Committee for Risk Assessment

RAC

Annex 1

Background document

to the Opinion proposing harmonised classification and labelling at Community level of

dimethenamid-P

EC number: -
CAS number: 163515-14-8

CLH-O-0000003037-80-03/A1

The background document is a compilation of information considered relevant by the dossier submitter or by RAC for the proposed classification. It includes the proposal of the dossier submitter and the conclusion of RAC. It is based on the official CLH report submitted to public consultation. RAC has not changed the text of this CLH report but inserted text which is specifically marked as 'RAC evaluation'. Only the RAC text reflects the view of RAC.

Adopted

4 June 2013

CLH report

Proposal for Harmonised Classification and Labelling

**Based on Regulation (EC) No 1272/2008 (CLP Regulation),
Annex VI, Part 2**

Substance Name: Dimethenamid-P

EC Number: **605-329-9**

CAS Number: **163515-14-8**

Index Number:

Contact details for dossier submitter:

BAuA
Federal Institute for Occupational Safety and Health
Federal Office for Chemicals
Friedrich-Henkel-Weg 1-25
D-44149 Dortmund, Germany

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PART A.

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Part A.

1 PROPOSAL FOR HARMONISED CLASSIFICATION AND LABELLING

1.1 Substance

Table 1: Substance identity

Substance name:	***Dimethenamid-P***
EC number:	***605-329-9***
CAS number:	***163515-14-8***
Annex VI Index number:	-
Degree of purity:	***≥ 890 g/kg***
Impurities:	No impurities of toxicological or environmental significance

1.2 Harmonised classification and labelling proposal

Table 2: The current Annex VI entry and the proposed harmonised classification

	CLP Regulation	**Directive 67/548/EEC (Dangerous Substances Directive; DSD)**
Current entry in Annex VI, CLP Regulation	-	-
Current proposal for consideration by RAC	H302-H317 Aquatic Acute 1; H400 Aquatic Chronic 1; H410	R22-R43 N; R50-53
Resulting harmonised classification (future entry in Annex VI, CLP Regulation)	H302-H317 Aquatic Acute 1; H400 Aquatic Chronic 1; H410	R22-R43 N; R50-53

1.3 Proposed harmonised classification and labelling based on CLP Regulation and/or DSD criteria

Proposed harmonised classification and labelling is summarized in Tables 3 and 4.

Table 3: Proposed classification according to the CLP Regulation

CLP Annex I ref	Hazard class	Proposed classification	Proposed SCLs and/or M-factors	Current classification [1)]	Reason for no classification [2)]
2.1.	Explosives				
2.2.	Flammable gases				
2.3.	Flammable aerosols				
2.4.	Oxidising gases				
2.5.	Gases under pressure				
2.6.	Flammable liquids				
2.7.	Flammable solids				
2.8.	Self-reactive substances and mixtures				
2.9.	Pyrophoric liquids				
2.10.	Pyrophoric solids				
2.11.	Self-heating substances and mixtures				
2.12.	Substances and mixtures which in contact with water emit flammable gases				
2.13.	Oxidising liquids				
2.14.	Oxidising solids				
2.15.	Organic peroxides				
2.16.	Substance and mixtures corrosive to metals				
3.1.	Acute toxicity - oral	Acute toxicity, cat. 4 (H302)			
	Acute toxicity - dermal				Conclusive but not sufficient for classification
	Acute toxicity - inhalation				Conclusive but not sufficient for classification
3.2.	Skin corrosion / irritation				Conclusive but not sufficient for classification
3.3.	Serious eye damage / eye irritation				Conclusive but not sufficient for classification
3.4.	Respiratory sensitisation				Data lacking
3.4.	Skin sensitisation	Skin sensitization, cat. 1 (H317)			
3.5.	Germ cell mutagenicity				Conclusive but not sufficient for classification
3.6.	Carcinogenicity				Conclusive but not

					sufficient for classification
3.7.	Reproductive toxicity				Conclusive but not sufficient for classification
3.8.	Specific target organ toxicity –single exposure				Conclusive but not sufficient for classification
3.9.	Specific target organ toxicity – repeated exposure				Conclusive but not sufficient for classification
3.10.	Aspiration hazard				
4.1.	Hazardous to the aquatic environment	Aquatic Acute 1; H400 Aquatic Chronic 1; H410	M-factor: 10		
5.1.	Hazardous to the ozone layer				Data lacking

[1)] Including specific concentration limits (SCLs) and M-factors
[2)] Data lacking, inconclusive, or conclusive but not sufficient for classification

Labelling:

Pictograms: GHS07, GHS09

Signal word: Warning

Hazard statements:
- H302 Harmful if swallowed.
- H317 May cause an allergic skin reaction
- H410 Very toxic to aquatic life with long lasting effects

Precautionary statements:
- P273 Avoid release to the environment
- P391 Collect spillage
- P501 Dispose of contents/container to …

Proposed notes assigned to an entry:

Table 4: Proposed classification according to DSD

Hazardous property	Proposed classification	Proposed SCLs	Current classification [1)]	Reason for no classification [2)]
Explosiveness				
Oxidising properties				
Flammability				
Other physico-chemical properties *[Add rows when relevant]*				
Thermal stability				
Acute toxicity	Xn R 22			
Acute toxicity – irreversible damage after single exposure				Conclusive but not sufficient for classification
Repeated dose toxicity				Conclusive but not sufficient for classification
Irritation / Corrosion				Conclusive but not sufficient for classification
Sensitisation	Xi R 43			
Carcinogenicity				Conclusive but not sufficient for classification
Mutagenicity – Genetic toxicity				Conclusive but not sufficient for classification
Toxicity to reproduction – fertility				Conclusive but not sufficient for classification
Toxicity to reproduction – development				Conclusive but not sufficient for classification
Toxicity to reproduction – breastfed babies. Effects on or via lactation				Conclusive but not sufficient for classification
Environment	N; R50-53	2.5 % ≤ Cn [3)] classification of preparation is N; R50-53 0.25 % ≤ Cn < 2.5 % classification of preparation is N; R51-53 0.025 % ≤ Cn < 0.25 % classification of preparation is R52-53		

[1)] Including SCLs
[2)] Data lacking, inconclusive, or conclusive but not sufficient for classification
[3)] Cn is the concentration of Dimethenamid-P in the preparation

Labelling:

Indication of danger:
Xn Harmful
N Dangerous for the environment

R-phrases:
R 22 Harmful if swallowed.
R 43 May cause sensitization by skin contact.

	R50/53	Very toxic to aquatic organisms, may cause long-term adverse effects to the aquatic environment
S-phrases:	S60	This material and its container must be disposed of as hazardous waste
	S61	Avoid release to the environment. Refer to special instructions/ safety data sheets

2 BACKGROUND TO THE CLH PROPOSAL

2.1 History of the previous classification and labelling

2.2 Short summary of the scientific justification for the CLH proposal

2.3 Current harmonised classification and labelling

2.3.1 Current classification and labelling in Annex VI, Table 3.1 in the CLP Regulation

There is no entry for Dimethenamid-P available in Annex VI, Table 3.1 in the CLP Regulation.

2.3.2 Current classification and labelling in Annex VI, Table 3.2 in the CLP Regulation

There is no entry for Dimethenamid-P available in Annex VI, Table 3.2 in the CLP Regulation.

3 JUSTIFICATION THAT ACTION IS NEEDED AT COMMUNITY LEVEL

Diemthenamid-P is an active substance in the meaning of Directive 91/414/EEC.
In accordance with Article 36(2) of the CLP Regulation, Diemthenamid-P should now be considered for harmonized classification and labelling. Therefore, this proposal considers all human health and environmental endpoints.

RAC general comment
The hazard classes evaluated by the RAC and documented in this opinion are: acute toxicity, skin sensitisation, carcinogenicity, reproductive toxicity and environmental hazards. The Committee did not evaluate any other hazard class related to this substance.

Part B.

SCIENTIFIC EVALUATION OF THE DATA

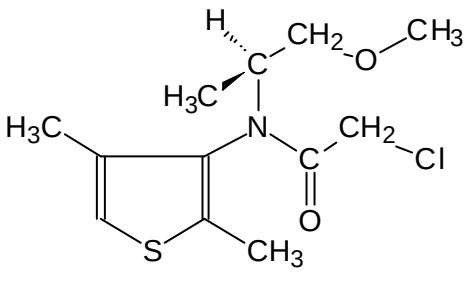
1 IDENTITY OF THE SUBSTANCE

1.1 Name and other identifiers of the substance

Table 5: Substance identity

EC number:	605-329-9
EC name:	Acetamide, 2-chloro-N-(2,4-dimethyl-3-thienyl)-N-[(1S)-2-methoxy-1-methylethyl]-
CAS number (EC inventory):	163515-14-8
CAS number:	163515-14-8
CAS name:	Acetamide, 2-chloro-N-(2,4-dimethyl-3-thienyl)-N-[(1S)-2-methoxy-1-methylethyl]-
IUPAC name:	S-2-chloro-N-(2,4-dimethyl-3-thienyl)-N-(2-methoxy-1-methylethyl)-acetamide
CLP Annex VI Index number:	-
Molecular formula:	$C_{12}H_{18}ClNO_2S$
Molecular weight range:	275.88

Structural formula:



1.2 Composition of the substance

The confidential information can be found in the "Confidential Annex" or the technical dossier.

Table 6: Constituents (non-confidential information)

Constituent	Typical concentration	Concentration range	Remarks
S-2-chloro-N-(2,4-dimethyl-3-thienyl)-N-(2-methoxy-1-methylethyl)-acetamide		≥ 890 g/kg	

Current Annex VI entry:

Table 7: Impurities (non-confidential information)

Impurity	Typical concentration	Concentration range	Remarks

Current Annex VI entry:

Table 8: Additives (non-confidential information)

Additive	Function	Typical concentration	Concentration range	Remarks

Current Annex VI entry:

Physico-chemical properties

Table 9: Summary of physico - chemical properties

Property	Value	Reference	Comment (e.g. measured or estimated)
State of the substance at 20°C and 101,3 kPa	clear yellow brown liquid		
Melting/freezing point	below – 50 °C		
Boiling point	no boiling point up to 280 °C		
Relative density	1.195 g/cm^3 at 20 °C		
Vapour pressure	2.5x10^{-3} Pa at 25 °C		
Surface tension	52.0 mN/m at 20 °C, concentration 0.1 %		
Water solubility	1.45 g/L at 25 °C and pH 6.2		
Partition coefficient n-octanol/water	log Po/w = 1.89		
Flash point	79 °C purity 93.5 %		
Flammability	n.a.		
Explosive properties	not explosive purity 96.7 %, Dimethenamid		
Self-ignition temperature	-		
Oxidising properties	no reaction with reducing agents		
Granulometry	-		
Stability in organic solvents and identity of relevant degradation products	-		
Dissociation constant	no dissociation at pH 1 … 11		
Viscosity	-		

2 MANUFACTURE AND USES

3 CLASSIFICATION FOR PHYSICO-CHEMICAL PROPERTIES

Table 10: Summary table for relevant physico-chemical studies

Method	Results	Remarks	Reference

4 HUMAN HEALTH HAZARD ASSESSMENT

In this report, only summaries are given. A more extensive description of the studies and of the observed findings are included in the draft assessment report, which is attached to the IUCLID dossier.

Dimethenamid is one of many organic substances that occur as "racemic" 50/50 mixtures of stereoisomers, i. e. mirror-image isomers that are chemically identical but refract polarised light in different directions. Dimethenamid was originally registered in Europe and other areas of the world using toxicology studies which were conducted with the 50/50 racemic mixture, which is the product that has been manufactured and marketed to this point. Recently, it was discovered that only the S isomer (Dimethenamid-P; SAN 1289) has useful herbicidal activity. Use of only the S isomer would result in a substantial reduction of the herbicide volume necessary for crop treatment (i. e., a reduction of the environmental burden) without any reduction in herbicidal activity. The other isomer (R) is simply a pesticidally inactive impurity, and removing this isomer should be thought of as removing an unneeded impurity.

For the inclusion of Dimethenamid-P (S-isomer enriched dimethenamid) in Annex I of Directive 91/414/EEC, the long-term and reproductive toxicity studies submitted were not performed with Dimethenamid-P. Instead, the effects of racemic (R,S)-dimethenamid were tested in these extensive studies, which had been completed prior to the discovery of the superior properties of the S-isomer. The so-called "Bridging" concept was applied to avoid the additional conduct of the above mentioned studies with Dimethenamid-P, and thus to save time and costs and avoid additional animal testing. By this Bridging approach, results from toxicological studies available for both racemic dimethenamid and Dimethenamid-P were compared (toxicological studies in mammals designed to directly compare the effects of S- and R,S-dimethenamid were conducted for assessment of dermal absorption only). Provided that the overall evidence attained by the comparative assessment is sufficient to deduce that elimination of the R-isomer from the racemic (R,S)-dimethenamid will not increase the toxicity of the resulting chemical (Dimethenamid-P), it is regarded to be scientifically justified to accept studies conducted with racemic dimethenamid as substitutes for not-available Dimethnamid-p studies.

By comparative assessment of all toxiclogical studies available for both Dimethenamid-P and racemic dimethenamid (acute toxicity, short-term toxicity, genotoxicity and teratogenicity studies), it can be concluded that the S-isomer (= Dimethenamid-P) alone is no more toxic than the R plus S isomers. NOAEL's in 90-d oral and teratogenicity studies were essentially the same for the racemic (R-isomer plus S isomer) as for the S-isomer alone, when normal study to study variation is taken into account. On this basis, it was concluded that in principle the test substances racemic dimethenamid and dimethenamid are equivalent entities and that all studies available for racemic dimethenamid should be considered in the toxicological evaluation of Dimethenamid-P.

There are no toxicological studies performed with impurities. The technical active substance Dimethenamid-P used in formulations is equivalent to Dimethenamid-P that has been used in the toxicological studies. The chemical composition of both is similar. Any component other than the pure active substance, which is present in the technical active substance as manufactured (impurities including non-active isomers) originating from the manufacturing process or from degradation during storage is covered by the toxicological studies. Therefore, no further toxicological studies with impurities have been performed.

4.1 Toxicokinetics (absorption, metabolism, distribution and elimination)

4.1.1 Non-human information

Dimethenamid was well absorbed (>90%) and extensively metabolised by rats. The test substance was widely distributed throughout the organism. The primary excretory route of dimethenamid and its metabolites was via the bile, followed by extensive re-absorption from the gastrointestinal tract. Ultimate elimination occurred via the faecal and urinary routes. By 168 hours after treatment, an average of 90% of the administered dose was eliminated by all routes (35-47% elimination via urine and 48-58% via faeces, low dose). The radioactivity level in blood decreased slowly in rat, which was associated with a certain affinity of dimethenamid an/or its metabolites to red blood cells. However, binding to blood components was demonstrated to not occur in human blood. Levels in other tissues after 168 h were small, and there was no evidence for a bioaccumulation potential (Villafranca et al., 1992 TOX1999-448; Völlmin et al., 1992 TOX1999-406).

The unchanged dimethenamid in excreta accounted for only 1-2% of the dose. There were over 40 metabolites detected in excreta. Over 20 metabolites were structurally identified by MS and NMR, and confirmed with the synthesised reference standards. Metabolism was primarily via glutathione conjugation pathways. Dimethenamid was also metabolised via reductive dechlorination, oxidation, hydroxylation, O-demethylation, and cyclisation. There was no significant difference in absorption, distribution, elimination and metabolism between sexes. There was also no significant difference in percent absorption between the low dose of 10 mg/kg bw and the high dose of 1000 mg/kg bw, or between the single and multiple doses. However, it appeared the elimination via bile was saturated at 1000 mg/kg bw because the elimination via kidney increased for the high dose (Völlmin et al., 1992 TOX1999-406; Dorobek et al., 1993 TOX1999-410; Ekdawi et al., 1992 TOX1999-407; Yu et al., 1992 TOX1999-409).

4.1.2 Human information

No other relevant information is available.

4.1.3 Summary and discussion on toxicokinetics

Following oral intake, dimethenamid was slowly but nearly completely absorbed from the gastrointestinal tract irrespective of dose level, dosage regimen or sex. The test substance was widely distributed throughout the organism and rapidly eliminated via bile and urine. Total elimination rate of radioactivity reached an amount of approx. 90% within 7 d following treatment. Apart from blood, tissue residues steadily declined. While dimethenamid and/or its metabolites did not bioaccumulate, at least in rats a certain affinity to red blood cells was observed. However, binding to blood components was demonstrated to not occur in human blood. Dimethenamid was rapidly and extensively metabolised.

4.2 Acute toxicity

4.2.1 Non-human information

Dimethenamid-P is characterised by a moderate acute toxicity orally and low acute toxicity dermally or by inhalation. The rat oral LD50 is 429 mg/kg bw, the rabbit dermal LD50 is > 2000 mg/kg bw and the rat 4-h inhalation LC50 is > 2.2 mg/l. The following clinical symptoms of acute

Dimethenamid-P intoxication in laboratory animals were observed after oral intake: decreased activity, lacrimation, excessive salivation, yellow ano-genital staining, black and/or brown staining on the snout, oral area, buccal area and/or extremities, lethargy, decreased food consumption and decreased fecal volume. Dimethenamid-P produces only slight reversible skin and eye irritation. According to EU legislation, classification and labelling of Dimethenamid-P as skin or eye irritant is not required. Dimethenamid-P is a skin sensitiser in the Buehler Test. Racemic dimethenamid gave a positive and equivocal test result in two Magnusson-Kligman tests, the other acute toxicity studies conducted with racemic dimethenamid gave similar results as Dimethenamid-P.

The results of the acute toxicity studies including irritancy and skin sensitization are summarised in Table 11.

Table 11: Summary table of relevant acute toxicity studies

Study	Test substance	Species	Results	Reference
Acute oral	Dimethenamid-P	Rat	LD_{50} (m): 429 mg/kg bw LD_{50} (f): 531 mg/kg bw	(Blaszcak, 1996 TOX1999-413)
	Racemic dimethenamid	Rat	LD_{50} (m): 371 mg/kg bw LD_{50} (f): 427 mg/kg bw	(Blaszcak, 1991 TOX1999-451)
Acute dermal	Dimethenamid-P	Rabbit	LD_{50} (m+f): > 2000 mg/kg bw	(Blaszcak, 1996 TOX1999-414)
	Racemic dimethenamid	Rabbit	LD_{50} (m+f): > 2000 mg/kg bw	(Blaszcak, 1991 TOX1999-452)
Acute inhalation (4-h nose-only)	Dimethenamid-P	Rat	LC_{50} (m+f): > 2mg/l (4-h)	(Hoffman, 1996 TOX1999-415)
	Racemic dimethenamid	Rat	LC_{50} (m+f): > 5mg/l (4-h)	(Ullmann, 1986 TOX1999-453)
Skin irritation	Dimethenamid-P	Rabbit	No irritation	(Blaszcak, 1996 TOX1999-416)
	Racemic dimethenamid	Rabbit	No irritation	(Lemen, 1988 TOX1999-454)
Eye irritation	Dimethenamid-P	Rabbit	No irritation	(Blaszcak, 1996 TOX1999-417)
	Racemic dimethenamid	Rabbit	No irritation	(Lemen, 1988 TOX1999-455)
Skin sensitization (Buehler-Test)	Dimethenamid-P	Guinea pig	Sensitizing	(Blaszcak, 1996 TOX1999-418)
Skin sensitization (Magnusson and Kligman)	Racemic dimethenamid	Guinea pig	Sensitizing	(Arcelin, 1995 TOX2000-1560)

4.2.1.1 Acute toxicity: oral

Dimethenamid-P (Blaszcak, 1996 TOX1999-413) and racemic dimethenamid (Blaszcak, 1991 TOX1999-451) has a moderate acute toxicity after single oral application. The rat oral LD50 is 429 mg/kg bw. The following clinical symptoms of acute Dimethenamid-P intoxication in laboratory animals were observed after oral intake: decreased activity, lacrimation, excessive salivation, yellow ano-genital staining, black and/or brown staining on the snout, oral area, buccal area and/or

extremities, lethargy, decreased food consumption and decreased fecal volume (Blaszcak, 1996 TOX1999-413).

4.2.1.2 Acute toxicity: inhalation

Dimethenamid-P and racemic dimethenamid show a low toxicity after inhalative exposure. The acute inhalation toxicity of Dimethenamid-P was determined in Sprague-Dawley rats in a limit test. According to EPA Guidelines, the exposure concentration required for a limit test amounts to > 2 mg/l. This limit differs from the respective OECD and EU requirement (> 5 mg/l). No mortality was observed after 4-h inhalative (nose-only) exposure of rats to a Dimethenamid-P aerosol at a concentration of 2.2 mg/l air or to an aerosol of racemic dimethenamid at a concentration of 4.99 mg/l air (maximum attainable concentration under the exposure conditions). In the study with Dimethenamid-P clinical signs could be observed for up to 2 d in some animals including secretory (lacrimation, chromodacryorrhea, red and clear nasal discharge and dried red facial material) and respiratory (laboured breathing and moist rales) responses. With 2.2 mg/l, the inhalative exposure concentration tested was below the concentration of 5 mg/l required in OECD Guideline No. 403 for limit tests. However, at 2.2 mg/l no mortality and only transient clinical signs clearly indicated low inhalation toxicity. The level tested was considered well above predicted human exposure levels.

4.2.1.3 Acute toxicity: dermal

Dimethenamid-P and racemic dimethenamid show a low toxicity after single dermal exposure. The rabbit dermal LD_{50} is > 2000 mg/kg bw for both, Dimethenamid-P and racemic dimethenamid.

4.2.1.4 Acute toxicity: other routes

No other relevant information is available.

4.2.2 Human information

No other relevant information is available.

4.2.3 Summary and discussion of acute toxicity

To sum up it can be said that no relevant differences betweeen the acute toxicity of racemic dimethenamid and Dimethenamid-P have been found in the submitted studies. In both acute oral toxicity studies with racemic dimethenamid and Dimethenamid-P the lowest LD_{50} were found in male rats. The LD_{50} was 429 mg/kg bw and 371 mg/kg bw for Dimethenamid-P and racemic dimethenamid, respectively. Dimethenamid-P and racemic dimethenamid show low toxicity after single dermal and inhalative exposure.

RAC evaluation of acute toxicity
Summary of the Dossier submitter's proposal The dossier submitter (DS) proposed classification for Acute toxicity Category 4 H302: Harmful if swallowed (Xn; R22 according to DSD). Acute toxicity classification via the inhalation or dermal route was not proposed. The DS's proposal on acute toxicity was based on the following information.

Acute toxicity oral:
Dimethenamid-P was tested for acute oral toxicity in rats and the LD_{50} (males) was 429 mg/kg bw. Clinical signs seen on the day after dosing with dimethenamid-P included: decreased activity, lacrimation, excessive salivation, yellow ano-genital staining, black and/or brown staining on the snout, oral area, buccal area and/or extremities, lethargy, decreased food consumption and decreased faecal volume. All surviving animals were free of clinical signs by day 5 after dosing. Similar signs were seen with the racemic dimethenamid, but were more pronounced at the (higher) top dose of 600 mg/kg bw (LD_{50} = (males) 371 mg/kg bw).

Acute toxicity inhalation:
Dimethenamid-P and racemic dimethenamid showed low toxicity after inhalation exposure. The acute inhalation toxicity of dimethenamid-P was determined in the limit test according to EPA Guidelines (> 2 mg/l) which differs from the OECD/EU requirement (> 5 mg/l). No mortality was observed after 4-h inhalation (nose-only) exposure of rats to a dimethenamid-P aerosol at a concentration of 2.2 mg/l air *(MMAD = approximately 3.4 µm, GSD = 2.0, approximately 4% of particles were ≤ 1.0 µm, approximately 58% were ≤ 4.9 µm and 94% were ≤ 10.0 µm)*. In the study with dimethenamid-P, clinical signs were observed for up to 2 d in some animals and included secretory (lacrimation, chromodacryorrhea, red and clear nasal discharge and dried red facial material) and respiratory (laboured breathing and moist rales) responses. Although an exposure of 2.2 mg/l was below the 5 mg/l limit required by OECD 403, no mortality and only transient clinical signs clearly indicated low inhalation toxicity.

Acute toxicity dermal:
Dimethenamid-P and racemic dimethenamid showed low toxicity after single dermal exposure. The rabbit dermal LD_{50} was > 2000 mg/kg bw for both dimethenamid-P and racemic dimethenamid.

Comments received during public consultation

Comments were received from two member states, both supporting the DS's classification proposal for acute toxicity.

Additional key elements

The CLH report did not summarise the acute toxicity studies in detail and therefore the following additional information concerning the acute inhalation toxicity of the racemic dimethenamid in rats is summarised from the DAR (Draft Assessment Report published in 2005). Five male and five female rats were exposed to a liquid aerosol of racemic (R,S) - dimethenamid at a concentration of 4.99 mg/l of air (maximum attainable concentration under the exposure conditions) for four hours. The observation time was 15 hours. Only 17.5% of the exposed particles were within an inhalable range of 0.4–5.8 µm. The highest percentage of particles (78.7%) were in the size range 9–10 µm and approx. 6% of the aerosol particles had a size of less than 1 µm. Clinical signs observed were sedation, dyspnea, curved body position and ruffled fur in all rats, from the termination of the exposure until day 3 (until day 4 in one animal). All animals survived and the LC_{50} was thus > 4.99 mg/l air. This information supports the proposal for no classification for dimethenamid-P.

Assessment and comparison with the classification criteria

The studies provided to support the classification proposal of the DS are considered reliable and sufficient to assess the classification proposal.

The acute oral toxicity of dimethenamid-P meets the DSD and CLP criteria. Based on the calculated LD_{50} of 429 mg/kg bw, dimethenamid-P should be classified as Acute toxicity, Cat. 4; H302 according to Annex VI of Regulation (EC) No. 1272/2008 (criteria: 300 >ATE < 2000) and R22 'Harmful if swallowed' according to Annex I of Council Directive

67/548/EEC (criteria: 200 < LD_{50} ≤ 2000 mg/kg).

The results of the acute inhalation toxicity studies do not meet the DSD and CLP criteria for classification. The acute inhalation toxicity was determined in a limit test and no mortality was observed after 4-h inhalation exposure of rats to a dimethenamid-P aerosol at a concentration of 2.2 mg/l air or to an aerosol of racemic dimethenamid at a concentration of 4.99 mg/l air (maximum attainable concentration under the exposure conditions). Classification and labelling of dimethenamid-P for acute inhalation is not required.

The results of the acute dermal toxicity studies do not meet the DSD and CLP criteria for classification as there were no mortalities following exposure to 2000 mg/kg bw (dimethenamid-P or dimethenamid). Classification and labelling of dimethenamid-P for acute dermal toxicity is not required.

4.2.4 Comparison with criteria

Table 12: presents the toxicological results in comparison with DSD and CLP criteria.

Toxicological result	DSD criteria	CLP criteria
Oral LD_{50}, rat: 429 mg/kg	Harmful: LD_{50} per oral, rat: 200 < LD_{50} ≤ 2 000 mg/kg	Cat. 4: 300 < LD_{50} ≤ 2000 mg/kg (oral)
Inhalation LC_{50}, rat: > 2 mg/l (aerosol, 4-h)	Harmful: LC_{50} inhalation, rat, for aerosols or particulates: 1 < LC_{50} ≤ 5 mg/litre/4h	Cat.3: 2,0 < LC_{50} ≤ 10,0 mg/l (vapours) Cat. 4: 10,0 < LC_{50} ≤ 20,0 mg/l (vapours)
Dermal LD_{50}: > 2000 mg/kg	Harmful: LD50 dermal, rat or rabbit: 400 < LD_{50} ≤ 2 000 mg/kg	Cat. 4: 1 000 < LD_{50} ≤ 2 000 mg/kg (dermal)

4.2.5 Conclusions on classification and labelling

The acute oral toxicity of Dimethenamid-P meets the DSD and CLP criteria. Based on the results of the acute oral toxicity study Dimethenamid-P has to be classified as harmful and assigned the symbol “Xn” and the indication of danger “harmful” accordingly. The following risk phrase should be assigned: “R22 Harmful if swallowed”.

The results of the acute inhalation toxicity studies do not meet the DSD and CLP criteria because the acute inhalation toxicity was determined in a limit test and no mortality was observed after 4-h inhalative exposure of rats to a Dimethenamid-P aerosol at a concentration of 2.2 mg/l air or to an aerosol of racemic dimethenamid at a concentration of 4.99 mg/l air (maximum attainable concentration under the exposure conditions).

The results of the acute dermal toxicity studies do not meet the DSD and CLP criteria. Classification and labelling of Dimethenamid-P concerning acute dermal or inhalation toxicity is not required.

4.3 Specific target organ toxicity – single exposure (STOT SE)

There is no evidence of specific target organ toxicity after single exposure of Dimethenamid-P or racemic dimethenamid.

4.3.1 Summary and discussion of Specific target organ toxicity – single exposure

No toxicity to a specific organ in the absence of lethality was observed in acute oral, inhalation or dermal toxicity studies. There are no relevant data to discuss specific target organ toxicity after single exposure.

4.3.2 Comparison with criteria

There are no relevant data to compare with criteria.

4.3.3 Conclusions on classification and labelling

Classification and labelling is not required.

4.4 Irritation

4.4.1 Skin irritation

4.4.1.1 Non-human information

The results of the eye irritation toxicity studies are summarised in Table 13.

Table 13: Summary table of relevant skin irritation studies

Study	Test substance	Species	Results	Reference
Skin irritation	Dimethenamid-P	Rabbit	No irritation	(Blaszcak, 1996 TOX1999-418)
Skin irritation	Racemic dimethenamid	Rabbit	No irritation	(Hamburger, 1987 TOX1999-456)

4.4.1.2 Human information

No other relevant information is available.

4.4.1.3 Summary and discussion of skin irritation

Dimethenamid-P produced only slight reversible skin irritation in rabbits. Three of six animals exhibited slight erythema with no edema and 2 animals exhibited very slight (barely perceptible) erythema with no edema. These animals were free of all dermal irritation by 72 h after test material removal. The mean erythema and oedema scores over the first three days were calculated to be 0.8 and 0.0, respectively (Blaszcak, 1996 TOX1999-418).

4.4.1.4 Comparison with criteria

Table 14: Toxicological results in comparison with DSD and CLP criteria.

Toxicological result	DSD criteria	CLP criteria
Mean erythema and oedema scores over the first three days: 0.8 and 0.0, respectively	Mean value of the scores for either erythema and eschar formation or oedema formation: ≥ 2	Mean value of ≥ 2,3 - ≤ 4,0 for erythema/eschar or for oedema

4.4.1.5 Conclusions on classification and labelling

The results of the skin irritation toxicity studies do not meet the DSD and CLP criteria. Classification and labelling of Dimethenamid-P as skin irritant is not required.

4.4.2 Eye irritation

4.4.2.1 Non-human information

The results of the eye irritation toxicity studies are summarised in Table 15.

Table 15: Summary table of relevant eye irritation studies

Study	Test substance	Species	Results	Reference
Eye irritation	Dimethenamid-P	Rabbit	No irritation	(Blaszcak, 1996 TOX1999-417)
Eye irritation	Racemic dimethenamid	Rabbit	No irritation	(Lemen, 1988 TOX1999-455)

4.4.2.2 Human information

No data are available.

4.4.2.3 Summary and discussion of eye irritation

Dimethenamid-P produces only slight reversible eye irritation. Dimethenamid-P was tested for its eye irritating potential in 6 New Zealand White rabbits. All 6 rabbits exhibited slight conjunctival redness and/or chemosis and moderate to severe conjunctival discharge at 1 h after exposure. The discharge and chemosis were not observed at 24 h after treatment. Four animals were free of conjunctival redness by 24 h and the remaining 2 animals were free by 48 h. There were no corneal or iridial effects observed.

4.4.2.4 Comparison with criteria

Table 16: Toxicological results in comparison with DSD and CLP criteria

Toxicological result	DSD criteria	CLP criteria
Mean Score: Corneal Opacity: 0 Conjunctival Redness: 0.11 Conjunctival Swelling: 0	Irritating to eyes: cornea opacity: ≥ 2 - < 3 iris lesion: ≥ 1 - < 1,5 redness of the conjunctivae: ≥ 2,5 oedema of the conjunctivae (chemosis): ≥ 2	Irritating to eyes (Category 2): corneal opacity: ≥ 1 iritis: ≥ 1 conjunctival redness: ≥ 2 conjunctival oedema (chemosis): ≥ 2

4.4.2.5 Conclusions on classification and labelling

Dimethenamid-P is not considered to have produced eye irritation according to DSD and CLP criteria. Therefore, classification and labelling of Dimethenamid-P as eye irritant is not required.

4.4.3 Respiratory tract irritation

4.4.3.1 Non-human information

In the acute (4-hour) inhalation toxicity study in rats with Dimethenamid-P respiratory (laboured breathing and moist rales) responses could only be observed for up to 2 d in some animals. No clinical signs were observed after Day 2. No abnormalities were noted at necropsy (Hoffman, 1996 TOX1999-415). In the acute (4-hour) inhalation toxicity study in rats with racemic dimethenamid only dyspnea as clinical sign was observed through Day 4 with 1 animal. No macroscopic pathology findings related to the test substance were noted at sacrifice (Ullmann, 1986 TOX1999-453).

4.4.3.2 Human information

No relevant data.

4.4.3.3 Summary and discussion of respiratory tract irritation

There is no evidence of respiratory tract irritation from animal tests after exposure of Dimethenamid-P or racemic dimethenamid.

4.4.3.4 Comparison with criteria

There are no relevant data to compare with criteria.

4.4.3.5 Conclusions on classification and labelling

Classification and labelling is not required.

4.5 Corrosivity

There is no evidence of corrosivity of racemic dimethenamid or Dimethenamid-P (see 4.4).

4.5.1 Non-human information

No relevant data.

4.5.2 Human information

No relevant data.

4.5.3 Summary and discussion of corrosivity

There are no relevant data to discuss corrosivity of racemic dimethenamid or Dimethenamid-P.

4.5.4 Comparison with criteria

There are no relevant data to compare with criteria.

4.5.5 Conclusions on classification and labelling

Classification and labelling is not required.

4.6 Sensitisation

4.6.1 Skin sensititsation

The skin sensitizing potential was assessed using the Buehler test. For induction, 20 Dunkin-Hartley Guinea pigs (10/sex) received topical applications of 0.3 ml of the undiluted (100%) test substance on one flank for 6 h under occlusive dressing. Treatments were once weekly for 3 wk. Ten untreated animals served as controls. A topical challenge application of 0.5 ml of undiluted (100%) test substance preparation was carried out 14 d after the third induction by treatment of the untreated, opposite flank using the same procedure as that for induction. The control animals were also treated during the challenge phase to differentiate dermal irritation scores from sensitization reactions. Readings for dermal changes were performed 24 and 48 h after patch removal.

Racemic dimethenamid was tested for its sensitizing effect on the skin of the Guinea pig in the Maximization Test according to Magnusson and Kligman. In a pretest, moderate to severe scale induction was observed after exposure to either a 1 or 5% solution in DMSO. Slight redness was induced in 1 of 2 Guinea pigs administered the 5% solution, therefore, the main test was performed using the 5% dilution. In the main test, 20 animals were used in each of the negative control, test and positive control groups. The first phase of induction was conducted by intracutaneous injections of adjuvant alone, 5% test substance solution in DMSO, or 5% test substance in adjuvant. After 7 d, the application site of both test and control groups were shaved and topically treated with a 10% Sodium laurylsulfate aqueous solution to induce skin irritation. 24 h later, the second phase of induction followed with a 48 h topical application of DMSO only (controls) or of 5% test substance solution in DMSO. The challenge performed 2 wk after the dermal induction consisted of 24-h

topical exposure of both control and treatment groups to 5% test substance solution in DMSO. Skin reactions were scored immediately, 24 and 48 h after patch removal.

The results of the skin sensitization toxicity studies are summarised in Table 17.

Table 17: Summary table of relevant skin sensitisation studies

Study	Test substance	Species	Results	Reference
Skin sensitization (Buehler-Test)	Dimethenamid-P	Guinea pig	Sensitizing	(Blaszcak, 1996 TOX1999-418)
Skin sensitization (Magnusson and Kligman)	Racemic dimethenamid	Guinea pig	Sensitizing	(Arcelin, 1995 TOX2000-1560)

4.6.1.1 Non-human information

No other relevant information is available.

4.6.1.2 Human information

No relevant data are available.

4.6.1.3 Summary and discussion of skin sensitisation

Dimethenamid-P is a skin sensitiser in the Buehler Test. Irritation increased in incidence and severity during the induction phase. At challenge, 17/20 test animals exhibited clear dermal responses compared to 0/10 in the controls. Racemic dimethenamid gave a positive test result in a Magnusson-Kligman test. No positive reactions were observed in the control group. All treatment animals had very slight to well defined erythema at the 24 hour reading, and 15/19 still showed a skin reaction at 48 hours.

4.6.1.4 Comparison with criteria

Table 18: Toxicological results in comparison with DSD and CLP criteria

Toxicological result	DSD criteria	CLP criteria
Dimethenamid-P: 85 % of the animals positive Racemic dimethenamid: 100 % of the animals positive	Adjuvant type test method: ≥ 30 % of the animals positive Other test method: ≥ 15 % of the animals positive	Adjuvant type test method: ≥ 30 % of the animals positive Non-adjuvant test method: ≥ 15 % of the animals positive

Table 19: Skin sensitisation potency of the Buehler occluded patch test

Concentration for intradermal induction (% w/v)	Incidence sensitised guinea pigs (%)	Potency
> 20	≥ 15 (17/20)	moderate

Table 20: Skin sensitisation potency of the Maximization Method of Magnusson and Kligman

Concentration for intradermal induction (% w/v)	Incidence sensitised guinea pigs (%)	Potency
5	≥ 30 (15/19)	moderate

4.6.1.5 Conclusions on classification and labelling

Dimethenamid-P is considered to be a skin sensitizer in the Buehler test and has to be classified accordingly. The result is confirmed by a maximization test according to Magnusson and Kligman with racemic dimethenamid. Racemic dimethenamid was shown to produce dermal sensitization in guinea pigs, too.

RAC evaluation of skin sensitisation

Summary of the Dossier submitter's proposal

The DS's proposal was Skin sensitisation Category 1B H317 according to CLP (Xi;R43 according to DSD). The proposal was based on two tests: a Buehler test where Guinea pigs were exposed to dimethenamid-P and a Magnusson and Kligman test where Guinea pigs were exposed to racemic (R,S)-dimethenamid.

Dimethenamid-P tested positive in a Buehler assay. The induction dose of aqueous 91.1% dimethenamid-P caused irritation which increased in incidence and severity during the induction phase. When challenged with undiluted test substance, 17/20 test animals (85%) exhibited clear dermal responses compared to 0/10 in the controls.

Racemic dimethenamid gave a strong positive test result in a Magnusson-Kligman test. 5% in DMSO was used for the intradermal and topical inductions and for challenge. All treated animals (100%) had very slight to well defined erythema (grade 2; 16/20, grade 1; 3/20 (1 mortality)) at the 24 hour reading, and 15/19 (79%) still showed a skin reaction (grade 2; 4/20, grade 1; 11/20, grade 0; 4/20) at 48 hours. No positive reactions were observed in the control group.

The DS concluded that dimethenamid-P was a skin sensitiser (1B) on the basis of the Buehler test and should be classified accordingly. The DS also concluded that the positive maximization test (Magnusson and Kligman) carried out with the racemic dimethenamid confirms the result of the Buehler test and supports the proposed classification.

Comments received during public consultation

Two member states supported the DS's proposal for classification as Skin sens. 1B (H317).

Additional key elements

Some additional information with regard to the degree of dermal reaction at both induction and challenge in the Buehler test is summarised below. This detailed information was not available in the CLH report and was obtained from the study report:

Table 1. Individual dermal scores* at induction (100% undiluted test substance, i.e. dimethenamid-P)

	Induction					
	1st		2nd		3rd	
	24 hours	48 hours	24 hours	48 hours	24 hours	48 hours

Males						
1	0	0	1	1	1	1
2	0	0	0.5	1	1	1
3	0	0	0.5	0.5	1	1
4	0	0	0.5	0.5	0.5	0.5
5	0	0	0.5	1	1	1
6	0	0	0.5	0.5	1	0.5
7	0	0	0.5	1	1ed	1ed
8	0	0	0.5	1	1ed	1ed
9	0.5	0	0.5	0.5	0.5	0.5
10	0	0	0.5	0.5	0.5	0.5
Females						
1	0	0	0	0	1	1
2	0	0	0.5	1	1	3w, ed
3	0	0	0.5	0.5	0.5	0.5
4	0	0	0.5	0.5	1	1
5	0	0	1	1.0	1	1
6	0	0	0	0	0.5	0.5
7	0	0	0.5	0.5	1	0.5
8	0	0	1	0.5	1ed	1ed
9	0	0	0.5	0.5	0.5	0.5
10	0	0	0.5	0	0.5	0.5
*erythema score according to Draize; w = white tissue; ed = edema						

Table 2. Incidence of dermal response to challenge (the original table in the DAR: Table B.6.2-8: Buehler Test – Incidence of Dermal Responses at Challenge).

Group	Hrs	Dermal scores 0	0.5	1	2	3	Ed	E	B	P[1]	N	IIS[2]
Treatment	24	0	4	16	0	0	4	0	0	17	20	85%
	48	2	7	10	1	0	2	0	0		20	
Irritation Control[3]	24	9	1	0	0	0	0	0	0	0	10	0%
	48	10	0	0	0	0	0	0	0		10	

[1] P = Positive response; number of animals with a score of 1 or greater at 24 and/or 48 h, out of the 10 or 20 animals per group

[2] Incidence Index of Sensitization =P/N x 100, where N =total number of animals

[3] Irritation control groups were treated at Challenge only

Ed=Edema; E=Eschar; B=Black/dark tissue

Assessment and comparison with the classification criteria

Two studies summarised in the CLH report were evaluated by the RAC.

The first study, a guideline-compliant Buehler test (Blaszcak, 1996) on dimethenamid-P, showed a strong positive dermal sensitising potential with 85% of the animals tested giving a positive response to undiluted test substance in both induction and challenge phases.

The second study, a maximation test according to Magnusson and Kligman (GPMT), was reported as acceptable. In this study in guinea pigs, 5% racemic (R,S)-dimethenamid was used for intradermal induction and 100% for topical induction. The challenge was performed with undiluted test substance. Slight to well defined erythema was seen in 100% of the guinea pigs at the 24 hour observation and in 79% at 48 hours.

CLP Criteria: According to the 2nd ATP CLP, classification in Cat 1 is appropriate where data are not sufficient for sub-categorisation into Cat 1A or Cat 1B. Sub-categorisation into either Cat 1A or 1B is on the basis of either frequency of occurrence in humans and/or degree of potency in animal studies as follows.

Classification into Cat 1 is based on a ≥ 30% positive response in an adjuvant type test such as the M&K test or a ≥15% positive response in a non-adjuvant test such as a Buehler test.

Sub-categorisation is based on the following:

Guinea pig maximisation test
Category 1A:
≥ 30 % responding at ≤ 0.1 % intradermal induction dose or
≥ 60 % responding at > 0.1 % to ≤ 1 % intradermal induction dose
Categrory 1B:
≥ 30 % to < 60 % responding at > 0.1 % to ≤ 1 % intradermal induction dose or
≥ 30 % responding at > 1 % intradermal induction dose
Buehler assay
Category 1A:
≥ 15 % responding at ≤ 0.2 % topical induction dose or
≥ 60 % responding at > 0.2 % to ≤ 20 % topical induction dose
Categrory 1B:
≥ 15 % to < 60 % responding at > 0.2 % to ≤ 20 % topical induction dose or
≥ 15 % responding at > 20 % topical induction dose

Given that there was a high level of responders after intradermal induction with 5% racemic dimethenamid in the GPMT, there is a strong possibility that a slightly lower intradermal induction concentration of 1% would still result in a high level of responders. As intradermal induction concentrations lower than 5% were not tested, the data are in principle insufficient to decide on the appropriate subcategory.

Accordingly, it is not possible to use the data presented for dimethenamid-P to sub-categorise, as the only dose tested in the induction phases was in excess of the limits described above and positive responses were between 79 and 100% in both tests.

RAC concluded that classification of dimethenamide-P as Skin Sens. 1 is therefore warranted.

According to the DSD criteria (≥ 30% positive in an M&K test, ≥15% positive in a Buehler test), classification as R43 is supported.

4.6.2 Respiratory sensitisation

4.6.2.1 Non-human information

No relevant data are available.

4.6.2.2 Human information

No relevant data are available.

4.6.2.3 Summary and discussion of respiratory sensitisation

There are no relevant data to discuss respiratory sensitisation.

4.6.2.4 Comparison with criteria

There are no relevant data to compare with criteria.

4.6.2.5 Conclusions on classification and labelling

No conclusion can be drawn on respiratory sensitisation potential.

4.7 Repeated dose toxicity

4.7.1 Non-human information

The short-term toxicity of Dimethenamid-P was investigated in 28-d and 90-d oral studies in rats. Furthermore, short-term oral feed studies using racemic dimethenamid were conducted in rats (5-wk and 90-d), mice (90-d) and dogs (90-d and 1-yr). In addition, the short-term toxicity following dermal exposure was determined in a 21-d study in rabbits. The results of the short-term toxicity of Dimethenamid-P and racemic dimethenamid are summarised in Table 21.

Table 21: Summary table of relevant repeated dose toxicity studies

Study	Dose levels	Results	Reference
4-d oral, rat (Investigations of liver enzyme Induction)	Racemic dimethenamid 0-25-100-200-400 mg/kg bw/d	400 mg/kg bw/d: ↓ bw gain, ↑ liver wt, ↑ ALAT, ↓ urine volume, ↓ urine creatinine, ↓ urine protein, ↓ urine urea, ↑ PROD, ↑ EROD, ↑ UDPGT, ↓ glutathione 200 mg/kg bw/d: ↑ UDPGT 100 mg/kg bw/d: ↑ liver wt, ≥ 25 mg/kg bw/d: ↑ glutathione s-transferase and NADPH reductase	(Dorobek et al., 1994 TOX1999-449)
28-d oral, rat (range-finding)	Dimethenamid-P 0–"150"–500–1500–3000 ppm (12 – 50 – 143 – 290 mg/kg bw/d)	≥ 500 ppm: ↑ liver wt 3000 ppm: ↓ bw and bw gain No histopathology performed NOAEL: not established	(Randall, 1996 TOX1999-419)
5-wk oral, rat (range-finding)	Racemic dimethenamid 0–30–100–300–1000–3000 ppm (2.92 – 9.5 – 28.8 – 95.6 – 285 mg/kg bw/d)	300 ppm: ↑ cholesterol, slight (m) ≥ 1000 ppm: ↑ liver wt, ↑ cholesterol, moderate (m) 3000 ppm: ↓ bw, bw gain and food intake, ↑ cholesterol (m+f), ↑ GGT, slight hepatocell. cytoplasmic swelling NOAEL: 29 mg/kg bw/d (300 ppm)	(Carpy et al., 1987 TOX1999-468)
90-d oral, rat	Dimethenamid-P 0–500–1500–3000 ppm (37 – 110 – 222 mg/kg bw/d)	≥ 1500 ppm: ↓ bw and bw gain, ↑ GGT (m); ↑ liver wt, hepatocellular hypertrophy (m+f). 3000 ppm: ↑ cholesterol (m+f) NOAEL: 37 mg/kg bw (500 ppm)	(Blanset, 1996 TOX1999-421)
90-d oral, rat	Racemic dimethenamid 0–50–150–500–1500–3000 ppm (3.5 – 10 – 34 – 98 – 204 mg/kg bw/d)	≥ 1500 ppm: ↓ bw and bw gain, ↓ feed intake; ↑ protein, ↑ cholesterol (f) ↑ liver wt (f); ↑ hepatocell. hypertrophy (f) 3000 ppm: ↑ GGT (m), cholesterol (m+f); ↑ liver wt (m) NOAEL: 33.5 mg/kg bw/d (500 ppm)	(Ruckman et al., 1987 TOX2002-916) (Kuettler, 1999 TOX1999-467)
90-d oral, mouse (range-finding)	Racemic dimethenamid 0–300–700–2000–5000 ppm (46 – 105 – 301 – 805 mg/kg bw/d)	≥700 ppm: ↑ liver wt ≥ 2000 ppm: Subdued behavior; ↑ rel. kidney wt; 5000 ppm: ↓ bw gain and food intake no ophthalmology, haematological or clinical chemistry investigations performd; histopathological assessment confined to liver and kidney NOAEL: 46 mg/kg bw/d (300 ppm)	(Warren et al., 1988 TOX1999-422)
90-d oral, dog	Racemic dimethenamid 0–91.5–750–2000 ppm (4.3 – 34 – 87 mg/kg bw/d)	≥ 750 ppm: ↓ bw gain; ↑ liver wt; hepatocyte periportal vacuolation and dilatation of liver sinusoids 2000 ppm: ↑ AP and cholesterol NOAEL: 4.3 mg/kg bw/d (91.5 ppm)	(Greenough et al., 1986 TOX1999-423) (Greenough et al., 1986 TOX1999-424)
1-yr oral, dog	Racemic dimethenamid 0–50–250–1500 ppm (2 – 10 – 49 mg/kg bw/d)	1500 ppm: ↓ bw gain, ↑ serum AP and cholesterol, hepatocyte enlargement and vacuolation, ↑liver wt NOAEL: 10 mg/kg bw/d (250 ppm)	(Greenough et al., 1988 TOX1999-433) (Greenough et al., 1988 TOX1999-434)

21-d dermal, rabbit	Racemic dimethenamid 0–1190 mg/kg bw/d	Dermal irritation; no substance-related systemic findings NOAEL: 1190 mg/kg bw/d	(Sommer et al., 1990 TOX1999-420)

4.7.1.1 Repeated dose toxicity: oral

After oral treatment, the signs of toxicity observed in rats, mice and dogs were overall similar with the liver as the target organ. The effects observed typically included the increase in one or more serum liver enzymes and changes in cholesterol levels. Increased liver weights were observed in all three species. Histologically, hepatocyte hypertrophy was observed in rats and hepatocyte vacuolation and dilatation of liver sinusoids occurred in dogs.

Feeding of racemic dimethenamid to dogs for 1 year resulted in decreased body weight gain and changes indicative of liver alteration at the high dose. Liver changes included increased alkaline phosphatase and cholesterol, increased liver weight and hepatocyte enlargement and vacuolation.

In order to assess the validity of the Bridging Concept, the toxicological effects observed in 13-wk oral rat studies conducted with either Dimethenamid-P or racemic dimethenamid revealed only marginal differences between the two studies. The NOAELs and LOAELs were the same irrespective of the test substance administered. Therefore, on the basis of the available data, the requirements were considered to have been met for a scientifically-based justification of the Bridging Concept for Dimethenamid-P / racemic dimethenamid.

4.7.1.2 Repeated dose toxicity: inhalation

No relevant data are available.

4.7.1.3 Repeated dose toxicity: dermal

In a 3-wk dermal toxicity study in rabbits no substance-related systemic findings were detected up to the highest dose level tested (1190 mg/kg bw/d).

4.7.1.4 Repeated dose toxicity: other routes

No relevant data are available.

4.7.1.5 Human information

No relevant data are available.

4.7.1.6 Other relevant information

In a further in vivo study with rats, the qualitative and quantitative effects of dimethenamid on liver enzymes, blood and urine parameters were investigated. Oral administration of dimethenamid to rats for 4 days induced several liver enzyme systems. It was demonstrated that the metabolism of dimethenamid involves oxidation steps mainly by cytochrome P450 dependent enzymes, and glutathione conjugation and glucuronidation. Upon removal from treatment, there was a recovery from the liver changes. The induction of these enzymes represent a physiological adaptation in the liver to remove the chemical (Dorobek et al., 1994 TOX1999-449).

4.7.1.7 Summary and discussion of repeated dose toxicity

After oral treatment, the signs of toxicity observed in rats, mice and dogs were overall similar with the liver as the target organ. The effects observed typically included the increase in one or more serum liver enzymes and changes in cholesterol levels. Increased liver weights were observed in all three species. Histologically, hepatocyte hypertrophy was observed in rats and hepatocyte vacuolation and dilatation of liver sinusoids occurred in dogs.

In vivo studies with rats demonstrated that there is a recovery from the liver changes upon removal from treatment (Ruckman et al., 1987 TOX2002-916; Dorobek et al., 1994 TOX1999-449). In longterm studies in rats and mice there was no evidence of a treatment-related increase in liver neoplasms. The liver effects observed in rats, mice and dogs are indicative of an adaptive response to oral exposure.

4.7.1.8 Summary and discussion of repeated dose toxicity findings relevant for classification according to DSD

The liver effects observed in rats, mice and dogs are indicative of an adaptive response to oral exposure. There is no evidence of repeated dose toxicity findings relevant for classification according to DSD.

4.7.1.9 Comparison with criteria of repeated dose toxicity findings relevant for classification according to DSD

There are no repeated dose toxicity findings relevant to compare with criteria for classification according to DSD.

4.7.1.10 Conclusions on classification and labelling of repeated dose toxicity findings relevant for classification according to DSD

Classification and labelling is not required.

4.8 Specific target organ toxicity (CLP Regulation) – repeated exposure (STOT RE)

4.8.1 Summary and discussion of repeated dose toxicity findings relevant for classification as STOT RE according to CLP Regulation

After oral treatment, the signs of toxicity observed in rats, mice and dogs were overall similar with the liver as the target organ. The effects observed typically included the increase in one or more serum liver enzymes and changes in cholesterol levels. Increased liver weights were observed in all three species. Histologically, hepatocyte hypertrophy was observed in rats and hepatocyte vacuolation and dilatation of liver sinusoids occurred in dogs.

In vivo studies with rats demonstrated that there is a recovery from the liver changes upon removal from treatment (Ruckman et al., 1987 TOX2002-916; Dorobek et al., 1994 TOX1999-449). In longterm studies in rats and mice there was no evidence of a treatment-related increase in liver neoplasms.

The liver effects observed in rats, mice and dogs are indicative of an adaptive response to oral exposure. There is no evidence of repeated dose toxicity findings relevant for classification according to CLP Regulation.

4.8.2 Comparison with criteria of repeated dose toxicity findings relevant for classification as STOT RE

There are no repeated dose toxicity findings relevant to compare with criteria for classification as STOT RE.

4.8.3 Conclusions on classification and labelling of repeated dose toxicity findings relevant for classification as STOT RE

Classification and labelling is not required.

4.9 Germ cell mutagenicity (Mutagenicity)

4.9.1 Non-human information

Dimethenamid-P was evaluated for its potential genotoxicity *in vitro* using bacterial and mammalian cell mutagenicity tests, a chromosome damage (clastogenicity) test and an unscheduled DNA synthesis test. In addition genotoxicity studies conducted with racemic dimethenamid were submitted for comparative evaluation. Overall, the results do not indicate that Dimethenamid-P or racemic dimethenamid possess a genotoxic potential.

The results of the mutagenicity tests of Dimethenamid-P and racemic dimethenamid are summarised in Table 22 and table 23.

Table 22: Summary table of relevant in vitro genotoxicity studies

Study/strains/species	Test Material	Results	Reference
Ames mutagenicity test TA-1535, 100, 1537, 98; E. coli WP2 uvrA; with & without	Dimethenamid-P	Positive in one assay with TA 100 in the absence of S-9 mix; negative in two independent repeat assays	(Wagner et al., 1996 TOX1999-425)
Ames mutagenicity test TA 1535, 1537, 1538, 98, 100; with & without	Racemic dimethenamid	Negative	(Haworth et al., 1989 TOX1999-459)
CHO/HGPRT mutagenicity test; with & without	Dimethenamid-P	Negative	(San et al., 1996 TOX1999-429)
V79/HGPRT mutagenicity test; with & without	Racemic dimethenamid	Negative	(Debets et al., 1986 TOX1999-460)
In vitro Chromosome aberration in CHO cells; with & without	Dimethenamid-P	Equivocal	(Curry et al., 1996 TOX1999-430)
In vitro UDS, rat primary hepatocytes	Dimethenamid-P	Negative	(San et al., 1996 TOX1999-431)
In vitro UDS, rat primary hepatocytes	Racemic dimethenamid	Inconclusive	(Müller, 1986 TOX1999-462)
In vitro UDS, rat primary hepatocytes	Racemic dimethenamid	Positive	(Cifone, 1989 TOX1999-463)

Table 23: Summary table of relevant in vivo genotoxicity studies

Study/strains/species	Test Material	Results	Reference
In vivo UDS, rat primary hepatocytes	Racemic dimethenamid	Negative	(Ward, 1993 TOX2001-472)
In vivo mouse micronucleus test 103 – 205 – 410 mg/kg bw (i.p. injection)	Dimethenamid-P	Negative	(Putman et al., 1996 TOX1999-432)
In vivo mouse micronucleus test 1000 mg/kg bw (oral gavage)	Racemic dimethenamid	Negative	(Völkner, 1986 TOX1999-465)
In vivo mouse micronucleus test 710 mg/kg bw/d, 2 d (oral gavage)	Racemic dimethenamid	Negative	(Marshall, 1993 TOX1999-466)

4.9.1.1 In vitro data

Dimethenamid-P was evaluated for its potential genotoxicity *in vitro* using bacterial and mammalian cell mutagenicity tests, a chromosome damage (clastogenicity) test and an unscheduled DNA synthesis test. The mutagenicity tests were negative, with the exception of a single positive result obtained in the Ames Test with *S.typhimurium* strain TA-100 in the absense of an exogenous metabolic activation system. This result could not be reproduced in several repeat assays. The *in vitro* chromosome aberration study gave equivocal test results both in the presence and absence of an exogenous metabolic activation system.

In addition to the studies mentioned above, additional genotoxicity studies conducted with racemic dimethenamid were submitted for comparative evaluation. The test results obtained in bacterial and mammalian mutagenicity testing were negative. An *in vitro* chromosome aberration assay with racemic dimethenamid was submitted but not performed according to currently accepted guidelines. Three *in vitro* assays for unscheduled DNA synthesis (UDS) conducted with racemic dimethenamid were submitted. One study gave a positive test result; the other two tests (one of which was not acceptable) gave inconclusive results due to poor experimental design or reporting.

4.9.1.2 In vivo data

However, the result of the corresponding *in vivo* assay for chromosomal aberration, *i.e.* the mouse micronucleus test, gave a clearly negative result, indicating that Dimethenamid-P has no chromosome-damaging potential. The results of the toxicokinetic studies confirmed that the test compound reached the bone marrow after oral treatment.

An *in vivo* UDS assay with rats and an *in vivo* micronucleus test with mice gave negative results with racemic dimethenamid.

4.9.2 Human information

No relevant information is available.

4.9.3 Other relevant information

No other relevant information is available.

4.9.4 Summary and discussion of mutagenicity

By comparative assessment of all toxiclogical studies available for both Dimethenamid-P and racemic dimethenamid (acute toxicity, short-term toxicity, genotoxicity and teratogenicity studies), it can be concluded that the S-isomer (= Dimethenamid-P) alone is no more toxic than the R plus S isomers. On this basis, it can be concluded that in principle the test substances racemic dimethenamid and dimethenamid are equivalent entities and that all studies available for racemic dimethenamid should be considered in the toxicological evaluation of Dimethenamid-P.

Overall, the results do not indicate that Dimethenamid-P or racemic dimethenamid possess a genotoxic potential.

4.9.5 Comparison with criteria

The results of the in vitro as well as the in vivo studies demonstrated, that Dimethenamid-P has no mutagenic or clastogenic potential.

4.9.6 Conclusions on classification and labelling

Classification and labelling is not required.

4.10 Carcinogenicity

4.10.1 Non-human information

Only studies with racemic dimethenamid were available for assessement of long-term toxicity. The findings of the long-term studies are summarised in Table 24.

Table 24: Summary table of relevant carcinogenicity studies

Study	Test Material	Results	Reference
104-wk oral feed, rat	racemic dimethenamid 0–100–700–1500 ppm	1500 ppm: ↓ food consumption and ↑ bw gain, lenticular opacities; ↑ serum γ-GGT (m) and cholesterol (f), ↑ urinary ketones (m); ↑ rel. liver wt (f) epithelial hyperplasia of the stomach (m), altered eosinophilic hepatocytes (m), bile duct hyperplasia (f), cystically dilated bile ducts (f), hyperplasia of parathyroid (m) 700 ppm: ↓ food consumption ↓ bw gain (f); ↑ rel. liver wt; bile duct hyperplasia (f), hyperplasia of parathyroid (m) NOAEL: 100 ppm (5 mg/kg bw/d)	(Ruckman et al., 1990 TOX1999-435) (Ruckman, 1995 TOX2002-939) (Ruckman, 1990 TOX1999-436)
94-wk oral feed, mice	racemic dimethenamid 0–30–300–1500–3000 ppm	≥1500 ppm: ↓ bw gain, ↑ rel. liver wt, ↑ rel. kidney wt (f) and enlarged hepatocytes 3000 ppm: ↑ incidence of stomach hyperkeratosis NOAEL: 300 ppm (40 mg/kg bw/d)	(Hooks et al., 1990 TOX1999-438) (Hooks, 1995 TOX2002-941)

m = male; f = female

4.10.1.1 Carcinogenicity: oral

The results of a 2-yr chronic/oncogenicity study in rats indicated that a maximum tolerated dose was clearly met at the high dose of 1500 ppm (ca. 80 mg/kg bw/d males; 109 mg/kg bw/d females). This is demonstrated by a body weight gain depression for the first 80 wk of treatment in males and females. The liver was a target organ for dimethenamid in the rat. Observations included an increase in serum γ-glutamyltransferase and cholesterol, an increase in liver weight and liver pathology including altered eosinophilic hepatocytes, bile duct hyperplasia and cystically dilated bile ducts. Other effects noted in high dose males were an increase in epithelial hyperplasia of the limiting ridge of the stomach and hyperplasia in the parathyroid. The mid dose of 700 ppm produced body weight gain decreases and liver alterations in females.

A carcinogenicity study in mice was conducted up to 3000 ppm, which represented the maximum tolerated dose as evidenced by significant body weight gain depression. As with the rat and dog, the liver was the apparent target organ in mice. Liver weights were increased, and hepatocyte enlargement was observed at the 2 highest dose levels. An additional finding in mice was hyperkeratosis of the limiting ridge of the stomach. There was no evidence of a treatment-related increase in neoplasms.

In summary, long-term feeding studies with dimethenamid in rats and mice demonstrated that the primary target organ was the liver.

4.10.1.2 Carcinogenicity: inhalation

No relevant data are available.

4.10.1.3 Carcinogenicity: dermal

No relevant data are available.

4.10.2 Human information

No relevant data are available.

4.10.3 Other relevant information

No other relevant data are available.

4.10.4 Summary and discussion of carcinogenicity

A slight increase in liver tumors was noted at the high dose. The incidence of carcinomas was not statistically different from controls and was within historical control range. The incidence of adenomas was also not statistically different from controls but was just slightly outside of historical control range at the conducting laboratory. The slight increase in adenomas was most likely due to a considerably increased survival at the high dose compared to control. The increased survival allowed for more old age animals to develop the spontaneously occurring adenoma which increases in incidence with age. In addition, the incidence for dimethenamid in high dose males was well within the historical control range for Sprague-Dawley rats as compiled by the Registry of Industry Toxicology Animals (RITA). There was no evidence of a treatment-related increase in neoplasms in mice. In summary, no evidence of a carcinogenic potential in rats and mice could be established.

4.10.5 Comparison with criteria

No evidence of a carcinogenic potential could be established.

4.10.6 Conclusions on classification and labelling

Classification and labelling is not required.

RAC evaluation of carcinogenicity
Summary of the Dossier submitter's proposal The DS did not propose classification for carcinogenicity. Chronic toxicity and oncogenicity studies were only conducted with racemic (R,S)-dimethenamid. The results of a 2-yr chronic/oncogenicity study in rats indicated that the high dose of 1500 ppm (ca. 80 mg/kg bw/d males; 109 mg/kg bw/d females) was a maximum tolerated dose This is demonstrated by a body weight gain depression for the first 80 wk of treatment (15% in males and 23% in females). The liver was a target organ for the racemic dimethenamid in the rat. Observations included an increase in serum γ-

glutamyltransferase and cholesterol, an increase in liver weight and liver pathology including altered eosinophilic hepatocytes, bile duct hyperplasia and cystically dilated bile ducts. Other effects noted in high dose males were an increase in epithelial hyperplasia of the limiting ridge of the stomach, posterior lenticular opacity, and hyperplasia in the parathyroid. There was no evidence of a treatment-related increase in neoplasms.

A carcinogenicity study in mice was conducted up to the maximum tolerated dose as evidenced by significant body weight gain depression. As with the rat, the liver was the apparent target organ in mice. Liver weights were increased, and hepatocyte enlargement was observed at the two highest doses. In addition, hyperkeratosis of the limiting ridge of the stomach was observed in high-dose animals at the interim sacrifice time-point only. Increased kidney weights observed in mid- and high-dose females were not accompanied by corresponding histopathological findings and were therefore regarded to be of equivocal toxicological significance. There was also no evidence of a treatment-related increase in neoplasms.

The overall combined (males and females) NOAELs obtained in long-term studies were:

Rats: 5 mg/kg bw/d
Mice: 40 mg/kg bw/d.

In summary, long-term feeding studies with the racemic dimethenamid in rats and mice demonstrated that the primary target organ was the liver. No treatment related increases in neoplasms were noted in mice or rats. It was concluded that the racemic dimethenamid has no carcinogenic potential.

Comments received during public consultation

There were no comments on carcinogenicity.

Assessment and comparison with the classification criteria

Rat study (Ruckman, 1990)

Liver adenoma: In addition to the findings addressed above, a slight increase in liver tumours was noted at the high dose in male rats only. The incidence of carcinomas was not statistically different from controls and was within the historical control range. The incidence of adenomas was also not statistically different from controls but was just slightly outside of historical control range at the conducting laboratory. The slight increase in adenomas in males was most likely due to a considerably increased survival at the high dose compared to control (36% in controls vs 62% at 1500 ppm). The increased survival allowed a larger number of older age animals to develop the spontaneously occurring adenoma which increases in incidence with age. The incidence for the racemic dimethenamid in high dose males was slightly outside the HRC historical control range but well within the historical control range for Sprague-Dawley rats as compiled by the Registry of Industry Toxicology Animals (RITA).
Overall, the slight increase in the benign liver tumour in high-dose males does not indicate that the racemic dimethenamid is carcinogenic. The increase was not statistically significant, was within historical control range for Sprague-Dawley rats and was most likely due to the considerable increase in survival at that dose.

Ovarian tubular adenoma: The original report indicated a slight increase in ovarian tubular adenomas. In view of the borderline nature of the ovarian findings, and of recent advances in diagnostic criteria for rodent ovarian neoplasia, a pathology peer review was conducted following the issue of the final report. The original and peer review analyses for ovarian tumours and hyperplasia are tabulated below. Between the original review and the peer review, pathology terminology had changed. Lesions originally diagnosed as ovarian tubular adenomas or hyperplasia were rediagnosed as sertoliform tubular adenoma or hyperplasia. This change in terminology reflects a change from the original

classification of these neoplasms as epithelial in nature (tubular adenoma) to their current grouping with the other sex cord-stromal neoplasms. Neoplasms diagnosed by the original pathologist as "tubular adenomas" were reclassified by the reviewers as "Sertoliform tubular adenomas". They consist of tubular structures lined by Sertoli-like cells. They differ from true Sertoli cell tumours in that the tubular cells lack basal nuclei and vertically oriented cytoplasm.

In general, the differentiation between Sertoliform tubular hyperplasia and adenoma is difficult and subjective because of the diffuse nature of the lesion. There is a biological continuum from hyperplasia to adenoma. In the original report pathologists diagnosed adenoma when at least 50% of the ovary was involved. Lesions below this threshold size were diagnosed as hyperplasia. The reviewers used similar criteria, but also considered compression of surrounding ovarian stroma to be indicative of neoplasia rather than hyperplasia.

The peer review found (relative to the original pathology report) 1 additional tumour in the control group, 2 additional tumours in the low and mid dose groups and 1 less tumour at the high dose.

The final analysis demonstrated that there is no statistical or biologically significant incidence of ovarian tumours. The incidence at the high dose is within historical control range, and the difference in incidence from control is not statistically significant.
When incidences of adenoma and hyperplasia were combined for analysis, there was only a minimal difference between the control group and the high dose group. The organ weights of the ovaries of the high dose group were not increased in comparison with the controls.
Sertoliform tubular hyperplasia and adenoma are mainly found in the Sprague-Dawley (SD) rat. These lesions are rarely found in other strains of rat.

There is also information available on sertoliform tubular adenoma in the literature(Boorman and Everitt 2006; Dixon *et al*. 1999; Gregson *et al.* 1984) that support the conclusion of the DS that these adenomas are more common in SD rats and support the discussion on reclassification of the original tumours. Boorman and Everitt (2006) state that sertifoliform tubular adenomas comprise the majority of sex cord/stromal adenomas in SD rats (Gregson et al. 1984), and gives the incidence of tubular ademonas (a definition which now includes the sertoliform tubular adenoma) in SD rats (5903 SD rats from 1978-1984) as approx 74% in long-term studies. Sertoliform tubular adenoma differs from sertoli cell tumour in that the tubular cells lack a basement nuclei and vertically oriented cytoplasm. These were more commonly seen in SD rats than other strains and were previously classified with epithelial tumours and described as tubular adenomas (Dixon et al 1999).

In conclusion, the possible increase in ovarian tubular hyperplasia and adenoma is not likely to be treatment-related.

RAC concluded that classification for carcinogenicity is not required for dimethenamid–P, as there was no increase in tumours which was considered related to treatment in the long-term studies in rats with the racemic dimethenamid. In addition, RAC agreed with the DS that there was no evidence that the racemic dimethenamid produced a carcinogenic effect in mice.

References

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Proliferative lesions of the ovary, uterus, vagina, cervix and oviduct in rats. URG-5. In: Guides for Toxicologic Pathology. STP/ ARP/AFIP. Washington. DC.

Gregson, R. L., Lewis, D. J. and Abbott, D. P. 1984. Spontaneous Ovarian Neoplasms of the Laboratory Rat. Vet Pathol 1984 21: 292.

4.11 Toxicity for reproduction

The reproductive and developmental toxicity of racemic dimethenamid was investigated in a 2-generation reproduction study in rats as well as in prenatal toxicity studies in rats and rabbits. Additionally as a part of the bridging concpept a prenatal toxicity study in rats with Dimethenamid-P was performed. The results of all reproduction toxicity studies are summarised in the following table.

Table 25: Summary table of relevant reproductive toxicity studies

Study	Test Material	Results	Reference
2-gen., oral feed, rat	Racemic dimethenamid 0–100–500–2000 (ppm)	Parental toxicity: 2000 ppm: ↓ food intake, ↓ bw gain (m), ↑ liver wt Pup toxicity: 2000 ppm: ↓ bw gain during lactation NOAEL (mg/kg bw/d): Systemic tox. parents: 50 (500 ppm) Systemic/developml. tox. pups: 50 Reproduct. function: 150 (2000 ppm)	(Sutter et al., 1989 TOX1999-439)
Prenatal tox., oral gavage, rat	Dimethenamid-P 0–25–150–300 (mg/kg bw/d)	Maternal toxicity: 300 mg/kg bw/d: ↓ bw gain and food consumption; clinical signs, ↑ liver wt 150 mg/kg bw/d: ↓ bw gain and food consumption 25 mg/kg bw/d: ↓ body weight gain and food consumption Embryo-fetal toxicity: ≥150 mg/kg bw/d: slightly lower fetal body weights, ↑ delayed skeletal ossifications (considered spurious) NOAEL (mg/kg bw/d): Maternal toxicity: < 25 Embryo-/fetotoxicity: 25	(York, 1996 TOX1999-440)
Prenatal tox., oral gavage, rat	Racemic dimethenamid 0–50–215–425 (mg/kg bw/d)	Maternal toxicity: ≥ 215 mg/kg bw/d: ↓ bw gain, ↓ feed consumption, clinical signs, ↑ liver wt Embryo-fetal toxicity: ≥ 215 mg/kg bw/d: ↑ early resorptions 425 mg/kg bw/d: ↓ live litter size NOAEL (mg/kg bw/d): Maternal toxicity: 50 Embryo-/fetotoxicity: 50	(Lochry, 1987 TOX1999-458)
Prenatal tox., oral gavage, rabbit	Racemic Dimethenamid 0–37.5–75–150 (mg/kg bw/d)	Maternal toxicity: ≥ 75 mg/kg bw/d: ↓ bw gain, clinical signs 150 mg/kg bw/d: ↓ food intake, ↓ bw loss Embryo-fetal toxicity: 150 mg/kg bw/d: Abortions in 2 animals NOAEL (mg/kg bw/d): Maternal toxicity: 37.5 Embryo-/fetotox.: 75.0	(Hoberman, 1988 TOX1999-441)

4.11.1 Effects on fertility

4.11.1.1 Non-human information

Racemic dimethenamid was administered to Wistar rats over 2 parental generations with 1 litter produced in each of the first and second parental generations. There were no adverse effects on

reproductive parameters of the parental animals at any dose level. Clear signs of general, systemic toxicity occurred in both parental generations at 2000 ppm. The only substance-related effect on pups was a decreased pup weight gain during lactation at 2000 ppm. Therefore, the NOAEL for reproductive function is 2000 ppm (151 mg/kg bw/d). The NOAEL for parental systemic toxicity and developmental toxicity is 500 ppm (37.5 mg/kg bw/d). No reproductive effects were noted up to parentally toxic doses in the 2-generation rat study.

4.11.1.2 Human information

No relevant information is available.

4.11.2 Developmental toxicity

4.11.2.1 Non-human information

The administration of Dimethenamid-P to pregnant Sprague-Dawley rats during organogenesis produced distinct signs of maternal toxicity at the high dose of 300 mg/kg bw/d as evidenced by initial body weight loss, subsequent reduced maternal body weight gain and food consumption, clinical observations and increased liver weight. Maternal body weight gain and food consumption were also reduced at 150 mg/kg bw/d. Slight fetal weight decreases were observed at 150 and 300 mg/kg bw/d. The only differences noted from control at 25 mg/kg bw/d were a slight and transient decrease in maternal body weight gain and reduced food consumption. during the first three days of treatment For this study, the NOAEL for maternal toxicity is <25 mg/kg bw/d. The NOAEL for developmental toxicity is 25 mg/kg bw/d.

In the prenatal toxicity study in rats using racemic dimethenamid significant maternal toxicity at 425 mg/kg bw/day was evidenced by initial body weight loss, subsequent reduced maternal weight gain, reduced food consumption, clinical observations and increased liver weight. A reduced maternal body weight gain and reduced food consumption also occurred at 215 mg/kg bw/day. Marginal fetal body weight decreases were observed at 215 and 425 mg/kg bw/day. An increase in early resorptions occurred at the high dose and to a lesser extent at the mid dose. Slight and transient decreases in body weight gain and food consumption during the first three d of treatment at 50 mg/kg bw/day were considered to not be of toxicological significance. Therefore, the NOAEL for maternal and develop¬mental toxicity is 50 mg/kg bw/day bw. There were no teratogenic effects observed which were considered related to treatment

In the rabbit prenatal toxicity study, racemic dimethenamid produced clear signs of maternal toxicity at 150 mg/kg bw/d as evidenced by reduced food consumption, bodyweight loss and clinical signs. Maternal toxicity, though less severe, was also observed at the mid dose including reduced body weight gain, reduced absolute food consumption and clinical signs. Although two abortions occurred in the high-dose group, this finding must be seen in connection with the accompanied clear maternal toxicity, especially for rabbits. The NOAEL for maternal toxicity was 37.5 mg/kg bw/d, and the developmental toxicity NOAEL was 75 mg/kg bw/d.

4.11.2.2 Human information

No relevant information is available.

4.11.3 Other relevant information

No other relevant information is available.

4.11.4 Summary and discussion of reproductive toxicity

Reproductive function was not affected in the 2-generation study, so the NOAEL for reproductive function is the highest dose tested (2000 ppm, ca. 150 mg/kg bw/d). The NOAEL concerning systemic toxicity for the parental animals in the 2-generation study was 500 ppm (ca. 50 mg/kg bw/d). The only pup effect noted was a decreased body weight gain during lactation at the high dose. The NOAEL for developmental toxicity in the F1 and F2 litters was 500 ppm (ca. 50 mg/kg bw/d).

In the prenatal toxicity study in rats using Dimethenamid-P, developmental toxicity was observed at the two highest doses tested. The developmental effects included reduced fetal weights and an increase in delayed ossifications. These variations have been shown to be reversible delays in development associated with slower growth in smaller fetuses. Further evaluation demonstrated that the increases in delayed ossifications were due to unusually low control values and not related to treatment. Maternal toxicity was observed in all dose groups The NOAEL for developmental toxicity was 25 mg/kg bw/d, the NOAEL for maternal toxicity was <25 mg/kg bw/d.

In the prenatal toxicity study in rats using racemic dimethenamid the NOAEL`s for maternal toxicity and developmental toxicity were 50 mg/kg bw/d.

The different NOAEL`s in the studies with racemic dimethenamid and Dimethenamid-P are partly caused by the different used dose levels in both studies. The different maternaltoxic dose levels could also be attributed to normal inter-study differences. The study with racemic dimethenamid was performed in 1987, the study with Dimethenamid-P in 1996. But the submitted studies on short term toxicity show that there is no relevant difference of the short term toxicity between racemic dimethenamid and Dimethenamid-P. Therefore the submitted studies on developmental toxicity in rats are nevertheless acceptable as part of the bridging concept.

In the rabbit prenatal toxicity study, significant maternal toxicity was observed at the high dose and less severe effects were noted at the mid dose. Abortions in 2 high-dose animals were considered treatment-related, but must be seen in conjunction with clear maternal toxicity. The NOAEL for maternal toxicity was 37.5 mg/kg bw/d and the developmental toxicity NOAEL was 75 mg/kg bw/d.

The lowest NOAEL for developmental toxicity was 25 mg/kg bw/d (rat prenatal toxicity study, Dimethenamid-P).

In summary, Dimethenamid-P does not show any adverse effects on sexual function and fertility in adult males and females or developmental toxicity in the offspring. Dimethenamid-P has not to be classified as reproductive toxicant.

4.11.5 Comparison with criteria

No evidence of a reproductive toxicity could be established.

4.11.6 Conclusions on classification and labelling

Classification and labelling is not required.

RAC evaluation of reproductive toxicity

Summary of the Dossier submitter's proposal

The DS did not propose classification for reproductive toxicity.

Fertility:
Reproductive function was not affected in the 2-generation study (Suter et al, 1989) and therefore the NOAEL for reproductive function is the highest dose tested (2000 ppm, ca. 150 mg/kg bw/d). The NOAEL for systemic toxicity in the parental animals in the 2-generation study was 500 ppm (ca. 50 mg/kg bw/d). The only pup effect noted was decreased body weight gain during lactation at the high dose. The NOAEL for developmental toxicity in the F1 and F2 litters was 500 ppm (ca. 50 mg/kg bw/d).

Development:
In the prenatal toxicity study in rats using dimethenamid-P, developmental toxicity was observed at the two highest doses tested. The developmental effects included reduced foetal weights and an increase in delayed ossifications. These variations have been shown to be reversible delays in development associated with slower growth in smaller fetuses. Further evaluation demonstrated that the increases in delayed ossifications were due to unusually low control values and were not related to treatment. Maternal toxicity was observed in all dose groups. The NOAEL for developmental toxicity was 25 mg/kg bw/d and the NOAEL for maternal toxicity was <25 mg/kg bw/d.

In the prenatal toxicity study in rats using racemic dimethenamid, the NOAELs for maternal toxicity and developmental toxicity were 50 mg/kg bw/d. The different NOAELs in the studies with racemic dimethenamid and dimethenamid-P are partly explained by the different dose levels used in these studies. The different maternally toxic dose levels between the studies could also be attributed to normal inter-study differences. The study with racemic dimethenamid was performed in 1987 and the study with dimethenamid-P in 1996. However, the submitted repeated dose toxicity studies show that there is no significant difference in the short term toxicity between racemic dimethenamid and dimethenamid-P. Due to the compatible findings in the repeated dose studies conducted with racemic dimethenamid and dimethenamid-P the submitted studies on developmental toxicity in rats are nevertheless acceptable as part of the bridging concept.

In the rabbit prenatal toxicity study, significant maternal toxicity was observed at the high dose and less severe effects were noted at the mid dose. Abortions in 2 high-dose animals were considered treatment-related, but must be seen in with the context of clear evidence for maternal toxicity at that dose. The NOAEL for maternal toxicity in rabbits was 37.5 mg/kg bw/d and the developmental toxicity NOAEL was 75 mg/kg bw/d. The lowest NOAEL for developmental toxicity was 25 mg/kg bw/d (rat prenatal toxicity study, dimethenamid-P).

In summary, dimethenamid-P does not show any adverse effects on sexual function and fertility in adult males and females or developmental toxicity in the offspring. Classification of dimethenamid-P as a reproductive toxicant is not warranted.

Comments received during public consultation

None

Assessment and comparison with the classification criteria

Overall Assessment

In the rat multigeneration study (7.5-151 mg/kg bw/d) there were no effects on reproductive function or offspring and parental toxicity was demonstrated at the high dose. The first rat developmental study (York, 1996) (25-300 mg/kg bw/d) showed clear maternal toxicity at 300 mg/kg and some toxicity at 150 mg/kg bw/d. In this study, the very marginal reductions in mean foetal weight and some reduced ossification were not considered to be significant or biologically relevant. In the 2nd rat developmental study

(Lochry, 1987) (50-425 mg/kg bw), the mid- and high-doses were maternally toxic and a significant increase in early resorptions occurred from the mid-dose. The mean resorption incidence was outside the historical controls although not statistically significant. In general, treatment-related increased early resorptions is infrequently observed. It may be associated with a very specific targeting of the foetus early in development and are not regarded as general non-specific developmental retardation/systemic toxicity, such as may be linked to severe maternal toxicity or generally retarded foetal development. This effect was not seen in the multigeneration study (litter size not affected) and also was not seen in the later rat study (York, 1996). In addition, there was no adverse effect on the developing embryo/foetus in the rabbit study. Therefore, the finding is inconsistent with the other data presented.

The RAC concludes that the findings in Lochry (1987) do not represent sufficient grounds for a classification proposal for Repr. 2; H361 (CLP)/Cat 3; R63 (DSD), as the finding has no support from the other data presented.

Supplemental information - In depth analyses by RAC

The level of information in the CLH report did not allow a full consideration of the apparent effects and developmental toxicity in the rat and rabbit, therefore the studies are evaluated by RAC in this section.

The evaluation concerns the apparently treatment-related increase in early resorptions at the intermediate and high dose in the rat study (Lochry, 1987). The extent of maternal toxicity and information with regard to statistical significance of the foetal effect are also evaluated. In addition, some discussion of the occurrence of abortions at the high dose in the rabbit study is also included (Hobermann, 1988).

Additional details are taken from the DAR (e.g. the tables below) and presented here to assist full analysis of these points.

<u>2-generation study in the rat, (Suter P., et al., 1989):</u>
Racemic dimethenamid was administered to groups of 25 male and 25 female sexually immature Wistar rats for 70 days prior to mating (F0 parental generation) in the diet at concentrations of 0; 100; 500 or 2000 ppm (approx. equiv. to 7.5, 37.5 and 151.0 mg/kg bw/day, respectively). Groups of 25 males and 25 females selected from F1 pups as the F1 parental generation were offered diets containing 0; 100; 500 and 2000 ppm of the test substance post weaning for 101 d, and the breeding program was repeated to produce an F2 litter. The study was terminated with the sacrifice of the F2 weanlings and F1 adult animals.

Results
Parental: Clear signs of general, systemic toxicity occurred in both parental generations at 2000 ppm. Toxicity was characterised by decreased food consumption and increased liver weight in both sexes and impaired body weight gain in males. At 500 ppm the increase in liver weight was very slight (F0 males 4%, females 10%; F1 males 3%, females 4%), and therefore was considered not to represent an adverse effect.
Offspring: There were no effects on pup survival. At 2000 ppm, pup body weight gains were reduced during the lactation period for both the F1 and F2 generations. There was no effect on pup body weights at 500 or 100 ppm.

RAC concludes that no detail is given on the extent of reduced weight gain post-natally. It could be assumed that this represents generally systemic toxicity resulting from substance intake once pups begin to eat the diet.

<u>Oral (gavage) developmental toxicity study in rats (York, R., 1996):</u>
Dimethenamid-P was administered to 25 pregnant female (SD) rats/group at dosages of 25,

150 and 300 mg/kg bw on Days 6–15 post coitum (p.c.). The test substance was suspended in 0.5% aqueous carboxymethylcellulose after first adhering the test substance to HiSil 233 as the carrier.

Results:

Table 5. Maternal findings

Findings:		Dose level (mg/kg bw/d)			
		0	25	150	300
Food consumption (Days 6–9 p.c.)	Mean±SD	23.9±2.6	21.7±2.2**	18.5±2.6**	16.5±3.3**
	[% control]	100	91	77	69
Body weight gain (Days 6–16 p.c.)	Mean±SD	+59.6±11.9	+51.3±9.0**	+48.7±8.0**	+44.5±9.9**
	[% control]	100	86	82	75
Rel. liver weight [% body weight]	Mean±SD	4.07±0.27	4.01±0.27	4.20±0.24	4.41±0.35**
	[% control]	100	98.5	103	108

**= Significnatly different from the control group value ($p<0.01$, Dunnett's test)

Significant reduction of mean food consumption and body weight gain occurred at all doses. There were no mortalities, abortions or premature deliveries. Clinical signs of toxicity at 300 mg/kg bw included; excess lacrimation, piloerection, excess salivation, decreased motor activity, orange substance on fur, swollen ocular membrane, ptosis, dark pink skin, urine stained abdominal fur and coldness to touch. Relative liver weight was increased at 300 mg/kg.

There were no treatment-related effects on pre- or postimplantation loss, on the number of resorptions or number of viable foetuses, or on the sex distribution of foetuses. Mean foetal weight was slightly reduced at 300 mg/kg bw/d (-3%) and 150 mg/kg bw/d (-2%) compared to the control value (not statistically significant).

No treatment-related findings occurred in relation to external, soft tissue or skeletal malformations. Distended ureters were seen in 7 high dose fetuses in 3 litters compared to 3 control group fetuses in 2 litters. Because the litter incidence did not differ significantly from control, this increase was not considered treatment related. At 300 and 150 mg/kg bw/d there was an increase in the incidence of retarded ossifications, sternal centra and pelvic pubes. Further evaluation of the delayed ossifications indicated that these differences were spurious, primarily due to unusually low control values, and were not related to treatment.

Conclusion: The administration of dimethenamid-P to pregnant Sprague-Dawley rats during organogenesis produced distinct signs of maternal toxicity at the high dose of 300 mg/kg bw/d; initial body weight loss, subsequent reduced maternal body weight gain and food consumption, clinical observations and increased liver weight. Maternal body weight gain and food consumption were also reduced at 150 mg/kg bw/d. Slight foetal weight decreases were observed at 150 and 300 mg/kg bw/d. The NOAEL for maternal toxicity is <25 mg/kg bw/d. The NOAEL for developmental toxicity is 25 mg/kg bw/d.

RAC verifies the findings as described above, i.e., some retarded ossification and very marginal, statistically non-significant reductions in foetal weight at the high dose which was associated with clear maternal toxicity.

<u>Developmental toxicity of racemic dimethenamid administered by gavage to SD rats (Lochry, E.A., 1987):</u>

Results - Maternal toxicity:

Table 6: Maternal toxicity

Observations	Dose group (mg/kg bw/d)			
	0	50	215	425
Mortality	2	0	0	0
Excess salivation	0/25	2/25 (2 rat×days)	20/25** (31 rat×days)	20/25** (63 rat×days**)
Urine-stained fur	1/25 (1 day)	0/25	0/25	2/25 (4 rat×days **)
Thin appearance	0/25	0/25	0/25	1/25 (3 d **)
Body weight gain				
– Dosing period (days 6–16)	+57.1 g	+51.8 g	+47.8 g**	+37.2 g**
–Gestational period (days 0–20)	+160 g	+156.5 g	+152.7 g	+143.2 g**
Final body weight (day 20)	415.5 g	413.1 g	409.3 g	401.0 g
Liver weight	16.82 g	17.80 g	17.94 g*	19.31 g**
Relative liver weight	4.06%	4.32%*	4.39%**	4.82%**

* Significantly different from the control value (P<0.05)
** Significantly different from the control value (P<0.01)

Significant maternal toxicity was seen at the high dose and consisted of; increased clinical signs of general toxicity; body weight loss during the first 3 days of treatment; reduced body weight gain up to day 12 p.c. (35% reduced weight for the overall treatment period at 425 mg/kg and also 16% reduced at 215 mg/kg). Relative liver weight was significantly increased at all doses (6%, 8% and 19%, respectively).

Table 7: Relevant caesarean and offspring data.

Observations		Dose group (mg/kg bw/d)			
		0	50	215	425
Animals tested	n	25	25	25	25
Animals pregnant	n(%)	24 (96)	25 (100)	23 (92)	23 (92)
Animals pregnant + sectioned on Day 20	n	22	24	23	23
Corpara lutea	mean	17.5	17.4	18.2	17.6
Implantations	mean	15.9	15.8	16.3	16.0
Live litter size	mean	15.2	14.8	14.9	13.9
Live fetuses	total n	335	355	342	320
Dead fetuses	total n	0	0	0	0
Early resorptions	total (mean ± S.D.)	14 (0.6 ± 1.0)	21 (0.9± 0.8)	32 (1.4 ± 1.3)	47 (2.0 ± 2.8)
– Historical Control (810 litters, 34 groups 1985–1986) mean (range): 0.8 (0.3 – 1.4)[1]					
Late resorptions	total (mean ± S.D.)	0 (0.0)	2 (0.1± 0.3)	0 (0.0)	2 (0.1± 0.3)
% dead or resorbed conceptuses/litter ± S.D.		3.8 ± 6.1	6.2± 6.0	9.0 ± 9.1	10.7 ± 10.4
– Historical Control (497 litters, 36 groups, 1985–1986) mean (range): 5.9 (2.1 – 9.4)					
Dams with any resorptions	n(%)	9 (41)	15 (63)	16 (70)	18 (78)
Dams with complete resorption	n(%)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.3)
Dams with viable foetuses	n (%)	22 (100)	24 (100)	23 (100)	22 (95.6)
No. (%) litters with altered development		6 (27.3%)	7 (29.2%)	4 (17.4%)	7 (31.8%)
No. (%) fetuses with any alteration		13 (3.9%)	9 (2.5%)	4 (1.2%)	9 (2.8%)
% fetuses with any alteration per litter		3.93%	3.59%	1.22%	3.36%

* Significantly different from the control value (P<0.05)
** Significantly different from the control value (P<0.01)

[1] An early resorption incidence of 1.4 was reached in 1 of 34 historical control groups only [the next highest incidence reported was 1.3 (1x) followed by 1.2 (2x) and 1.1 (1x)].

A dose-related increase in resorption was observed in groups administered 215 and 425 mg/kg bw/d, which in the high-dose group resulted in a decrease in the average live litter size. Neither of these observations were significantly different from concurrent control values upon statistical data analysis. However, based on historical control data, the increased incidences of early resorptions observed at 215 and 425 mg/kg bw/d are regarded as related to treatment. At doses of 215 and 425 mg/kg bw/d, a dose-dependent increase in the average percentage of resorbed conceptuses per litter was observed. Although not statistically significant, the high-group value exceeded the historical control range. No other Caesarean-delivery parameter was affected.

Foetal body weights were marginally decreased at 215 (-1%) and at 425 (-2%) mg/kg bw/d. However, these very slight differences from control were not considered toxicologically significant, and were not discussed in the original report. They are mentioned here only for comparison to similar slight foetal body weight effects observed with the p isomer.

Table 8: Mean foetal body weights (gms/litter)

Dose (mg/kg/day)	**0**	**50**	**215**	**425**
Live foetal body weights				

- means	3.67±0.23	3.67±0.23	3.63±0.20	3.60±0.42
- male foetuses	3.78±0.24	3.87±0.33	3.74±0.23	3.72±0.44
- females	3.56±0.24	3.52±0.38	3.54±0.20	3.48±0.43

Conclusion: Significant maternal toxicity at 425 mg/kg/d was evidenced by initial weight loss, reduced weight gain, reduced food consumption, clinical observations and increased liver weight. Reduced food consumption and weight gain were also noted at 215 mg/kg/day. Marginally lower foetal weight was observed at 215 and 425 mg/kg bw/d, and is not statistically significant and not considered to be biologically relevant. An increase in early resorptions at 425 mg/kg/d (not statistically significant) was outside the range of the historical control data and is considered treatment-related and biologically relevant. RAC notes that this effect was seen at a significantly maternally toxic dose level.

Developmental Toxicity Study of dimethenamid-p administered Orally (Stomach Tube) to New Zealand White Rabbits (Hoberman, A, 1988):

Racemic dimethenamid was tested for prenatal toxicity in NZW rabbits. The test substance was combined with equal amounts of HiSil and suspended in aqueous 0.5% carboxylmethylcellulose (CMC). 20 pregnant female rabbits/group were administered the test substance by stomach tube at doses of 37.5, 75 and 150 mg/kg bw on Days 6–18 post insemination (p.i.). A dose volume of 10 ml/kgbw was used. The control group was dosed with an amount of HiSil in CMC equal to that given the high dose group.

Results
Clear maternal toxicity occurred at 150 mg/kg bw/d, as evidenced by reduced food consumption weight loss from days 6-19 and clinical signs. 2 dams aborted at the high dose; this was considered treatment-related. Slightly reduced weight gain was seen at the mid-dose and significant ($p<0.05$) inhibition occurred at 150 mg/kg bw/d between days 12-15; weight loss between days 15-19 ; and a reduction in weight gain overall in the dosing period 6-19 days.

Table 9. Substance related maternal findings

	Dose level (mg/kg bw/day)			
	0	**37.5**	**75**	**150**
Abortion/premature delivery	0/20	0/20	0/20	2/20
Localised alopecia				
-incidence	5/20	4/20	3/20	10/20
-maximum incidence	53/480	47/480	25/480	92/480**
Reduced faeces	0/20	0/20	1/20	2/20
Rel feed consumption [g feed/kg bw/d]				
(% control)	100%	95.8%	94.7%	76.5%*
-days 6-19	100%	89.5%	82.7%	60.0%*
-days 15-19				
Body weight change (kg)				
-days 6-19	+0.18±0.11	+0.12±0.17	+0.14±0.21	0.03±0.28
-days 12-15	+0.10±0.05	+0.00±0.11	-0.04±0.13	-0.07±0.10*
-days 15-19	+0.04±0.08	+0.00±0.11	-0.04±0.17	-0.07±0.12

Maximum incidence: No. rabbits observed / examined multiplied by the numbers of days observed
*=Statistically significant from control ($p<0.05$)
**= Statistically significant from control ($p<0.01$)

There were no effects on implantation, live litter size, foetal sex ratio or foetal body weight. Likewise, there were no effects on external, soft tissue or skeletal variations or malformations.

Conclusion: Clear maternal toxicity was seen in rabbits at 150 mg/kg bw/d, at which dose

two abortions also occurred. Given the well-recognised sensitivity of pregnant rabbits to toxicity which is often associated with abortion, the incidences at this dose level are considered as evidence of maternal toxicity. There were no adverse effects on foetal development.

References

Hoberman, A. M. (1988): Developmental toxicity (embryo/fetal toxicity and teratogenic potential)
study of SAN 582 H administered orally (stomach tube) to New Zealand white rabbits; document
number(s): ARGUS 1319-003 / 1988/11376; document date: 1988-05-10; BfR document number:
TOX1999-441

Lochry, E. A. (1987): Developmental toxicity (embryo/fetal toxicity and teratogenic potential)
study of SAN 582 H administered orally via gavage to Crl:COBS CD (SD)BR presumed pregnant
rats; document number(s): ARGUS 1319-001 / 1987/11225; document date: 1987-07-23; BfR
document number: TOX1999-458

Suter, P., Biedermann, K., Wilson, J. Th, and Terrier, Ch (1989): SAN 582 H: Two-generation
reproduction study in the rat; document number(s): 201205 / 60/90 / 1990/11140; document date:
1989-05-17; BfR document number: TOX1999-439

York, R. G. (1996): Oral (gavage) developmental toxicity study of SAN 1289 H in rats; document
number(s): ARGUS 1819-010 / 1997/5274; document date: 1996-10-23; BfR document number:
TOX1999-440

4.12 Other effects

4.12.1 Non-human information

4.12.1.1 Neurotoxicity

Acute toxicity studies with racemic dimethenamid and Dimethenamid-P gave no evidence of a neurotoxic effect. Therefore, a specific acute neurotoxicity study was not warranted.

Racemic dimethenamid and Dimethenamid-P have been investigated in several subchronic and chronic exposure studies in three species. Parameters investigated included daily observations of the animals for behavioral effects and a complete histopathological investigation of the nervous system. There was no evidence of an effect on the nervous system in any of these studies. Therefore, a specific subchronic test was not warranted.

A study of delayed neurotoxicity in hens has not been conducted because Dimethenamid-P does not belong to organophosphorous or carbamate compounds and there was no evidence of an effect on the nervous system in other toxicological studies.

4.12.1.2 Immunotoxicity

Toxicity studies with racemic dimethenamid and Dimethenamid-P gave no evidence of immunotoxicity.

4.12.1.3 Specific investigations: other studies

The pharmacokinetic studies indicated that dimethenamid may bind to blood components in rats. This was based on 3% of the radiolabled material administered remaining in the blood fraction. Therefore, the nature of the interaction between dimethenamid and rat blood was investigated. The results of the study showed that dimethenamid did not produce methemoglobin in rat blood following a four day treatment. Dimethenamid was shown to bind to rat hemoglobin, primarily to the globin portion, but no binding was demonstrated using human blood (Villafranca M. et al., 1992).

The difference in hemoglobin binding between humans and rats is explained by the difference in three dimensional structure between the 2 species. It is known from the literature that the cysteine residue β-125 in rat hemoglobin is accessible for chemical substitution, but in human hemoglobin, the sequence does not contain a cysteine residue in position 125. In summary, it can be concluded that the interaction between dimethenamid and hemoglobin is a species-specific reaction. This binding is irrelevant for humans (Villafranca et al., 1992 TOX1999-448).

In a further in vivo study with rats, the qualitative and quantitative effects of dimethenamid on liver enzymes, blood and urine parameters were investigated. Oral administration of dimethenamid to rats for 4 days induced several liver enzyme systems. It was demonstrated that the metabolism of dimethenamid involves oxidation steps mainly by cytochrome P450 dependent enzymes, and glutathione conjugation and glucuronidation. Upon removal from treatment, there is a recovery from the liver changes (Dorobek et al., 1994 TOX1999-449).

4.12.1.4 Human information

No data available.

4.12.2 Summary and discussion

There are no other relevant effects.

4.12.3 Comparison with criteria

There are no other relevant effects to compare with criteria for classification and labelling.

4.12.4 Conclusions on classification and labelling

Classification and labelling is not required.

5 ENVIRONMENTAL HAZARD ASSESSMENT

5.1 Degradation

Table 26: Summary of relevant information on degradation

Method	Results	Remarks	Reference
Ready biodegradability(OECD 301F)	No study submitted.	Dimethenamid-P is presumably not readily biodegradable	
Water/sediment study (OECD 308)	DT50 water: 20.3 and 27.7 d (1st order, river and pond system, resp.) DT90 water: 67.4 and 92.1 d DT50 whole system: 23.4 and 33.4 d DT90 whole system: 77.8 and 110.9 d		Wyss-Benz, M.: RCC Project No. 361146, BASF Doc. 94/10641, 1994
Adsorption/Desorption (OECD 106)	K_{OC} values of 90 – 474, Dimethenamid-P can be predicted to have a medium to high mobility in soil.		Tong, T. M. and Su, L.Y. (1997): BASF RegDoc.# 97/5180; BOD 1999-504
Hydrolytic degradation (EPA 161-1; OECD 111)	stable at pH 5, 7 and 9 (31 days, 25 °C)		Guirguis (1997): WAS1999-164
Photochemical degradation in water (EPA 161-2)	DT_{50} = 13.7 days (pH 7, continuous irradiation Xe-lamp λ > 290 nm) Quantum yield of direct phototransforma¬tion in water at > 290 nm : 0.0074 (pH 7, 313 nm, racemic dimethenamid)		Guirguis (1997): WAS1999-165; Guirguis, A. S.: S LUF 1999-148; Sen, P. K. and Yu, C. C.: LUF 1999-150: Scharf, J.: LUF 1999-151
Photochemical degradation on soil (EPA 161-3)	58-64 % parent, 8.4-9.3 % bound residues, 10-12 % mineralisation after 23 d; no major metabolites > 10 %		Nietschmann, D. and Yu, C.(1997): BOD 1999-495; Sabat, M. and Yu, C.: BOD 1999-496
Votalisation (BBA, Part IV, 6-1)	from plant surfaces: 14 % in 24 h (24 °C) from soil: 6.6 % in 24 h (21 °C)		Jonas, W. (1994): BASF Reg-Doc.# 94/10642; BOD 1999-517

5.1.1 Stability

Hydrolytic degradation

Guirguis, A. S.: Hydrolysis of S-dimethenamid, BASF RegDoc.# 97/5184 (24 March 1997); WAS 1999-171

Fostiak, W. and Hsieh, T.: Hydrolysis of SAN 582 H; BASF RegDoc.# 88/11332 (10 June 1988); WAS 1999-172

Dimethenamid-P is hydrolytically stable at pH 5, 7, and 9. There is no difference in the behaviour of Dimethenamid-P and racemic dimethenamid regarding hydrolysis.

Photochemical degradation in water

Guirguis, A. S.: S-dimethenamid: photodegradation study in an aqueous solution, BASF RegDoc.#97/5195 (22 January 1997); LUF 1999-148

After 16 d continous irradiaton (Xe-lamp) residual active substance accounted for 44 %AR (CO_2: 6.5 %AR, volatiles: 2.3 %AR). None of the metabolites exceeded 4.3 % AR. 1st order half-life was calculated to be 13.7 ± 1.9 d. Total 14C recoveries were 98 – 103 %AR.

Sabat, M.: SAN 582 H: Photodegradation Study in Aqueous Solution; BASF RegDoc.# 92/12388(24 March 1992); LUF 1999-149

At pH7 Dimethenamid-P is gradually photodegraded (DT50 = 13.7d) yielding several minor degradation products none of which accounted for more than 4.3 % AR. There is no difference in the behaviour of Dimethenamid-P and racemic dimethenamid regarding aqueous photolysis.

Sen, P. K. and Yu, C. C.: SAN 582 H: Quantum Yield Determination; BASF RegDoc.# 94/10636 (8 February 1994); LUF 1999-150

The molar decadic absorption coefficient at of dimethenamid at 313 nm was determined to be e = 20.34 l mol-1 cm-1. The photolytic degradation rate of dimethenamid was found to be k = 0.01976 min-1. The quantum yield was calculated to be F = 0.007402. Based on the quantum yield a life-time of 5.97 days was estimated for photolysis in the top layer of aqueous systems under spring conditions at 40 °N.

Scharf, J.: Photolytical Halflife of Dimethenamid in the top layer of aqueous systems; BASF Reg-Doc.# 99/10073 (9 March 1999); LUF 1999-151

The photolytical half-life (DT50) of dimethenamid in the top layer of aqueous systems was calculated using the quantum yield and a program (Quantum.301) which uses algorithms developed by FRANK and KLÖPFFER for the direct phototransformation of chemicals in water [Frank, R. and Klöpffer, W. (1985): Ermittlung von Strahlungsdaten und Entwicklung eines Programms zur Abschätzung der abiotischen Transformation von Chemikalien in natürlichen Gewässern,

Forschungsbericht Nr. 106 020 46]. The calculation was performed with the program Quantum.301using the following parameters:

Application Month :	April	May
Day length:	13.67 hours	15.44 hours
Thickness of the aqueous layer.	1 cm	1 cm
Substance concentration:	1 µg/ml	1 µg/ml
Losses by reflection.	10 %	10 %
Cut-off for photoreactions;:	420 nm	420 nm
Water	distilled	distilled

Estimated photolytic half-life of dimethenamid in the top layer of aqueous systems under Central European conditions:

Month of application	Half-life	Half-life (calendar days)
April	12852 s = 3.6 h irradiation	0.3
May	11346 s = 3.2 h irradiation	0.2

Photochemical degradation on soil

Nietschmann, D. and Yu, C.: Comparative photolysis of R,S-dimethenamid (SAN 582 H) and S-dimethenamid

Sabat, M. and Yu, C.: SAN 582 H: photodegradation study on soil, BASF RegDoc.# 92/12387(24 March 1992); BOD 1999-496

For the comparative study the material balance for the irradiated soil ranged from 98 % AR to 106.7 % AR. In the second study with only the racemic compound the material balance ranged from 93.7 % AR to 101 % AR. Dimethenamid-P and dimethenamid both showed slow degradation under continuous irradiation on Elliot clay loam soil. The concentrations of the optically active and racemic compounds were 64.3 % AR and 57.6 % AR after 23 days, respectively. Dimethenamid-P and dimethenamid were not degraded in the dark control. During photolysis the increase in $14CO_2$ production, indicated mineralization of Dimethenamid-P and dimethenamid. After the 23 day irradiation period, $14CO_2$ accounted for 10.1 % AR and 12.3 % AR for Dimethenamid-P and dimethenamid, respectively. Characterization of individual radiocarbon regions showed that the TLC bands were comprised of multiple polar and less polar components, which did not approach 10 % AR, and no further characterization was performed. In the study with racemic dimethenamid degradation was more rapid and concentration of dimethenamid was 27 % AR at 9 days, so the irradiation was terminated. The application rate was sufficiently high that some products could be identified. Among these were M9, M7 and M11 along with trace amounts of a second bicyclic component (M20) and a putative hydroxylated metabolite. The results of this study suggest several degradative pathways: replacement of chlorine by a hydroxyl group, Odemethylation, two modes of cyclization, and hydroxylation at one of the thiophene methyls or the thiophene itself.

The results in both studies indicate that no major metabolites are formed under artificially isolated photolysis conditions. Degradation in the dark controls was minimal and showed that degradation under light is more rapid. The lack of degradation under dark conditions may be due to insufficient moisture content during the incubation compared to the conditions in the aerobic soil metabolism.

During soil photolysis no major metabolites are formed.

5.1.2 Biodegradation

5.1.2.1 Biodegradation estimation

5.1.2.2 Screening tests

Readily biodegradability

A study investigating the ready biodegradability was not submitted. A respective test was not performed since it was assumed that the compound is not readily biodegradable which can be inferred from the results of the aerobic soil metabolism studies.
The aerobic biodegradation of ^{14}C-Dimethenamid-P and ^{14}C-dimethenamid was evaluated in an Elliot clay loam soil in the aerobic soil metabolism study (cf. B.8.1.1). Biologically produced carbon dioxide evolved from soil treated with either ^{14}C-Dimethenamid-P or ^{14}C-dimethenamid was trapped and measured over six months (182 days). Recovery of $^{14}CO_2$ as a percent of the total applied radioactivity (AR) from ^{14}C-Dimethenamid-P treated soil ranged from 7.1 at 28 days to 29.2 at 182 days. Similarly, recovery of ^{14}C-dimethenamid treated soil ranged from 6.7 % AR at 28 days to 28.5 % AR at 182 days. These data indicate that both ^{14}C-Dimethenamid-P and ^{14}C-dimethenamid are not rapidly degraded to $^{14}CO_2$.
The investigation of biological degradation in aqueous systems is covered by the aerobic water/sediment study.

5.1.2.3 Simulation tests

Biodegradation in water/sediment systems

Wyss-Benz, M. and Völkel, W.: [3-14C-thienyl] dimethenamid degradation and metabolism in aerobic aquatic systems; BASF RegDoc.# 94/10641 (11 November 1994); BOD 1999-516

Test system
The degradation of dimethenamid (3-^{14}C-thienyl dimethenamid, radiochemical purity > 98 %; dimethenamid,purity 99.8 %) was investigated in two water/sediment systems taken from Rhine River(sampling site near Mumpf, canton Aargau, Switzerland) and a pond (Anwil, canton Baselland, Switzerland).
Temperature, pH, oxygen concentration, redox potential, hardness and phosphate concentration of the water and redox potential of the sediment were analyzed before sampling.

Testsystems	pH (Water)	pH (Sediment)
I) Rhein, Mumpf,AG, Schweiz, loamy sand, 0.78% TOC	7.46	7.06
II) Anwil (See), Schweiz, sandy loam, 1.42% TOC	7.60	6.98

Duration: 105 d, 20°C

Table 27: Degradation data of dimethenamid in aerobic water/sediment systems

System	*DT 50*	*DT 90*	*ST.*	*kinetics T, huminity..*	*class*
Primary degradation (active substance) in water					
I	20.3	67.4	0.93	1st	II
II	27.7	92.1	0.98	1st	II
Primary degradation (active substance) in total system					
I	23.4	77.8	0.99	1st	II
II	33,4	110,9	0,992	1st	III

Metabolites:
water: M3: max. 9,1% after d 105 (end of study)

sediment: M3: max. 6,0% after d 105 (end of study)

Table 28: Proportion of radioactive components in % AR in water and sediment after application of 14C-dimethenamidallocation of dimethenamid in water/sediment-system

time [d]	**active substance** syst.1/syst.2		**metabolite M3** syst.1/syst.2		**metabolite M23** syst.1/syst.2	
	water	sediment	water	sediment	water	sediment
0	99.9/98.8	-/-	n.d./n.d.	n.p./n.p.	n.p./n.p.	n.p./n.p.
0.25	92.5/94.3	6.2/5.1	n.d./n.d.	n.d./n.d.	n.p./n.d.	n.d./n.d.
1	86.5/89.2	11.0/10.3	n.d./n.d.	0.2/n.d.	n.p./n.d.	n.d./n.d.
2	79.8/83.6	15.8/14.3	n.d./n.d.	0.6/n.d.	n.p./n.d.	n.d./n.d.
7	62.8/70.6	20.1/21.4	1.5/n.d.	2.0/1.0	0.4/n.d.	n.d./n.d.
14	41.0/60.0	19.2/22.8	4.5/1.7	2.9/2.0	1.4/n.d.	0.3/n.d.
28	22.7/41.0	12.2/16.3	8.1/3.5	4.4/3.3	1.9/1.5	1.3/1.1
56	10.5/21.2	6.1/10.6	8.5/6.3	4.7/4.8	3.0/2.8	1.5/1.4
105	2.6/6.9	2.0/4.6	9.1/8.0	5.2/6.0	4.2/4.7	1.5/2.3

n.d. = not detected

n.p. = not performed

Degradation of dimethenamid was similar in the river and pond water/sediment systems in this study. Within 105 d the active substance was degraded down to 4.7 % AR (river system) and 11.6 % AR (pond system). Bound residues in the sediment increased to £ 53.5 % AR; mineralization to CO2 was low. One main metabolite (M3) was detected at a maximum of > 10 % AR in the whole system (14 % AR at day 105) but individual portions of M3 in sediment and water phase were < 10 % AR.

DT50 values for dimethenamid in the water phase were found to be 20 and 28 days, and in the total system 23 and 33 days for the river and pond systems respectively.

5.1.3 Summary and discussion of degradation

A ready biodegradability test was not performed since it was assumed that Dimethenamid-P is not readily biodegradable.

In water/sediment systems DT_{50} values for dimethenamid in the water phase were found to be 20 and 28 days, and in the total system 23 and 33 days for the river and pond systems respectively.

Based on the findings from water/sediment simulation tests dimethenamid appears to be susceptible for primary degradation and not ultimate mineralisation. Considering the levels of mineralisation in the simulation studies, Dimethenamid-P is considered not readily/ rapidly biodegradable (a degradation > 70 % within 28 days) for purposes of classification and labelling.

5.2 Environmental distribution

5.2.1 Adsorption/Desorption

Tong, T. M. and Su, L.Y.: Soil adsorption and desorption of SAN 1289H, unaged, by the batch equilibrium method, BASF RegDoc.# 97/5180 (29 April 1997); BOD 1999-504

Adsorption and desorption characteristics of 14C-Dimethenamid-P (3-^{14}C-thienyl Dimethenamid-P, radiochemical purity 96.0 %; Dimethenamid-P, purity 94.0 %) were determined on 5 European and 5 U.S. soils by the batch equilibrium method.

Table 29: Freundlich adsorption coefficients of Dimethenamid-P

Texture class	Organic carbon (%)	pH	Kf	Koc	1/n
sandy clay loam (EU)	1.4	5.6	6.61	474	0.92
clay loam, (EU)	2.03	8.0	2.51	123	0.96
sandy loam, (EU)	2.38	5.5	2.14	90	1.00
silt loam, (EU)	1.22	6.6	1.23	101	1.07
Sand, (EU)	3.43	3.9	13.49	393	0.94
clay (US)	0.99	8.0	2.09	211	1.05
clay loam (US)	2.38	6.4	2.51	105	0.97
loam (US)	1.22	7.3	3.02	247	1.04
sandy loam (US)	0.35	7.0	1.38	396	1.04
silt loam (US)	1.51	6.7	1.95	129	0.96

Taking into account K_{OC} values of 90 – 474, Dimethenamid-P can be predicted to have a medium to

high mobility in soil.

5.2.2 Volatilisation

Jonas, W.: Evaporation behaviour from soil and plants (large-scale model chamber) test product: frontier (SAN 582 H 900 EC 408 DP) test substance: [3-14C-thienyl] dimethenamid; BASF Reg- Doc.# 94/10642 (21 September 1994); BOD 1999-517

The volatilization from soil and plants was investigated with dimethenamid in the formulated product Frontier (EC formulation) prepared as a mixture of 3-14C-thienyl dimethenamid (purity 99.8 %), dimethenamid (purity 99.8 %) and blank formulation.

The volatilization experiment was performed in a model chamber in the dark with a wind velocity of 1-2 m/s (flow rate of air 32 l/min corresponding to ca. 6 volume exchanges/h), 40 % relative air humidity. The temperature was kept at 21 °C (soil volatilization) and 24 °C (plant volatilization), respectively.

Within 24 h dimethenamid was found to volatilize in amounts of 6.6 % AR and 14.1 % AR from soil and plant surfaces, respectively.

5.2.3 Distribution modelling

Not relevant.

5.3 Aquatic Bioaccumulation

Table 30: Summary of relevant information on aquatic bioaccumulation of Dimethenamid-P

Method	Results	Remarks	Reference
Lepomis macrochirus Flow-through, 42 days U.S. EPA-FIFRA 40 CFR, Section 158-130, Guideline 165-4	BCF_{ss}: 58 L/kg ww (whole fish)	No normalization for lipid content possible, because of data lacking	Sabourin, T.D (1988)

5.3.1 Aquatic bioaccumulation

5.3.1.1 Bioaccumulation estimation

Dimethenamid-P has a log Kow of 1.89.

5.3.1.2 Measured bioaccumulation data

A bioconcentration study with ^{14}C-SAN-582 H = Dimethenamid (Razemat) and Bluegill sunfish (*L. macrochirus)* under flow-through conditions (uptake phase: 28 days, depuration phase: 14 days) produced a steady state BCF of 58 L/kg ww related to total radioactivity and whole fish. The clearance time CT_{50} was 10.7 d. The lipid content of whole fish in the test was not measured. (Sabourin, 1988)

5.3.2 Summary and discussion of aquatic bioaccumulation

Dimethenamid-P has a log Kow of 1.89. The experimentally derived steady state BCF value of 58 L/kg ww (without lipid normalization) for dimethenamid is below the trigger of 100 (criterion for bioaccumulating potential conform Directive 67/548/EEC) for not rapidly biodegradable substances and is also below the trigger of 500 (criterion for bioaccumulating potential conform Regulation EC 1272/2008) for not rapidly biodegradable substances.

5.4 Aquatic toxicity

Table 31: Summary of relevant information on aquatic toxicity of Dimethenamid-P

Method	Results	Remarks	Reference
OECD 203 *Oncorhynchus mykiss* Flow through, 96 hours	LC_{50} (96h) = 6.3 mg/L mean measured (m.m.)		Graves, W. and Swigert, J.(1996a)
OECD 202, part 1 *Daphnia magna* static, 48 hours	EC_{50} (48h) = 12 mg/L (m.m.)		Graves, W. and Swigert ,J.(1996b)
EPA 850.5400, 122-2, 123-2 *Selenastrum capricornutum* static, 120 hours	E_bC_{50} = 0.0143 mg/L (m.m.) **E_rC_{50} = 0.0378 mg/L** (m.m.) **NOEC = 0.0021 mg/L** (m.m.)		Hoberg, J (1997a)
EPA 850.4400, 122-2, 123-2 *Lemna gibba* semistatic, 14 days	E_bC_{50} = 0.0089 mg/L (m.m.) **E_rC_{50} = 0.0311 mg/L** (m.m.) **NOEC = 0.0012 mg/L** (m.m.)		Hoberg, J.(1997b)

5.4.1 Fish

5.4.1.1 Short-term toxicity to fish

The acute toxicity of Dimethenamid-P (SAN 1289H; aktives Isomer) to rainbow trout *(Oncorhynchus mykiss)* was tested for mortality in a 96 hr flow through test. The endpoint is LC_{50} = 6.3 mg/L mean measured (Graves, W. and Swigert, J. (1996a).

5.4.1.2 Long-term toxicity to fish

No data available.

5.4.2 Aquatic invertebrates

5.4.2.1 Short-term toxicity to aquatic invertebrates

The acute toxicity of Dimethenamid-P (SAN 1289H; aktives Isomer) to aquatic invertebrates (*Daphnia magna)* was tested for mortality in a 48 h static test. The endpoint is EC_{50} = 12.0 mg/L nominal (Graves, W. and Swigert, J.1996b).

5.4.2.2 Long-term toxicity to aquatic invertebrates

No data available.

5.4.3 Algae and aquatic plants

The toxicity of Dimethenamid-P to algae (*Selenastrum capricornutum)* was tested in a 120 hr static test. The endpoints are EbC_{50} = 0.0143 mg/L, ErC_{50} = 0.0378 mg/L and NOEC = 0.0022 mg/L based on mean measured concentrations. (Hoberg, J. 1997a)

This study is regarded as the key study for the acute aquatic toxicity of Dimethenamid-P and hence for classification and labeling. Therefore the study is presented in more detail below.

Title: SAN 1289H Technical - toxicity to the freshwater green alga, Selenastrum capricornutum (Hoberg, J. 1997).

Guidelines: U.S. EPA, EPA 850.5400, FIFRA guidelines 122-2, 123-2
GLP**:** Yes. Valid study

Materials and methods:
Freshwater green alga, Selenastrum capricornutum were exposed to Technical Dimethenamid-P (SAN 1289H, lot no. 6683-50-1; purity: 91.1 %) at nominal test concentrations of 0.0016, 0.003, 0.0063, 0.013, 0.025 and 0.05 mg as/L and mean measured concentrations of 0.0013, 0.0021, 0.0054, 0.0096, 0.021 and 0.044 mg as/L, representing 72-88 % of nominal test concentrations.

Findings:
Cell density in the exposure levels (0.0013, 0.0021, 0.0054, 0.0096, 0.021 and 0.044 mg as/L) averaged 181, 237, 198, 167, 66 and 1.8 x 10^4 cells/mL, respectively, at test termination. Statistical analysis (Williams' test) of this data established a significant reduction in cell density in the 0.0054, 0.0096, 0.021 and 0.044 mg as/L treatment levels when compared to the performance of the control. No statistically significant effects on cell density were found in the 0.0013 and 0.0021 mg as/L in comparison to the control at test termination. Therefore, the 120-hour no-observed effect concentration (NOEC) was 0.0021 mg as/L.
The 120-h EC_{50} for cell density was 0.0017 mg as/L with 95 % confidence intervals of 0.0041 to 0.03 mg as/L and the calculated 120-h ErC_{50} of Dimethenamid-P was 0.0378 mg as/L with 95 % confidence intervals of 0.0364 to 0.0392 mg as/L.

The toxicity of Dimethenamid-P to aquatic plants (*Lemna gibba)* was tested in a 14 day semistatic test. The endpoints are EbC_{50} = 0.0089 mg as/L, ErC_{50} = 0.0311 mg as/L and NOEC = 0.0012 mg as/L based on mean measured concentrations. (Hoberg, J. 1997b)

5.4.4 Other aquatic organisms (including sediment)

No data available.

5.5 Comparison with criteria for environmental hazards (sections 5.1 – 5.4)

In aquatic toxicity studies acute LC_{50} value for fish and EC_{50} value for invertebrates were obtained at Dimethenamid-P concentrations about 10 mg/L. The relevant acute ErC_{50} value for algae and aquatic plants is < 1 mg/L. In long- term toxicity studies NOEC < 1 mg/L for algae and aquatic plants were determined. There are no data for fish and invertebrates available.

Based on the findings from water/sediment simulation tests Dimethenamid-P appears to be susceptible for primary degradation and not ultimate mineralisation. Considering the levels of mineralisation in the simulation studies, Dimethenamid-P is considered not readily/ rapidly biodegradable (a degradation > 70 % within 28 days) for purposes of classification and labelling

Dimethenamid-P has a log Kow of 1.89. The experimentally derived steady state BCF value of 58 L/kg ww (without lipid normalization) is below the trigger of 100 (criterion for bioaccumulating potential conform Directive 67/548/EEC) for not rapidly biodegradable substances and is also below the trigger of 500 (criterion for bioaccumulating potential conform Regulation EC 1272/2008) for not rapidly biodegradable substances.

5.6 Conclusions on classification and labelling for environmental hazards (sections 5.1 – 5.4)

Conclusion of environmental classification according to Directive 67/548/EEC

Dimethenamid-P fulfils the criteria for classification with N; R50-53.

Based on the toxicity data for the algae *Selenastrum capricornutum* (E_rC50 = 0.0378 mg/L) in a 120-h static study and for the aquatic plant *Lemna gibba* (E_rC50 = 0.0311 mg/L) in a 14-d semistatic study the following specific concentration limits should be applied:

Concentration	Classification
$C \geq 2.5\%$	N; R50-53
$0.25\% \leq C < 2.5\%$	N; R51-53
$0.025\% \leq C < 0.25\%$	R52-53

where C is the concentration of Dimethenamid-P in the preparation

Conclusion of environmental classification according to Regulation EC 1272/2008

Dimethenamid-P fulfils the criteria for classification as aquatic environmental hazard acute category 1, H400 and aquatic environmental hazard chronic category 1, H410.

The M-factor is 10, based on the lowest acute toxicity data for the algae *Selenastrum capricornutum* (E_rC50 = 0.0378 mg/L) in a 120-h static study and for the aquatic plant *Lemna gibba* (E_rC50 = 0.0311 mg/L) in a 14-d semistatic study.

RAC evaluation of environmental hazards

Summary of the Dossier submitter's proposal

The DS proposed Aquatic Acute 1 with an M-factor 10 and Aquatic Acute 1 with an M-factor 10 (according to DSD N; R50-53 with the specific concentration limits as given below).

A ready biodegradability test was not available. Based on the findings from water/sediment simulation tests, dimethenamid-P appears to be susceptible to primary degradation and not to ultimate mineralisation. Considering the levels of mineralisation in the simulation studies, dimethenamid-P is considered not rapidly (readily according to DSD) biodegradable (a degradation >70 % within 28 days) for purposes of classification and labelling.

Dimethenamid-P has an experimentally measured log K_{ow} of 1.89. The experimentally derived steady state BCF value of 58 l/kg ww (without lipid normalization) for dimethenamid is below the trigger of 100 (criterion for bioaccumulating potential conform Directive 67/548/EEC) for not rapidly biodegradable substances and is also below the trigger of 500 (criterion for bioaccumulating potential conform Regulation EC 1272/2008) for not rapidly biodegradable substances.

All the reported LC_{50}, EC_{50} or NOEC values for aquatic species were based on the mean measured concentrations. The acute LC_{50} value for fish (*Oncorhynchus mykiss*) was 6.3 mg/l and the EC_{50} value for invertebrates (*Daphnia magna*) was 12 mg/l. The reported acute ErC50 value was 0.0378 mg/l for algae (*Pseudokirchneriella subcapitata*) and 0.031 mg/l for an aquatic plant (*Lemna gibba*). There are no chronic toxicity data for fish and invertebrates available.

Classification according to CLP. The DS concluded that dimethenamid-P fulfils the criteria for classification for short-term aquatic hazard as Aquatic Acute 1 (H400) with an M-factor 10 based on the data for the algae *S. capricornutum* (ErC50 = 0.0378 mg/l) in a 120-h static study. The conclusion on long-term aquatic hazard was Aquatic Chronic 1 (H410) with an M-factor 10 based on not proven rapid degradation and the chronic toxicity in the duckweed (*L. gibba*, NOEC = 0.0012 mg/l) in a 14-d semistatic study.

Classification according to DSD. Based on the toxicity data for the algae *P. subcapitata* (ErC_{50} = 0.0378 mg/l) in a 120-h static study and for the aquatic plant *Lemna gibba* (ErC_{50} = 0.0311 mg/l) in a 14-d semistatic study and not being readily degradable, dimethenamid-P fulfils the criteria for classification with N; R50-53 in DSD the following specific concentration limits should be applied: N; R50-53 C ≥ 2.5%, N; R51-53 when 0.25% ≤ C < 2.5% and R52-53 when 0.025% ≤ C < 0.25%.

Comments received during public consultation

The environmental hazard classification was supported by three MSCAs. Supplementary data on batches used for the different tests and aerobic biodegradation of dimethenamid-P were provided during the PC by the DS. The latter confirmed that the substance is not rapidly (CLP) or readily (DSD) biodegradable.

Additional key elements

The DS provided the following information during the PC to complete the degradation studies given in chapter *5.1.2.3 Simulation tests of the CLH report*

<u>Biodegradation in soil</u>

Wendt, D. R.: Comparative aerobic soil metabolism of SAN 1289H and SAN 582H, BASF RegDoc.# 97/5257 (6 March 1997); BOD 1999-491

Test system

The aerobic soil metabolism of 14C-dimethenamid (3-14C-thienyl dimethenamid,

radiochemical purity 98.5 %; dimethenamid, purity 99.7 %) and 14C-dimethenamid-P (3-14C-thienyl dimethenamid-P, radiochemical purity 96.0 %; dimethenamid-P, purity 98.6 %) were compared in Elliot clay loam soil (Champaign County, Illinois, USA). The soil parameters are listed in Table B-1. The concentrations of both 14C-dimethenamid and 14C-dimethenamid-P were 1.595 mg/kg moist soil (1.994 mg/kg dry soil). Incubation conditions were: aerobic by continuous flow of air, temperature maintained at 23.1 °C, and soil moisture at 75 % of field capacity. Duplicate soil samples were collected at 0, 1, 3, 7, 14, 21, 28, 42, 56, 84, 119 and 182 days. Volatiles were trapped by continuously washing the effluent gas with 1 M NaOH and ethylene glycol. Soil was extracted with methanol, then methanol/0.1 M HCl. The extracts were pooled, concentrated, and characterised by TLC and HPLC. Bound residues were characterised by extraction with 0.1 M NaOH to separate the fulvic acid, humic acid, and humin fractions. In addition, exaggerated rate incubations (21 days, 9.5 mg/kg dry soil) were conducted in order to generate products in quantities sufficient for identification by GC-MS.

Table B-1: Aerobic soil metabolism of 14C-dimethenamid and 14C-dimethenamid-P: Characterisation of the soil used

Soil designation		Elliot Clay Loam
Textural class (USDA)		Clay loam
Origin		Champaign County, Illinois (USA)
Particle size distribution (%): sand silt clay		 24 44 32
Organic C (%)		2.4 *
Cation exchange capacity (meq/100 g)		15.6
pH		6.4
Field capacity determined at 0.33 bar (g H_2O/100 g soil)		33.37
Bulk density (g/cm³)		1.12
Microbial counts (CFU/g dry soil)	aerobic bacteria	$7.7 \cdot 10^6$
	actinomycetes	$11 \cdot 10^6$
	mould	$1.7 \cdot 10^3$

* calculated from organic matter content specified in the study (4.1 %)

Findings

The total recoveries for individual incubations ranged from 91.7 to 102.8 % AR and from 93.5 to 103.6 % AR in the case of dimethenamid-P and dimethenamid, respectively. The degradation of both dimethenamid-P and dimethenamid coincided with the formation of up to seven polar metabolites. These seven metabolites, shown in the table below, were identified as: metabolite M23 (oxalamide) the thioglycolic acid conjugate of dimethenamid (TGA, M32) the sulfoxide of the thioglycolic acid conjugate (STGA, M31) the thiolactic acid conjugate (TLA, M26) the sulfoxide of the thiolactic acid conjugate (STLA, M30) the hydroxyacetyl metabolite (M11) and a sulfonic acid metabolite (sulfonate, M27). Identification was accomplished by co-chromatography with authentic reference standards (TLC and HPLC) and confirmed by MS. The distribution of recovered radioactivity among volatiles, non-extractable residues, extractable active substance and metabolites M23, M27 and M31 is shown in Table B.-2. None of the other degradation products exceeded 5 % AR. $14CO_2$ was the sole volatile degradation product and accounted for 28 – 29 % AR for both

treatments after the 182 day incubation period. For both dimethenamid-P and dimethenamid non-extractable residues were found to increase to about 40 % AR. Up to 9 % AR (day 56) and 25 % AR (day 84) was associated with fulvic acid and humic acid fraction, respectively. The humin fraction contained approximately 10 % AR at the end of the study.

Dimethenamid-P							
DAT	CO_2	as	M23	M27	M31	NER*	Balance**
0	0.0	94.1	0.3	0.1	0.3	0.7	101.5
1	0.4	77.7	1.0	1.1	1.6	6.3	97.1
3	0.8	69.1	3.3	2.0	3.7	10.9	96.2
7	1.6	48.9	5.2	3.5	6.6	18.3	95.8
14	3.3	32.7	7.7	6.2	9.6	26.8	96.8
21	5.2	19.1	7.9	6.6	8.9	33.1	92.9
28	7.1	14.8	7.2	7.3	7.0	34.7	94.3
42	10.7	8.4	6.3	7.8	8.4	38.0	94.5
56	14.0	6.1	4.6	5.9	4.2	38.7	95.2
84	18.9	4.3	4.3	6.8	3.6	40.3	94.2
119	23.5	2.7	3.6	5.9	3.6	39.9	92.9
182	29.2	1.6	2.4	4.9	2.4	39.9	93.8
Dimethenamid							
DAT	CO_2	as	M23	M27	M31	NER*	Balance**
0	0.0	93.3	0.3	0.1	0.2	0.4	101.7
1	0.4	76.5	1.0	0.8	1.2	5.3	95.3
3	0.8	70.6	3.4	1.7	3.0	11.3	97.0
7	1.5	50.0	5.2	3.4	5.9	19.0	96.5
14	3.2	30.5	8.1	6.2	9.5	27.5	96.5
21	4.9	20.3	8.2	6.7	8.5	33.2	94.1
28	6.7	15.9	8.1	7.6	7.1	34.8	94.1
42	10.2	9.6	6.4	8.0	7.8	38.4	93.8
56	13.3	6.6	4.8	6.0	3.6	38.7	95.1
84	18.5	4.4	4.8	7.6	2.7	43.5	98.7
119	23.1	2.7	3.5	6.3	3.8	40.8	95.0
182	28.5	1.5	2.7	5.9	2.5	39.5	94.7

* Includes humic and fulvic acid and humin fractions

** Sum of recovered radioactivity of volatiles, methanol/0.1 *M* HCl extract, fulvic acid, humic acid and unextractable residue (humin)

The DS considered the study as acceptable. With regard to the metabolic pattern in aerobic soil degradation there is no difference between racemic dimethenamid and dimethenamid-P.

Assessment and comparison with the classification criteria

RAC agrees that the substance is not rapidly (CLP) or readily (DSD) degradable (a degradation >70 % within 28 days), either in water/sediment systems or aerobic biodegradation in soil.

Dimethenamid-P has a log K_{ow} of 1.89. Experimental BCF_{ss} in bluegill (*Lepomis macrochirus*) was calculated as 58 l/kg w.w. Both values are below the reference values for bioaccumulative substances (log K_{ow} >4 and BCF > 500 in CLP; log K_{ow}>3 and BCF > 100 in DSD). The substance is slightly surface active (surface tension, 53 mN/m), a circumstance

that may underestimate its bioaccumulative capacity (IR/CSA R.7C). In fact, the calculated K_{ow} is clearly below the predicted XlogP value, 2.6 (http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=13633097). However, as even this predicted higher value is below the guidance criteria, RAC considers the substance not meeting the criteria for a potential to bioaccumulate.

RAC agrees with the public consultation comment that 72h ErC_{50} values for algae should be used to conclude on short-term aquatic hazard instead of the 120 h values. The most sensitive species in the reported acute studies is the algae *P. subcapitata* (ErC_{50} = 0.030 mg/l, 72-h static study). RAC agrees also that dimethenamid-P should be considered as not rapidly degradable and that the long-term aquatic hazard classification should be based on the chronic toxicity in the duckweed (*L. gibba*, NOEC (14-d) = 0.0012 mg/l). The resulting classification for dimethenamid-P is Aquatic Acute 1 (H400) with an M-factor 10 and Aquatic Chronic 1 (H410) with an M-factor 10.

Based on the classification and labelling criteria in accordance with DSD, the LC_{50} for the most sensitive species *P. subcapitata* ErC_{50} (72-h) equals to 0.030 mg/l. As the substance is not readily degradable, dimethenamid-P should be classified as N, R50-53 with specific concentration limits N; R50-53: C ≥ 2.5%, N; R51-53: 0.25% ≤ C < 2.5% and R52-53: 0.025% ≤ C < 0.25%.

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