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: **-**

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

Index Number: **-**

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CONTENTS

PART A.

PART B.

Part A.

1 PROPOSAL FOR HARMONISED CLASSIFICATION AND LABELLING

1.1 Substance

Table 1: Substance identity

Substance name:	***Dimethenamid-P***
EC number:	**-**
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 (2nd ATP)	**Directive 67/548/EEC (Dangerous Substances Directive; DSD)**
Current entry in Annex VI, CLP Regulation	-	-
Current proposal for consideration by RAC	Acute toxicity 4; H302 Skin sensitiser 1B; H317 Aquatic Acute 1; H400 Aquatic Chronic 1; H410 M- acute = 10 M- chronic = 10	Xn; R22 Xi; R43 N; R50/53
Resulting harmonised classification (future entry in Annex VI, CLP Regulation)	Acute toxicity 4; H302 Skin sensitiser 1B; H317 Aquatic Acute 1; H400 Aquatic Chronic 1; H410 M- acute = 10 M- chronic = 10	Xn; R22 Xi; 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	-			Conclusive but not sufficient for classification
2.2.	Flammable gases	-			-
2.3.	Flammable aerosols	-			-
2.4.	Oxidising gases	-			-
2.5.	Gases under pressure	-			-
2.6.	Flammable liquids	-			Conclusive but not sufficient for classification
2.7.	Flammable solids	-			-
2.8.	Self-reactive substances and mixtures	-			-
2.9.	Pyrophoric liquids	-			Data lacking
2.10.	Pyrophoric solids	-			-
2.11.	Self-heating substances and mixtures	-			Conclusive but not sufficient for classification
2.12.	Substances and mixtures which in contact with water emit flammable gases	-			-
2.13.	Oxidising liquids	-			Conclusive but not sufficient for classification
2.14.	Oxidising solids	-			-
2.15.	Organic peroxides	-			-
2.16.	Substance and mixtures corrosive to metals	-			Data lacking
3.1.	Acute toxicity - oral	Acute toxicity 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 1B (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				Data lacking
4.1.	Hazardous to the aquatic environment	Aquatic Acute 1 (H400) Aquatic Chronic 1 (H410)	M- acute = 10 M- chronic = 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

Table 4: Proposed labelling based according to the CLP Regulation

	Labelling	Wording
Pictograms	GHS07, GHS09	
Signal Word	Warning	
Hazard statements	H302 H317 H410	Harmful if swallowed. May cause an allergic skin reaction Very toxic to aquatic life with long lasting effects
Suppl. Hazard statements		
Precautionary statements	P273 P391 P501	Avoid release to the environment Collect spillage Dispose of contents/container to …

Proposed notes assigned to an entry:

-

Table 5: Proposed classification according to DSD

Hazardous property	**Proposed classification**	**Proposed SCLs**	**Current classification [1)]**	**Reason for no classification [2)]**
Explosiveness	-			Conclusive but not sufficient for classification
Oxidising properties	-			Conclusive but not sufficient for classification
Flammability	-			Conclusive but not sufficient for classification
Thermal stability	-			Conclusive but not sufficient for classification
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

Table 6: Proposed labelling according to DSD

	Labelling	Wording
Hazard Symbols, Indications of danger	Xn N	Harmful Dangerous for the environment
R-phrases	R22 R43 R50/53	Harmful if swallowed. May cause sensitization by skin contact. Very toxic to aquatic organisms, may cause long-term adverse effects to the aquatic environment
S-phrases	S60 S61	This material and its container must be disposed of as hazardous waste Avoid release to the environment. Refer to special instructions/ safety data sheets

2 BACKGROUND TO THE CLH PROPOSAL

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 as plant protection product 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.

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).

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 the opinion of the RMS 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. This was agreed during the peer-review process under directive 91/414/EEC.

In conclusion, the bridging studies conducted with dimethenamid-P can be used in conjunction with the studies conducted with racemic dimethenamid to support a harmonised classification and labelling proposal of the dimethenamid S-isomer (dimethenamid-P).

No REACH registration dossiers for dimethenamid-P were available on 27 September 2012.

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

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

Part B.

SCIENTIFIC EVALUATION OF THE DATA

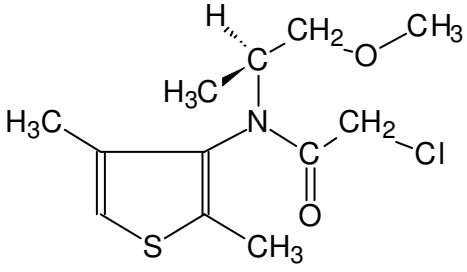
1 IDENTITY OF THE SUBSTANCE

1.1 Name and other identifiers of the substance

Table 7: Substance identity

EC number:	-
EC name:	-
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:	2-chloro-N-(2,4-dimethyl-3-thienyl)-N-[(2S)-1-methoxypropan-2-yl]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

Table 8: 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 9: Impurities (non-confidential information)

Impurity	Typical concentration	Concentration range	Remarks
No impurities of toxicological or environmental significance			

Current Annex VI entry:

The confidential information for non-relevant impurities can be found in the "Confidential Annex" or the technical dossier.

Table 10: Additives (non-confidential information)

Additive	Function	Typical concentration	Concentration range	Remarks
none				

Current Annex VI entry:

1.3 Physico-chemical properties

Table 11: 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	Draft Assessment Report (DAR)	
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		Method EEC A6 (column elution method)
Partition coefficient n-octanol/water	log Po/w = 1.89 at 24 °C, pH not stated		Method EEC A8 (shake flask method). Effect of pH was not investigated since there is no dissociation in water
Flash point	79 °C purity 93.5 %		
Flammability	n.a.		
Explosive properties	not explosive purity 96.7 %, Dimethenamid		
Self-ignition temperature	395 °C purity: 97.9 % racemic dimethenamid		Method EEC A15
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	-		no data available; (no data requirement for pesticide active substances)

2 MANUFACTURE AND USES

3 CLASSIFICATION FOR PHYSICO-CHEMICAL PROPERTIES

Not relevant for this dossier.

Table 12: Summary table for relevant physico-chemical studies

Method	Results	Remarks	Reference
Auto flammability Method EEC A.15	395 °C purity: 97.9 % racemic dimethenamid		Draft Assessment Report (DAR)
Explosive properties Method US EPA Sub. D, No. 63-16	not explosive purity 96.7 %, Dimethenamid		Draft Assessment Report (DAR)
Oxidising properties Method US EPA	no reaction with reducing agents		Draft Assessment Report (DAR)
Flammability	n.a. (liquid)		Draft Assessment Report (DAR
Flash point Method EEC A.9	79 °C purity 93.5 %	instead of flammability	Draft Assessment Report (DAR)

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.

Changed criteria according to Commission Regulation (EU) No 286/2011 were taken into account, when assessing the study results.

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 dimethenamid-P studies.

By comparative assessment of all toxicological 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 and/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. 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 13.

Table 13: 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.

4.2.4 Comparison with criteria

Table 14: 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: $200 < LD_{50} \leq 2\,000$ mg/kg	Cat. 4: $300 < LD_{50} \leq 2000$ mg/kg (oral)
Inhalation LC_{50}, rat: > 2 mg/l (aerosol, 4-h)	Harmful: LC_{50} inhalation, rat, for aerosols or particulates: $1 < LC_{50} \leq 5$ mg/litre/4h	Cat.3: $2{,}0 < LC_{50} \leq 10{,}0$ mg/l (vapours) Cat. 4: $10{,}0 < LC_{50} \leq 20{,}0$ mg/l (vapours)
Dermal LD_{50}: > 2000 mg/kg	Harmful: LD50 dermal, rat or rabbit: $400 < LD_{50} \leq 2\,000$ mg/kg	Cat. 4: $1\,000 < LD_{50} \leq 2\,000$ 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 according to Annex I of Council Directive 67/548/EEC and assigned the symbol "Xn" and the indication of danger "harmful" accordingly. The following risk phrase should be assigned: R22 "Harmful if swallowed" according to Annex I of Council Directive 67/548/EEC and Acute toxicity, cat. 4; H302 according to Annex VI of Regulation (EC) No. 1272/2008).

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 15.

Table 15: 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 oedema and 2 animals exhibited very slight (barely perceptible) erythema with no oedema. 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 16: 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 17.

Table 17: 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 18: 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 sensitisation

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.

Dimethenamid-P is a skin sensitizer 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 was tested for its sensitizing effect on the skin of the Guinea pig in the Maximization Test according to Magnusson and Kligman. In a pre-test, 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.

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.

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

Table 19: 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 sensitizer 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 20: Toxicological results in comparison with DSD and CLP criteria

Toxicological result	DSD criteria	CLP criteria
Arcelin, 1995 (M&K), (Racemic dimethenamid): 19/19 (100 %) animals positive 5 % intra dermal induction concentration	Adjuvant type test method: ≥ 30 % of the animals positive	**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
Blaszcak, 1996 (Buehler-Test), (Dimethenamid-P): 17/20 (85 %) animals positive 100 % dermal induction concentration	Other test method: ≥ 15 % of the animals positive	**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

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.

Based on the results in the study according to M&K and Buehler test design, dimethenamid-P fulfils the criteria in DSD to be classified as a skin sensitizer (R43).

Based on the results in the study according to M&K and Buehler test design dimethenamid-P fulfils the criteria in CLP regulation to be classified as a skin sensitizer (H317, sub-category 1B).

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 19.

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 20 and Table 21.

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 assessment 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.

Report:	Ruckman S.A. et al., 1990 (TOX1999-435) SAN 582 H: Potential Tumorigenic and Toxic Effects in Prolonged Dietary Administration to Rats Huntingdon Research Centre, Ltd., Huntingdon, U.K. unpublished, 1 March 1990, BASF RegDoc.#90/11138 (Experimental work from 16 December 1986 – 3 January 1989)
Test Material:	Racemic dimethenamid (SAN 582 H); batch No. 8605; purity: 91.3%.
Test Animals:	Crl:CD (SD) BR rats, age at start of treatment: bw: Source: Charles River Breeding Lab., Portage, Michigan, U.S.A.
GLP:	yes (laboratory certified by The Department of Health and Social Security of the Government of the United Kingdom)
Test Method:	OECD-Guideline 453
Deviations:	Deviations from OECD-Guideline 453 (adopted 12.05.1981): (1) After 5 wk on study clinical examinations were performed only at weekly intervals; (2) Haematology was perfomed only on 10 rats/sex/group
Acceptability:	The study is considered to be acceptable.
Amendments:	Ruckman S., 1990 (TOX1999-436), BASF RegDoc. #90/11179 Alison R. and Gopinath C., 1993 Review of Ovarian Neoplasia in Sandoz Study SDZ335 (Compound SAN 582H), 22March 1993; unpublished BASF RegDoc. #93/11798

Material and Methods:

Racemic dimethenamid was administered to groups of 70 male and 70 female Sprague-Dawley rats at dietary concentrations of 0, 100, 700 and 1500 ppm. 50 animals/sex/group were treated for 24 mo. Satellite animals of 20/sex/group were used in the chronic toxicity evaluations and sacrificed after 12 months of treatment. Analyses for stability and homogeneity of the test substance in the diet were performed prior to study start. Analyses to verify correct concentrations in the diet were conducted throughout the treatment period.

Food consumption and body weight were determined once a week. Water consumption was determined daily during weeks 12, 25 and 51 for the satellite animals. The animals were examined for mortality once a day; moreover, comprehensive clinical examinations and palpations of the animals were performed once a week. Ophthalmological examinations were carried out prior to study start and towards the end of dosing on all animals, and also at week 53 for control and high dose animals. Urinalysis, clinicochemical and hematological examinations were carried out during weeks 13, 26, 52, 78 and 104 of the administration period using 10 animals/sex/group. Satellite animals were used through week 52, and main group animals were used for weeks 78 and 104. All animals were subjected to gross pathological assessment and selected organs were weighed. Histopathological examinations were performed on all control and high dose animals, animals that

died during the study, lungs liver, kidney and any macroscopically abnormal tissue from low and intermediate dose animals, and on tissues from low and intermediate dose animals for which a treatment-related change was noted in the high dose group.

Findings:

The stability and homogeneity of the test substance in the diet was demonstrated. Verification of correct concentrations were also confirmed by analysis.

The test substance intake is given in Table 25.

Table 25: Test substance intake

Dietary dose level (ppm)	Test substance intake (mg/kg bw/d)	
	males	Females
100	5	7
700	36	49
1500	80	109

There was no treatment-related impairment of survival (see Table 26).

Table 26: Survival in chronic rat study (wk 104)

	Dose Group (ppm)			
	0	100	700	1500
No. of male survivors	18/50	20/50	25/50	31/50
% male survival	36	40	50	62
No. of female survivors	25/50	22/50	30/50	31/50
% female survival	50	44	60	62

Note:

Survival rates were below 50% for male controls and for low-dose group males and females. According to OECD Guidelines, the study cannot be accepted to prove the absence of a tumourigenic effect when groups have survival rates below 50%. However, since survival was still at 50% for both the low dose and control at week 96 (very near end of the study) it can be assumed that carcinogenic effects would have been detected in these groups. Also, survival was sufficient in the two highest dose groups where one would expect to see tumour development if it occurs. It is unlikely that the tumour profile in the control and low dose groups would have changed significantly in the last few weeks of the study.

The clinical, ophthalmoscopical and clinicochemical are summarised in Table 27. Organ weight changes and histopathological findings are summarised in Table 28.

Table 27: Clinical, ophthalmoscopical and clinicochemical findings

	Sex	Dose level (ppm)			
		0	100	700	1500
Clinical findings:					
Food consumption, wk 1-10 (% of control)	m	100	98	95**	92*
	f	100	99	96*	91**
Body weight change wk 0-104 (% of control)	m	100	94	93	84*
	f	100	88	90	69**
Body weight change wk 0-10 (% of control)	m	100	97	94**	86**
	f	100	99	91**	81**
Ophthalmoscopy:					
Posterior capsular lenticular opacities (Incidence)	m	4/20	5/21	6/27	13/32
	f	4/26	4/23	5/33	11/34
Clinicochemical findings:					
Cholesterol, week 104; % of control; females	f	100	98.7	125.6	147.4*
Gamma-GT, week 104, % of control, males	m	100	123.3	210.0	263.3**

*= p<0.05 (Williams test), **= p<0.01 (Williams test), m = male; f = female

Table 28: Organ weight and histopathological findings

	Sex	Dose level (ppm)			
		0	100	700	1500
Organ weights (% of control):					
Relative liver weight, wk 53	f	100	95.5	114.9**	115.7**
Relative liver weight, wk 105	f	100	100.6	104.6	111.0*
Histopathology (incidence):					
Stomach: epithelial hyperplasia at limiting ridge	m	1/18	7/20	8/25	18/31
Liver: bile duct hyperplasia	f	0/25	4/22	9/29	13/31
Liver: cystically dilatated bile ducts	f	1/25	1/22	3/29	6/31
Parathyroid: focal or diffuse hyperplasia	m	4/18	7/20	8/25	13/31

**= p<0.01 (Williams test), m = male; f = female

The maximum tolerated dose (MTD) was clearly met at the high dose in both sexes as demonstrated by a body weight gain depression of 16% in males and 31% in females (week 104). A body weight gain decrease (13%) was also observed in females at 700 ppm (week 0-10 and 10-80). The incidence of posterior capsular lenticular opacities was increased in both sexes at 1500 ppm (41% vs. 20%. and 32% vs. 16%, respectively). Although the increased incidence was still within historical control ranges (males: 22–44%, females: 12–50%), the finding was regarded to be a treatment-related exacerbation of a normal age-related change. In addition, in high-dose males, hyperplasia in the stomach and parathyroid were observed.

The liver was a target organ for dimethenamid in rats. Alterations at the high dose included increased cholesterol and liver weight in females and increased serum GGT in males.

Bile duct hyperplasia and dilated bile ducts were observed in high dose females. The bile duct hyperplasia was also observed in females at 700 ppm.

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. Table 29 shows the original and peer review analyses for ovarian tumors and hyperplasia. The peer review found 1 additional tumor in the control, 2 additional in the low and mid dose groups and 1 less at the high dose.

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 to their current grouping with the other sex cord-stromal neoplasms. Neoplasms diagnosed by the original pathologist as “tubular adenomas” have been reclassified by the reviewers as “Sertoliform tubular adenomas”. They consist of tubular structures lined by Sertoli-like cells. They differ from true Sertoli cell tumors 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 review consisted of 2 steps. The first step was a “blind” review by Dr. Alison of all ovaries from the study. In a second step Dr. Gopinath made his own evaluation of the slides in the light of the findings of the original report and Dr. Alison. All discrepancies were examined and discussed and a consensus was reached between the two reviewers.

The final analysis demonstrates that there is no statistical or biologically significant evidence to indicate that dimethenamid causes ovarian tumors. The incidence at the high dose is within historical control range, and the difference in incidence from control is not statistically significant.

When 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 Sprague-Dawley rat. These lesions are rarely found in other strains of rat, and are not found in man or domestic animals. They have therefore only very limited relevance for man.

Table 29: Incidence of ovarian tumors and hyperplasia

Dose level (ppm)	0	100	700	1500
Animals investigated	50	50	50	50
Ovary – Original Analysis				
Granulosa cell tumor	0	1	1	0
Tubular adenoma	2	1	2	6
Tubular hyperplasia	12	7	14	22
Ovary – Peer Review Analysis				
Granulosa cell tumor	0	0	1	0
Sertoliform tubular adenoma	3	3	4	5
Sertoliform tubular hyperplasia	18	12	12	23
Sertoliform tubular hyperplasia + adenoma	21	12	14	24

A marginal increase was observed for liver tumors in male rats. The incidence numbers are given in Table 30.

Table 30: Incidence of liver tumors in male rats

Dose level (ppm)	0	100	700	1500	Historical control range
Animals investigated	50	50	50	50	
Hepatocellular adenomas	0	0	1 (2%)	3 (6%)	HRC[a]: 0–1.8% (same diet) HRC 0–4.0% (other diet) CRL[b]: 0–15.4% RITA[c]: 0–12.0%
Hepatocellular carcinomas	0	0	0 (0%)	2 (4 %)	HRC[a]: 0–3.6%(same diet) 0–6.0% (other diet) CRL[b]: 0–7.7% RITA[c]: 0–8.0%

[a] Nine SD rat studies started at HRC during 04/1985–07/1986 with same stock diet (SDS)
[b] Nineteen studies with Charles River rats started during 04/1984–09/1986 (Charles River Historical Database, Patricia Lang, 1991, personal communication)
[c] Sixteen SD rat studies, different breeders, studies started between 1986–1990

The incidence of hepatocellular carcinomas was not statistically different from control and within historical control ranges. The incidence of adenomas was only slightly outside of historical range (6% at 1500 ppm compared to 4% in historical control), but was not statistically significant.

The statistically non-significant increased incidence of benign liver tumors in male rats is most likely due to a large increase in survival at this dose as indicated in Table 25.

Survival in high dose males was 72% greater than control males. This increased survival allowed considerably more animals to reach an older age and develop the liver adenomas which are spontaneously occurring tumors that increase in incidence with age. In support of this position, high dose females had a much more modest increase in survival and there was no increase in liver tumors.

In addition, the incidence of adenomas at the high dose is well within historical control range for Sprague-Dawley rats as given in the Registry of Industrial Toxicology Animal (RITA) database. This database was started in 1988 and collects historical control data for rats and mice. For long-term studies conducted between 1986 and 1990 with Sprague-Dawley rats, the historical (spontaneous) incidence for hepatocellular adenomas has a range of 0 to 12% and a mean of 3.6%. In 4 of 16 studies the incidence of hepatocellular adenomas was 6% (equal to the incidence in the dimethenamid study) or greater.

Overall, the slight increase in the benign liver tumor in high-dose males does not indicate that 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.

Conclusion:

The maximum tolerated dose (MTD) was clearly met at the high dose of 1500 ppm as evidenced by significant body weight gain depression and liver alterations in both sexes. Histopathological changes were noted at the high dose in the liver, stomach and parathyroid. The mid dose of 700 ppm produced body weight gain decreases and liver alterations in females. Dimethenamid did not produce a carcinogenic response. The NOAEL was found to be 100 ppm (ca. 5 mg/kg bw/d).

Report:	Hooks W. et al., 1990 SAN 582 H: Potential Tumorigenic Effects in Prolonged Dietary Administration to Mice Huntingdon Research Centre, Huntingdon, England unpublished, 24 August 1990, BASF RegDoc.#90/11139 (Experimental work: November 1987- September 1989)
Test Material:	Racemic dimethenamid; batch No. 8605; purity: 91.4%.
Test Animals:	Charles River Crl:CD-1 (ICR)BR mice
GLP:	yes (laboratory certified by The Department of Health and Social Security of the Government of the United Kingdom)
Test Method:	OECD Guideline 451
Deviations:	No deviations from OECD Guideline 451
Acceptability:	The study is considered to be acceptable.

Material and Methods:

Racemic dimethenamid was administered to groups of 52 male and female CD-1 mice at dietary concentrations of 0, 30, 300, 1500 and 3000 ppm for 94 wk. Satellite groups of 16 animals/sex received 0 or 3000 ppm dimethenamid for 65 wk. Analyses for stability and homogeneity of the test substance in the diet were performed prior to study start, and analyses to confirm target concentrations were performed periodically during the treatment period.

Food consumption and body weights were determined once a week. At least once a day the animals were examined for evident signs of toxicity and mortality, and once a week were subjected to an additional comprehensive clinical examination (including palpation). Blood smears were prepared from all mice killed during the study, and from all surviving mice at weeks 52, 78 and at terminal sacrifice (week 66 for satellite animals and week 95 for main study animals). At the end of the of treatment period, all surviving animals were sacrificed, subjected to gross pathological assessment, and selected organs were weighed. A histopathological examination was performed on all organs from the control and high dose satellite groups, and on all organs from all animals in the main study.

The test substance intake is given in Table 29.

Table 31: Test substance intake

Dietary dose level (ppm)	Test substance intake (mg/kg bw/d	
	males	Females
30	3.8	4.1
300	41	40
1500	205	200
3000	431	411

Findings:

The stability and homogeneity of the test substance in the diet, and the correct concentrations were confirmed by analysis.

There were no adverse treatment-related effects on survival or clinical observations. The clinical and clinicochemical findings, as well as organ weight changes and histopathological findings are summarised in Table 32.

Body weight changes were reduced in males and females at 1500 and 3000 ppm. Reduced body weight gains at lower doses (30 and 300 ppm) are considered to be without toxicological relevance because they were without dose relation or were observed only in short periods and were compensated in other periods. The body weight change impairment at the high dose demonstrated that a Maximum Tolerated Dose (MTD) was attained.

Body weight adjusted liver weights were increased in females by 25% at 1500 ppm and by 18% at 3000 ppm. Kidney weights were also increased in females at 1500 and 3000 ppm, but considering the lack of any histopathological findings in the kidney, the toxicological significance of this finding is equivocal. There were no other organ weight changes considered related to treatment.

Effects on the liver were also noted with histopathology. The incidence of enlarged hepatocytes was increased in a dose-related manner at doses of 300 to 3000 ppm. However, at 300 ppm, enlarged hepatocytes were observed in only 1 male and 2 females and the severity was only minimal. The minimal enlargement of hepatocytes in the absence of any other toxicity at this dose is not considered an adverse effect.

Table 32: Clinical, organ weight and histopathological findings

	Sex	Dose level (ppm)				
		0	30	300	1500	3000
Body weight gain, wk 0-52,]% of control]	m	100	110.0	101.9	86.9*	85.0**
	f	100	87.7	93.6	84.2*	71.1**
Rel. liver weightt, wk 95 [% of control]	f	100	101.2	102.9	120.9**	117.5**
Rel. kidney weight, wk 95 [% of control]	f	100	97.2	102.3	115.9**	116.8**
Liver: enlarged hepatocytes [incidence]	m	3/15	1/24	8/25	6/19	19/22
	f	0/33	2/41	5/41	14/34	29/37

*= p<0.05 (Williams test), **= p<0.01 (Williams test), m = male; f = female

Also, the incidence of hyperkeratosis of the limiting ridge of the stomach was increased at the high dose, but only minimally at the interim sacrifice. By the terminal sacrifice, this effect was not noted indicating a recovery had occurred. This effect may have been due to an irritating effect of the chemical.

There were no test substance-related findings at 30 ppm. In addition, there was no evidence that dimethenamid caused a treatment-related increase in tumors at any dose level.

Conclusion:

Evidence of toxicity was observed at the highest doses tested of 1500 and 3000 ppm in the form of reduced body weight gains, increased liver weights and enlarged liver cells. The NOAEL was found to be 300 ppm (ca. 40 mg/kg bw/d). There was no evidence that dimethenamid produced a carcinogenic effect in mice.

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 in Sprague-Dawley rats. 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.

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 Table 33.

Table 33: 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.

4.12 Other effects

4.12.1 Non-human information

4.12.1.1 Neurotoxicity

No studies on neurotoxicity submitted.

4.12.1.2 Immunotoxicity

No studies on immunotoxicity submitted.

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 radiolabeled 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 34: 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 $\lambda > 290$ 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 (3-14C-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 35: 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 36: 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 37: 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 38: 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) and is also below the trigger of 500 (criterion for bioaccumulating potential conform Regulation EC 1272/2008).

5.4 Aquatic toxicity

Table 39: 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* *(Pseudokirchneriella subcapitata)* 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) Amendment: Kubitza, J. (2004a)
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) Amendment: Kubitza, J. (2004b)

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

5.4.3.1 Algae

The toxicity of dimethenamid-P to algae (*Selenastrum capricornutum* = *Pseudokirchneriella subcapitata)* 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 and chronic aquatic toxicity of dimethenamid-P and hence for classification and labelling. 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.

An amendment to the study " SAN 1289H technical – Toxicity to the freshwater green alga *Selenastrum capricornutum*" has been submitted in 2004.

Title: Amendment to Study BASF DocID 1997/10746 "SAN 1289H TECHNICAL – TOXICITY TO THE FRESHWATER GREEN ALGA *Selenastrum capricornutum*" (Kubitza, J. 2004a)

In this amendment results from further observation times are documented.

Findings:

ErC50 (72h) = 0.0303 mg/L (95% limits: 0.0296 – 0.0310 mg/L)
EbC50 (72h) = 0.0191 mg/L (95% limits: 0.0186 – 0.0197 mg/L)

ErC50 (96h) = 0.0339 mg/L (95% limits: 0.0327 – 0.0352 mg/L)
EbC50 (96h) = 0.0140 mg/L (95% limits: 0.0135 – 0.0145 mg/L)

5.4.3.2 Aquatic Plants

The toxicity of dimethenamid-P to Duckweed (*Lemna gibba)* was tested in a 14 d semistatic test. The endpoints are EbC_{50} = 0.0089 mg a.i./L, ErC_{50} = 0.016 mg a.i/L and $NOEC_{Biomass}$ = 0.0012 mg a.i./L based on initial measured concentrations (Hoberg, J. 1997b).

Title: SAN 1289H Technical - toxicity to Duckweed, *Lemna gibba* (Hoberg, J. 1997b).

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

Materials and methods:
Duckweed, *Lemna gibba G3* were exposed to Technical dimethenamid-P (SAN 1289H, lot no. 6663-50-1; purity: 91.1 %) at nominal test concentrations of 0.0010, 0.003, 0.0089, 0.027 and 0.081 mg as/L and initial measured concentrations of 0.0012, 0.0032, 0.0073, 0.026 and 0.074 mg as/L, representing 82-120 % of nominal test concentrations.

Findings:
Measured concentrations at test termination decreased significantly and ranged from 15 to 36 % of the nominal concentrations. Based on the observed decline in test substance concentration over the renewal period, results are based on initial measured concentrations.
Mean frond density and observations of the fronds recorded during the 14-day exposure are presented in the following table:

Initial measured concentration (mg a.i./L)	Mean Fronds/Replicate					14-Day inhibition (%)
	Day 3	Day 6	Day 9	Day 12	Day 14	
Control	41	132	305	498	841	NA
0.0012	41	131	333	511	799	4.9
0.0032	41	129	330[ab]	520[ab]	907[ab]	-7.9
0.0073	41	130[a]	342[abcd]	489[abcd]	772[abcd]	8.1
0.026	30[a]	55[ac]	72[bcde]	84[bcde]	86[bcdef]	90
0.074	25[ac]	32[acd]	34[bceg]	40[bceg]	35[bcdef]	96

a Fronds were observed to have less root formation

b Fronds were observed to be smaller

c Curled fronds were observed

d Frond were observed to be slightly chlorotic

e Fronds were observed to have very little root formation

f Significantly reduced as compared to the control based on Williams' Test

g Chlorotic fronds were observed

At test termination fromds exposed to the 0.0032 and 0.0073 treatment levls were observed to be smaller and to have less root formation as compared to the control fronds. In addition, fronds exposed to the 0.0073 mg a.i./L treatment level were observed to be slightly chlorotic and curled in comparison to the control. Fronds exposed to the 0.026 and 0.074 mg a.i./L treatment levels were

observed to be curled, slightly chlorotic, have very little root formation and to be smaller in comparison to the control.

At test termination, the control averaged 841 fronds per replicate. Frond production in the treatment levels (0.0012, 0.0032, 0.0073, 0.026 and 0.074 mg a.i./L) averaged 799, 907, 772, 86 and 35 fronds per replicate, respectively. A significant reduction in frond density was observed in the 0.026 and 0.074 mg a.i./L treatment levels when compared to the control, based on Williams' Test. Based on frond density, the **14-day NOEC** was established to be **0.0073 mg a.i./L**. The **14-day EC50** value calculated to be **0.016 mg a.i./L** (95% CI = 0.0055 – 0.048 mg a.i./L).

The 14-day biomass (dry weight) for the control averaged 0.2224 g. Biomass in the treatment levels tested, 0.0012, 0.0032, 0.0073, 0.026 and 0.074 mg a.i./L, averaged 0.1984, 0.1833, 0.1592, 0.0229 and 0.0149 g, respectively. The biomass in the 0.0032, 0.0073, 0.026 and 0.074 mg a.i./L treatment levels was significantly reduced compared to the control. Based on these results, the **14-day NOEC** for frond biomass was determined to be **0.0012 mg a.i./L**. Based on biomass, the **14-day EC50** value was calculated to be **0.0089 mg a.i./L** (95% CI = 0.0025 – 0.032 mg a.i./L).

The NOEC was determined using Williams' Test (Williams, 1971, 1972). Data were first checked for normality using Shapiro-Wilks' Test (Weber *et al.*, 1989) and for homogeneity of variance using Bartlett's Test (Horning and Weber, 1985).

An amendment to the study " SAN 1289H technical – Toxicity to Duckweed; *Lemna gibba*" has been submitted in 2004.

Title: Amendment to Study BASF DocID 1997/10742 "SAN 1289H TECHNICAL – TOXICITY TO DUCKWEED; *Lemna gibba*" (Kubitza, J. 2004b)

In this amendment results from further observation times are documented.

Findings:

ErC50 (3d) = 0.0713 mg/L (95% limits: 0.0654 – 0.0777 mg/L)
EbC50 (3d) = 0.0483 mg/L (95% limits: 0.0451 – 0.0517 mg/L)

ErC50 (6d) = 0.0473 mg/L (95% limits: 0.0444 – 0.0503 mg/L)
EbC50 (6d) = 0.0256 mg/L (95% limits: 0.0244 – 0.0268 mg/L)

ErC50 (9d) = 0.0390 mg/L (95% limits: 0.0372 – 0.0409 mg/L)
EbC50 (9d) = 0.0211 mg/L (95% limits: 0.0204 – 0.0219 mg/L)

ErC50 (12d) = 0.0378 mg/L (95% limits: 0.0360 – 0.0397 mg/L)
EbC50 (12d) = 0.0192 mg/L (95% limits: 0.0185 – 0.0199 mg/L)

Statistical analyses were performed with the software programme "Toxstat", version 3.5.

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 < 0.1 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) and is also below the trigger of 500 criterion for bioaccumulating potential conform Regulation EC 1272/2008).

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 acute M-factor is 10, based on the 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. The chronic M-factor is 10, based on the chronic toxicity

data for the algae *Selenastrum capricornutum* (NOEC = 0.0021 mg/L) in a 120-h static study and for the aquatic plant *Lemna gibba* (NOEC = 0.0012 mg/L) in a 14-d semistatic study

6 OTHER INFORMATION

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