{R(O)}$ = (AR x NA x D x DFR x IgR x OA) / BW		
			(0.00864 x 1 x % x 20 % x 25 x 100 %) / 16.15		
			External oral exposure	0.001197	mg/person
			External oral exposure	0.000074	mg/kg bw/d
			Systemic oral exposure	**0.000074**	**mg/kg bw/d**
Total systemic exposure: $SE_R = SDE_R + SIE_R$			Total systemic exposure: $SE_R = SDE_R + SIE_R + SOE_{R(H)} + SOE_{R(O)}$		
Total systemic exposure	0.068137	mg/person	Total systemic exposure	0.030251	mg/person
Total systemic exposure	**0.001136**	**mg/kg bw/d**	**Total systemic exposure**	**0.001873**	**mg/kg bw/d**
% of AOEL	**2.8**	**%**	**% of AOEL**	**4.7**	**%**

A 1.3 Worker exposure

Table A 11: Input parameters considered for the estimation of worker exposure

Intended use(s):	maize, sugar beet, soybean, sunflower		**Dislodgeable foliar residues (DFR):**	1	µg/cm²/kg as
Application rate (AR):	0.864	kg as/ha	**Transfer coefficient (TC):**	2500	cm²/person/h
Number of applications (NA):	1		**Work rate per day (WR):**	2	h/d
Body weight (BW):	60	kg/person	**PPE**	5	%
Dermal absorption (DA):	39	% ('worst case')			
AOEL	0.04	mg/kg bw/d			

Table A 12: Estimation of worker exposure towards dimethenamid-P using the German re-entry model

Without PPE			**With PPE (gloves, workwear)**		
Worker (re-entry): Systemic dermal exposure after application in maize, sugar beet, soybean, sunflower					
SDE_W = (DFR x TC x WR x AR x NA x DA) / BW			SDE_W = (DFR x TC x WR x AR x NA x PPE x DA) / BW		
(1 x 2500 x 2 x 0.864 x 1 x 39 %) / 60			(1 x 2500 x 2 x 0.864 x 1 x 5 % x 39 %) / 60		
External dermal exposure	4.32	mg/person	External dermal exposure	0.216	mg/person
External dermal exposure	0.072	mg/kg bw/d	External dermal exposure	0.0036	mg/kg bw/d
Total systemic exposure	1.6848	mg/person	Total systemic exposure	0.08424	mg/person
Total systemic exposure	**0.02808**	**mg/kg bw/d**	**Total systemic exposure**	**0.001404**	**mg/kg bw/d**
% of AOEL	**70.2**	**%**	**% of AOEL**	**3.5**	**%**