Committee for Risk Assessment

RAC

Annex 1

Background document

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

dichlofluanid (ISO); N-[(Dichlorofluoromethyl)thio]-N',N'-dimethyl-N-phenylsulfamide

EC Number: 214-118-7
CAS Number: 1085-98-9

CLH-O-0000001412-86-57/F

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

Adopted

03 June 2015

CLH report

Proposal for Harmonised Classification and Labelling

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

Substance Name: Dichlofluanid

EC Number: **214-118-7**

CAS Number: **1085-98-9**

Index Number: **616-006-00-7**

Contact details for dossier submitter: **UK Competent Authority**

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United Kingdom

Version number: **2** **Date:** **September 2014**

ANNEX 1 – BACKGROUND DOCUMENT TO THE RAC OPINION ON DICHLOFLUANID (ISO)

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Part A.

1 PROPOSAL FOR HARMONISED CLASSIFICATION AND LABELLING

1.1 Substance

Table 1: Substance identity

Substance name:	Dichlofluanid
EC number:	214-118-7
CAS number:	1085-98-9
Annex VI Index number:	616-006-00-7
Degree of purity:	≥ 96% (Typical 98%)
Impurities:	Confidential – full information on the impurities is provided in the technical dossier. None of the identified impurities are relevant for classification and labelling.

1.2 Harmonised classification and labelling proposal

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

	CLP Regulation
Current entry in Annex VI, CLP Regulation	Skin Sens 1; H317 – May cause an allergic skin reaction Eye Irrit 2; H319 – Causes serious eye irritation Acute Tox 4* H332 – Harmful if inhaled Aquatic Acute 1 ; H400 – Very toxic to aquatic life M=10
Current proposal for consideration by RAC	Skin Sens 1B; H317 – May cause an allergic skin reaction Acute Tox 4; H332 0 Harmful if inhaled
Resulting harmonised classification (future entry in Annex VI, CLP Regulation)	Skin Sens 1B; H317 – May cause an allergic skin reaction

	Eye Irrit 2; H319 - Causes serious eye irritation Acute Tox 4; H332 - H332 – Harmful if inhaled Aquatic Acute 1; H400 - Very toxic to aquatic life M=10

1.3 Proposed harmonised classification and labelling

Table 3: Proposed classification

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	Not classified	Not applicable	Not classified	conclusive but not sufficient for classification
2.2.	Flammable gases	Not classified	Not applicable	Not classified	conclusive but not sufficient for classification
2.3.	Flammable aerosols	Not classified	Not applicable	Not classified	conclusive but not sufficient for classification
2.4.	Oxidising gases	Not classified	Not applicable	Not classified	conclusive but not sufficient for classification
2.5.	Gases under pressure	Not classified	Not applicable	Not classified	conclusive but not sufficient for classification
2.6.	Flammable liquids	Not classified	Not applicable	Not classified	conclusive but not sufficient for classification
2.7.	Flammable solids	Not classified	Not applicable	Not classified	conclusive but not sufficient for classification
2.8.	Self-reactive substances and mixtures	Not classified	Not applicable	Not classified	conclusive but not sufficient for classification
2.9.	Pyrophoric liquids	Not classified	Not applicable	Not classified	conclusive but not sufficient for classification
2.10.	Pyrophoric solids	Not classified	Not applicable	Not classified	conclusive but not sufficient for classification
2.11.	Self-heating substances and mixtures	Not classified	Not applicable	Not classified	conclusive but not sufficient for classification
2.12.	Substances and mixtures which in contact with water emit flammable gases	Not classified	Not applicable	Not classified	conclusive but not sufficient for classification
2.13.	Oxidising liquids	Not classified	Not applicable	Not classified	conclusive but not sufficient for classification
2.14.	Oxidising solids	Not classified	Not applicable	Not classified	conclusive but not sufficient for classification
2.15.	Organic peroxides	Not classified	Not applicable	Not classified	conclusive but not sufficient for classification

2.16.	Substance and mixtures corrosive to metals	Not classified	Not applicable	Not classified	conclusive but not sufficient for classification
3.1.	Acute toxicity - oral	**Acute Tox 4; H332 – Harmful if inhaled**	Not applicable	**Acute Tox 4*; H332 – Harmful if inhaled**	
	Acute toxicity - dermal	Not classified	Not applicable	Not classified	conclusive but not sufficient for classification
	Acute toxicity - inhalation	Not classified	Not applicable	Not classified	conclusive but not sufficient for classification
3.2.	Skin corrosion / irritation	Not classified	Not applicable	Not classified	conclusive but not sufficient for classification
3.3.	Serious eye damage / eye irritation	**Eye Irrit 2; H319 – causes serious eye irritation**	Not applicable	**Eye Irrit 2; H319 – causes serious eye irritation**	
3.4.	Respiratory sensitisation	Not classified	Not applicable	Not classified	Data lacking
3.4.	Skin sensitisation	**Skin Sens 1B; H317 – may cause an allergic skin reaction**	Not applicable	**Skin Sens 1; H317 – may cause an allergic skin reaction**	
3.5.	Germ cell mutagenicity	Not classified	Not applicable	Not classified	conclusive but not sufficient for classification
3.6.	Carcinogenicity	Not classified	Not applicable	Not classified	conclusive but not sufficient for classification
3.7.	Reproductive toxicity	Not classified	Not applicable	Not classified	conclusive but not sufficient for classification
3.8.	Specific target organ toxicity – single exposure	Not classified	Not applicable	Not classified	conclusive but not sufficient for classification
3.9.	Specific target organ toxicity – repeated exposure	Not classified	Not applicable	Not classified	conclusive but not sufficient for classification
3.10.	Aspiration hazard	Not classified	Not applicable	Not classified	conclusive but not sufficient for classification
4.1.	Hazardous to the aquatic environment	**Aquatic Acute 1; H400 – very toxic to aquatic life**	**M = 10**	**Aquatic Acute 1; H400 – very toxic to aquatic life**	
5.1.	Hazardous to the ozone layer	Not classified	Not applicable	Not classified	conclusive but not sufficient for classification

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

Labelling:

Pictogram(s): GHS07, GHS09

Signal word: Warning

Hazard statements: H317, H319, H332, H400

Precautionary statements: Not included in Annex VI

Proposed notes assigned to an entry:

None

2 BACKGROUND TO THE CLH PROPOSAL

2.1 History of the previous classification and labelling

Dichlofluanid is a biocidal active substance in the scope of Reg 528/2012. The substance was first included in Annex I to Dir 67/548/EEC at the 25th ATP (1998), with the following classification and labelling Xn; R20, Xi; R36, R43, N; R50-53 in accordance with DSD. The classification and labelling was reviewed in 1999 by the Working Group on the classification and labelling of Dangerous Substances – Pesticides (May and November 1999 meetings), where it was concluded that the existing classification was appropriate. During this time, the substance was also discussed by the Specialised Experts. In March-April 2004, the classification was discussed at the Meeting on Environmental Effects of Existing Chemicals, Pesticides and New Chemicals, where it was agreed to remove the R53 classification.

At the entry into force of CLP, the classification in table 3.1 of Annex VI to CLP was translated as Skin Sens 1; H317, Eye Irrit 2; H319, Acute Tox 4*; H332, Aquatic Acute 1; H400 and Aquatic Chronic 1: H410. The classification in Annex VI of CLP was updated at the 1st ATP to CLP to remove the classification for Aquatic Chronic 1; H410 and to include the acute M factor.

At the time of submission, the substance does not have a separate REACH registration as it is an active biocide substance.

It should be noted that dichlofluanid was also a pesticidal active substance within scope of Directive 91/414/EEC. However, it was not approved in the EU as the necessary dossier was not submitted in the specified timeframe (Regulation 2076/2002).

2.2 Short summary of the scientific justification for the CLH proposal

Dichlofluanid already has an existing entry in Annex VI of CLP therefore this proposal only seeks to confirm the classification for acute inhalation toxicity and update the classification for skin sensitisation with a subcategory. The lowest reported LC50 value is 1.2 mg/l, confirming classification with Acute Tox 4; H332 (dusts and mists) and removal of the *. In a standard skin sensitisation study (guinea pig maximisation study), a positive response was observed in 87% of animals receiving an intradermal induction dose of 10%. This meets the criteria for classification in Category 1B.

No new relevant data are available to support classification in another hazard class, category or differentiation or to require further consideration of specific concentration limits or M-factors.

2.3 Current harmonised classification and labelling

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

Classification :

Skin Sens 1; H317

Eye Irrit 2; H319

Acute Tox 4* H332

Aquatic Acute 1 ; H400

M=10

Labelling:

GHS07, GHS09

Warning

H317, H319, H332, H400

2.4 Current self-classification and labelling

2.4.1 Current self-classification and labelling based on the CLP Regulation criteria

The current classification and labelling applied by the applicant and notified to the C&L Inventory is in line with the existing harmonised classification.

3 JUSTIFICATION THAT ACTION IS NEEDED AT COMMUNITY LEVEL

Dichlofluanid is an active substance in the scope of Reg 528/2012. As such it is subject to the harmonised classification and labelling process in accordance with Article 36(2) of CLP. However, dichlofluanid already has an entry on Annex VI of CLP and this proposal therefore only seeks to confirm the classification for acute inhalation toxicity and update the classification for skin sensitisation with a subcategory. No relevant new data that support classification in an additional or different hazard class, category or differentiation have been made available since the classification of the substance was last considered at the EU level.

Part B.

SCIENTIFIC EVALUATION OF THE DATA

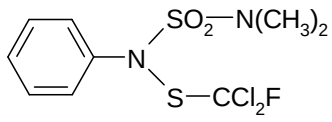
1 IDENTITY OF THE SUBSTANCE

1.1 Name and other identifiers of the substance

Table 4: Substance identity

EC number:	214-118-7
EC name:	Dichlofluanid *N*-dichlorofluoromethylthio-*N*',*N*'-dimethyl-*N*-phenylsulfamide
CAS number (EC inventory):	1085-98-9
CAS number:	1085-98-9
CAS name:	Methanesulfenamide, 1,1-dichloro-N-[(dimethylamino)sulfonyl]-1-fluoro-N-phenyl-
IUPAC name:	N-[(Dichlorofluoromethyl)thio]-N',N'-dimethyl-N-phenylsulfamide
CLP Annex VI Index number:	616-006-00-7
Molecular formula:	$C_9H_{11}C_{l2}FN_2O_2S_2$
Molecular weight range:	333.2

Structural formula:



1.2 Composition of the substance

Table 5: Constituents (non-confidential information)

Constituent	Typical concentration	Concentration range	Remarks
Dichlofluanid	98%	≥ 96%	

Table 6: Impurities (non-confidential information)

Impurity	Typical concentration	Concentration range	Remarks
Confidential			

There are 6 process impurities in the substance. These have been taken into consideration and are not considered to further impact on the classification proposed in this dossier. Further information on the impurities is considered to be confidential but full details are provided in the technical dossier.

Table 7: Additives (non-confidential information)

Additive	Function	Typical concentration	Concentration range	Remarks
Confidential				

There is 1 additive in the substance. This has been taken into consideration and is not considered to further impact on the classification proposed in this dossier. Further information on the additive is considered to be confidential but full details are provided in the technical dossier.

1.2.1 Composition of test material

The material used in the referenced studies was considered to be representative of the substance as identified above during the review of dichlofluanid as a biocidal active substance.

1.3 Physico-chemical properties

Table 8: Summary of physico - chemical properties (ref. CAR Doc. III-A Section A3)

Property	Value	Reference	Comment (e.g. measured or estimated)
State of the substance at 20°C and 101,3 kPa	White/yellow Solid		
Melting/freezing point	103 oC	Schneider 2001	Dir 92/69/EC A1 – Melt microscope Purity 99.4%
Boiling point	Decomposes at 120 oC	Klusacek & Krasemann 1986	OECD 113 Purity 99.9%
Relative density	1.575 at 20oC	Jungheim 2001	Dir 92/69/EC A3 Pycnometer 96%
Vapour pressure	2.15 x 10-5 Pa at 20oC 5.37 x 10-5 Pa at 25oC 3.03 x 10-3 Pa at 50oC	Treckmann, 1994	Dir 92/69/EC A4 Effusion method – vapour pressure balance 96%
Surface tension	72.75mN/m at 20 oC	Olf, 2001	OECD 115; ring method 96%
Water solubility	pH 4: 0.92 mg/l at 10 °C 1.58 mg/l at 20 °C 2.69 mg/l at 30 °C At high pH the substance rapidly hydrolyses	Schneider, 2002	OECD 105; Column elution 99.4%
Partition coefficient n-octanol/water	3.5	Schneider, 2002	OECD 117; HPLC method 99.4%
Flash point	Not applicable		
Flammability	Not flammable, not pyrophoric and does not liberate gases in hazardous amounts upon contact with water.	Heinz, 2003	Dir 92/69/EC A10, A12 and A13 Tests conducted on product Preventol A4-S(1) 89.9%
Explosive properties	Not predicted to be explosive based on a consideration of the structure.		
Self-ignition temperature	Spontaneous ignition temperature is 370 oC	Heinz, 2003	Dir 92/69/EC, A16 Tests conducted on product Preventol A4-S(1) 89.9%
Oxidising properties	Not predicted to be oxidising based on a consideration of the structure.		
Granulometry	No data		

Dissociation constant	No acidic or basic properties in water at pH 4-9	Schneider, 2002	OECD 112 99.4%
Viscosity			

(1) 90% technical dichlofluanid plus 6% silicon dioxide 1% magnesium oxide and 3% mineral oil

2 MANUFACTURE AND USES

2.1 Manufacture

The substance is manufactured in the EU for use as a biocidal active substance.

2.2 Identified uses

Dichlofluanid is used in the EU as a biocidal active substance in wood preservatives, film preservatives and antifouling products.

RAC general comment
During public consultation, two Member State Competent Authorities (MSCA) requested that the STOT RE and environmental hazard classifications should be assessed by the Dossier Submitter (DS), since data that can be used for classification of these two endpoints are available in the biocide Competent Authority Report (CAR). Neither the STOT RE nor the environmental hazard classification were considered for classification in the CLH report and therefore these hazard classes were not opened for comments during public consultation. Consequently they cannot be assessed in the context of this CLH proposal. In order to address the classification of diclofluanid for these hazard classes, a new CLH proposal including the relevant information would need to be submitted.

3 CLASSIFICATION FOR PHYSICO-CHEMICAL PROPERTIES

3.1 Physical Hazards

Not considered in this report.

4 HUMAN HEALTH HAZARD ASSESSMENT

4.1 Toxicokinetics (absorption, metabolism, distribution and elimination)

4.1.1 Non-human information

See section 4.1.3

4.1.2 Human information

None available

4.1.3 Summary and discussion on Toxicokinetics

Following oral administration in rats, dichlofluanid is rapidly and extensively absorbed from the gastrointestinal tract (70 % - 90 %), with the peak plasma concentration occurring from 1.5 to 3.0 hours post-dose. In contrast however, the single and repeated dermal application toxicodynamic studies suggest that technical dichlofluanid is poorly absorbed across the skin as indicated by no evidence of systemic toxicity. However, an *in vitro* dermal penetration study conducted using a mineral oil-based formulation, indicates that dichlofluanid in a solvent is absorbed following single dermal application. As dichlofluanid is almost completely absorbed from the gastrointestinal tract, it is predicted that it will also be well absorbed from the respiratory tract. This prediction is supported by the single inhalation exposure toxicodynamic study in rats, which provides qualitative evidence that dichlofluanid might be systemically available following exposure via this route.

Following oral dosing of radiolabelled dichlofluanid, the absorbed radioactivity is widely distributed, with erythrocytes, the liver and the thyroid gland being the sites of greatest localisation. There was some evidence that radioactivity was retained in the thyroid, suggesting the potential for accumulation at that site.

Orally administered dichlofluanid is rapidly and extensively metabolised, with no parent compound detected systemically. Initial metabolism of dichlofluanid proceeds via loss of the fluorodichloromethyl-sulphenyl group in reactions with cellular thiols to generate DMSA. No qualitative differences in metabolite profiles were observed between oral and intravenous administration, suggesting no significant 'first-pass' effect. It is predicted that any dichlofluanid available systemically following dermal or inhalation exposure would be similarly metabolised.

Elimination of radiolabelled dichlofluanid was rapid, with the majority of the administered radioactivity cleared during the first 48 hours. The predominant elimination route for the ring-labelled moiety is via the urine (over 90%), with a small amount eliminated via the bile. For the side-chain, the predominant route of elimination is via the urine (around 50%), with the remainder either exhaled as carbon dioxide (20-30%) or eliminated via the bile (20-30%). It is predicted that dichlofluanid metabolites produced following dermal or inhalation exposure would be similarly excreted.

(ref. CAR Doc. III-A Section A6.2)

4.2 Acute toxicity

Table 9: Summary table of relevant acute inhalation toxicity studies

Acute Inhalation		
Method	**LC50**	**Observations and remarks**
Rat (Wistar 5/sex/group) 0, 0.1, 0.5, 1.5, and 2.58 mg/l (head only) Dust aerosol (MMAD 4.8-6 µm) 4 hours (14 days post exposure) OECD 403 GLP	1.2 mg/l	Clinical signs of toxicity noted included dyspnoea, laboured breathing and lethargy at 0.5 mg/l and above. Deaths occurred at concentrations of 0.5 mg/l and above from day 0 to day-3 post exposure. No histopathological examinations were conducted, Pauluhn, J. (1988) (ref. CAR Doc. III-A Section A6.1.3)
Rat (Sprague Dawley 10/sex/group) 0, 1.09, 2.0, or 2.5 mg/l (head only) An additional group of females were exposed to 0.77 mg/l. Dust aerosol (MMAD 3.5-4.7 µm) 4 hours (14 days post exposure) US-EPA FIFRA 81-3 GLP	1.2 mg/l (m) and 1.3 mg/l (f)	Mortalities occurred in both males (0/10, 3/10, 8/10 and 10/10 at 0, 1.09, 2.0, or 2.5 mg/l respectively) and females (0/10, 4/10, 4/10, 5/10 and 9/10 at 0, 0.77, 1.09, 2.0, or 2.5 mg/l respectively), from day 0 to day 3 post exposure. Those animals dying during the study were found to have: nasal, ocular, oral and generalised facial and ventral thoracic stains; wet red or minimally firm lungs; red turbinates and ocular opacity. No treatment-related lesions were reported in surviving animals at the end of the study, Shiotsuka (1986) (ref. CAR Doc. II-A Section 3.2)

4.2.1 Non-human information

4.2.1.1 Acute toxicity: oral

Not considered in this report.

4.2.1.2 Acute toxicity: inhalation

The lowest 4 hour LC_{50} (dust and mists) observed was approximately 1.2 mg/l in male and female rats.

4.2.1.3 Acute toxicity: dermal

Not considered in this report.

4.2.1.4 Acute toxicity: other routes

4.2.2 Human information

No data.

4.2.3 Summary and discussion of acute toxicity

The lowest 4 hour LC_{50} (dust and mists) observed was approximately 1.2 mg/l in male and female rats.

4.2.4 Comparison with criteria

The values for classification as Acute Toxicity Category 4 for a dust/mist under CLP range from 1.0 – 5 mg/l. As the lowest 4 hour LC_{50} observed in male and females rats is 1.2 mg/l, dichlofluanid should be classified as Acute Tox 4; H332 and the * removed.

4.2.5 Conclusions on classification and labelling

Acute Tox 4; H332 – Harmful if inhaled

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

Not considered in this report.

4.4 Irritation

Not considered in this report.

4.5 Corrosivity

Not considered in this report.

RAC evaluation of acute toxicity

Summary of the Dossier submitter's proposal

Acute toxicity: inhalation

Two rat acute inhalation toxicity studies were reported in the CLH report. In the first study, a 4-hour LC_{50} value of 1.2 mg/L was reported for males and females combined. In the second study, 4-hour LC_{50} values of 1.2 mg/L and 1.3 mg/L were reported for male and female rats, respectively.

Removal of the minimum classification for Acute Tox. 4; H332 was proposed on the basis of the lowest 4-hour LC_{50} value (1.2 mg/L) observed in rats exposed to dust aerosol for 4 hours. This value is within the range ($1.0 < ATE \leq 5.0$) which, according to the CLP Regulation, justifies classification as Acute Tox. 4; H332.

Comments received during public consultation

No comments were received for this hazard class.

Assessment and comparison with the classification criteria

The rat acute inhalation toxicity studies (Pauluhn 1988; Shiotsuka 1986) are summarised in the table below. RAC notes that these studies were the basis for classifying dichlofluanid with Xn; R20 under the Dangerous Substances Directive (DSD; ECB 1997 & 1998) and that no new studies have become available since then.

Summary of acute inhalation toxicity studies for dichlofluanid

<table>
<tr><th>Strain</th><th>Obs period (Days)</th><th>Design</th><th>Exposure</th><th>LC_{50} / Lethality</th><th>Reference</th></tr>
<tr><td>Wistar</td><td>14</td><td>N=5/sex/group, 5 dose levels (OECD TG 403 & US-EPA FIFRA 81 – 3, GLP).</td><td>4hr to dust aerosol (head only).</td><td>LC_{50} (combined) = 1.2 mg/L.
<table><tr><th>Conc. (mg/L)[1]</th><th>Part ⩽5 µm (%)</th><th>MMAD ±GSD[2] (µm)</th><th>M</th><th>F</th></tr><tr><td>0</td><td>-</td><td>-</td><td>0/5</td><td>0/5</td></tr><tr><td>0.1</td><td>53</td><td>4.8±1.8</td><td>0/5</td><td>0/5</td></tr><tr><td>0.5</td><td>44</td><td>5.5 ± 1.7</td><td>0/5</td><td>2/5</td></tr><tr><td>1.5</td><td>41</td><td>5.8 ± 1.8</td><td>1/5</td><td>2/5</td></tr><tr><td>2.6</td><td>35 (M) 45 (F)</td><td>6.0 ±1.6</td><td>5/5</td><td>5/5</td></tr></table></td><td>Pauluhn, 1988 (CAR DOC III-A, section A6.1.3).</td></tr>
<tr><td>Sprague Dawley</td><td>14</td><td>N=10/sex/group. 5 dose levels.

(OECD TG 403 & US-EPA FIFRA 81 – 3, GLP).</td><td>4hr to dust aerosol (head only)

MMAD[2]: only range provided, 3.5–4.7 µm.</td><td>LC_{50} = 1.2 mg/L (M) and 1.3 mg/L (F).
<table><tr><th>Conc. (mg/L)[1]</th><th>Part ⩽5 µm (%)</th><th>MMAD ±GSD[2],[3] (µm)</th><th>M</th><th>F</th></tr><tr><td>0</td><td>-</td><td>-</td><td>0/10</td><td>0/10</td></tr><tr><td>0.8</td><td>*</td><td>3.9</td><td>NA**</td><td>4/10</td></tr><tr><td>1.1</td><td>*</td><td>4.6</td><td>3/10</td><td>4/10</td></tr><tr><td>2.0</td><td>*</td><td>3.5</td><td>8/10</td><td>5/10</td></tr><tr><td>2.5</td><td>*</td><td>4.7</td><td>10/10</td><td>9/10</td></tr></table>*) No data provided in the CAR or CLH report.
**) Not applicable since only females</td><td>Shiotsuka, 1986 (CAR DOC. II-A section 3.2, and CLH dossier).</td></tr>
</table>

				were exposed at this dose level.	

1)According to information provided by the DS during RAC consultation, the original study report states that the concentration referes to the actual concentration. 2) MMAD ± GSD = Mass Median Aerodynamic Diameter ± General Standard deviation. 3) According to information provided by the DS during RAC consultation, the original study report contained this information.

It is noted that clinical signs of toxicity (including dyspnea, labored breathing, respiratory noises and reduced motility) were recorded at 0.1 mg/L and above in the study by Pauluhn (1988). No data on clinical signs was provided in the CAR for the study by Shiotsuka (1986). For both studies the reported gross pathological findings in deceased animals were similar among the dose groups and death occurred between day 0 and day 3 post exposure in both studies.

Based on the mortality data from the study by Pauluhn (1988), females seem somewhat more sensitive compared to male rats. At 0.5 mg/L, mortalities were recorded only in female rats (2/5). At the next dose level (1.5 mg/L) no increase in the incidence was seen in female rats (mortality incidence 2/5) wheras mortality for male rats was also recorded (1/5). At the next dose level 100% mortality was seen for both male and female rats. Although females seem more sensitive than male rats, it is very unlikely that the female LC_{50} value would have been below the only reported LC_{50}value in this study (1.2 mg/L) which was for females and males combined. However, RAC notes that the size of the particles tested (MMAD of 4.8–6.0 µm) in the study by Pauluhn (1988) exceeded the recommendation of both the OECD TG 403 and the CLP Regulation (Annex I: 3.1.2.3.2.) of a MMAD of 1-4 µm to achive a respirable particle size. The reported particle size clearly deviates from the latter range at all dose levels tested and therefore RAC concludes that this study is less reliable and that more weight should be given to the study by Shiotsuka (1986). In this study, which used another rat strain (Sprague Dawley), the reported MMADs (3.5–4.7 µm) were reasonably well within the recommended range. Also, this study provides data approximately at the cut off concentrations between the Acute Tox. 3 and Acute Tox. 4 classifications (1 mg/L). In this study a similar level of mortality was seen at 1.1 and 2.0 mg/L (4/10 and 5/10, respectively) for females, whereas for males a much higher incidence of mortality (8/10) was seen at 2.0 mg/L, compared to the incidence (3/10) at 1.1 mg/L . This study also examined (using an additional group of females) the toxicity at 0.8 mg/L. The observed incidence of mortality (40%) was identical to that observed at 1.1 mg/L. Thus it is unlikely (as also the reported LC_{50} values of 1.2 and 1.3 mg/Lindicate) that dichlofluanid would fulfil the criteria for classification as Acute Tox. 3.

RAC concludes that the calculated LC_{50} values (1.2 and 1.3 mg/L in males and females, respectively) in the study by Shiotsuka (1986) are within the range $1.0 < ATE \leq 5.0$ mg/L for dusts and mists, which according to the CLP Regulation, justifies classification as Acute Tox. 4; H332. Although some limitations were noted in the study by Pauluhn (1988), the reported LC_{50} value in this study (1.2 mg/L) also supports the classification as Acute Tox. 4; H332. Therefore, as proposed by the DS, RAC concludes that it is justified to remove the minimum classification and classify dichlofluanid as Acute Tox. 4, H332.

4.6 Sensitisation

4.6.1 Skin sensititsation

Table 10: Summary table of relevant skin sensitisation studies

Species/Method	Doses	No. sensitised/total no.	Result	Reference
Guinea Pig Male Pirbright 15 test and 15 control Conducted prior to guideline, but method considered to be comparable to OECD 406, GPMT Not GLP (not compulsory at the time of the study) Description, purity, and stability of the test substance were not documented.	Induction: Intadermal: 10% Topical: 5% Challenge: 12.5% and 25% 25% was determined to be the maximum non-irritant concentration.	12.5% Test: 11/15 (73%) and 13/15 (87%) at 24 and 48 hours Negative Control: 1/15 and 0/15 at 24 and 48 hours. 25% Test: 13/15 (87%) and 13/15 (87%) at 24 and 48 hours Negative control: 0/15 and 1/15 at 24 and 48 hours. Positive control not included.	Positive	Bomhard et al (1980) (ref. CAR Doc. III-A Section A6.1.5)
Guinea Pig Male Pirbright DRAIZE Test, 15 test and 15 control No guideline, Not to GLP	Induction: A series of intradermal injections with 0.1 % aqueous dichlofluanid Challenge: Single intradermal injection of 0.1% aq dichlofluanid	Test: Erythema 5/15 grade 3; 10/15 grade 4. Oedema measurement 1.1 cm Control: Erythema 15/15 grade 1 Oedema measurement 0.43 cm	Positive; The study authors concluded dichlofluanid is sensitising	Bomhard,E; Loeser, E. (1980a) (ref. CAR Doc. II-A Section 3.4.1)
Guinea pig (female Pirbright) 28 animals /induction concentration. Each group	Induction: 20 dermal applications of 1%, 3%, 10% or 30% aqueous dichlofluanid. Challenge Induction groups receiving the same induction	1st challenge At all challenge concentrations, mild erythema (grade 1) observed in the majority of animals receiving induction concentrations of	Positive; The study authors concluded dichlofluanid is sensitising	Bomhard,E; Loeser, E. (1980b) (ref. CAR Doc. II-A Section 3.4.1)

receiving the same induction concentration was then divided into 4 groups of 7 for challenge. KLECAK Open Epicutaneous Test Not guideline Not GLP	concentration were divided into 4 groups of 7 and received 3%, 10%, 30% or 100% dichlofluanid respectively.	>3% (incidence not provided). 2nd and 3rd challenges At all challenge concentrations, positive skin reactions (grade 1) were observed in animals receiving an induction concentrations of 1%. Controls Positive skin reaction in 1 animal after 2nd challenge only. No further information was provided.		

4.6.1.1 Non-human information

4.6.1.2 Human information

Limited information is available on skin sensitisation in humans. In a patch test in 11 workers occupationally exposed to dichlofluanid, the subjects were challenged with aqueous suspensions of dichlofluanid at concentrations of up to 0.2%. No adverse skin reactions that could be clearly attributed to dichlofluanid were reported (Machemer, 1987). It should be noted that there is no evidence that aqueous dichlofluanid can cross the skin and the doses used in the study were very low.

Five brief routine health surveillance reports have been conducted between 1982 and 2003 for a few individual workers (ranging from 15-75 in the individual reports) involved in dichlofluanid manufacture. These found no evidence of adverse skin reactions that could be directly attributed to dichlofluanid. (Faul 1982, Faul 1989, Kehrig & Steffens 2003a, Kehrig and Steffens 2003b and Ochs & Heyne 2004).

(ref. CAR Doc. III-A Section A6.12 (1-6)

4.6.1.3 Summary and discussion of skin sensitisation

The skin sensitisation potential of dichlofluanid has been investigated in a study that is considered to be comparable to a standard guinea pig maximisation test (GPMT) and in two non-standard guinea pig studies. Dichlofluanid gave clear positive results in the GPMT with a response in 87% of animals at challenge concentrations of 12.5% and 25% following intradermal induction at 10%. Positive skin reactions were also observed in the non-standard studies, although it is difficult to further interpret the results of these studies in line with the CLP criteria. Some human data are available from workers potentially exposed to dichloflunaid, in which no adverse skin reactions directly attributed to dichlofluanid were observed. However, these studies are of limited value due

to the small number of subjects, lack of information on exposure, low concentrations used and questions about the dermal absorbtion of aqueous dichlofluanid.

4.6.1.4 Comparison with criteria

A substance is classified in Category 1A where there is a ≥ 30% response in animals receiving an intradermal induction dose of ≤ 0.1% or ≥ 60% response at > 0.1% to ≤ 1% intradermal induction does in a GPMT.

Where there is no information to suggest that classification in Category 1A should be considered, a substance is classified in Category 1B where there is a ≥ 30% to <60% response in animals receiving an intradermal induction dose of > 0.1% ≤ 1% or a ≥ 30% response at > 1% intradermal induction dose in a GPMT,

In a study that was considered to be comparable to a standard GPMT, a positive response was observed in 87% of animals receiving an intradermal induction dose of 10%, which meets the criteria for classification in Category 1B. However, it should be noted that a relatively high response (87%) was observed with an induction dose of 10% and no data are available from standard studies at lower induction concentrations. As such it could be that classification in Category 1A can not be excluded and a simple argument for retaining Category 1 could also be made (refer to the guidance document on the application of the CLP criteria section 3.4.2.2.3.2).

4.6.1.5 Conclusions on classification and labelling

CLP: Skin Sensitisation 1B; H317 – May cause an allergic skin reaction

4.6.2 Respiratory sensitisation

Not considered in this report

RAC evaluation of skin sensitisation

Summary of the Dossier submitter's proposal

Skin sensitisation
Dichlofluanid has an existing entry as Skin Sens. 1; H317, and a sub-categorisation as Skin Sens. 1B was proposed by the DS based on a positive response in a non-GLP guinea pig maximisation test (GPMT) study (Bomhard *et al*., 1980) conducted prior to implementation of the relevant guideline (OECD TG 406, GPMT). The DS considered the study as being comparable to the OECD TG 406 method. Since a positive response was obtained in 87% of animals at challenge concentrations of 12.5% or 25% following intradermal induction at 10%, the DS considered that the result met the criteria for classification as Skin Sens. 1B; H317 under CLP. However, since no standard GPMT study data using lower induction concentrations was available, the DS noted that classification in sub-category 1A could not be excluded as indicated in the guidance on the application of CLP criteria, section 3.4.2.2.3.2.

In addition to the study mentioned above, the CLH report also contained information from two non-standard (non-guideline, non-GLP) studies (Bomhard & Loeser, 1980 a & b). The DS concluded that positive skin reactions were observed in these studies but that it was difficult to further interpret these studies in line with the CLP criteria.

Limited human data were available in workers potentially exposed to the substance. The DS referred to a report from a patch test in 11 workers (using a patch test concentration

of up to 0.2% dichlofluanid) occupationally exposed to dichlofluanid. No skin reactions that could be clearly attributed to dichlofluanid were reported. The DS noted however that there was no evidence that aquous dichlofluanid could cross the skin and that the doses used were very low. The DS also referred to five brief routine health surveillance reports conducted between 1982 and 2003, for a few workers (15-75 in the individual reports) involved in the manufacture of dichlofluanid. According to the DS, these studies found no evidence of adverse skin reactions that could be directly attributed to dichlofluanid.

Comments received during public consultation

Four MSCAs commented on this endpoint. One MS supported the proposed classification (but without a justification) whereas three MS argued that the result from the GPMT study (which was the basis for the proposal from the DS) was insufficient for the proposed subcategorisation (Skin Sens. 1B) of dichlofluanid. In addition, one of these MSCAs commented that no positive control was used and that the use of Freund's complete adjuvant was not documented at all. This MSCA also remarked that the induction dose should be the highest dose causing mild-to moderate skin irritation and questioned whether the dose used for induction (10%) caused even mild skin irritation since the CLH report stated that the 25% concentration was determined to be the maximum non-irritant concentration.

In their response the DS agreed with the argumentation put forward by the MSCAs and indicated that a rationale for also retaining Skin Sens. 1 had been provided in the CLH report. The DS had no specific response to the comments on the lack of confirmation that the used induction dose fulfilled the criteria of OECD TG 406, except to state that the method was considered to be comparable to OECD TG 406.

One MSCA also provided references (inserted under the subheading "Additional references") to case reports that claimed that dichlofluanid caused skin sensitisation in humans. This MSCA indicated, however, that the data provided in these reports were not sufficient for sub-categorisation. Another MSCA pointed out that the result from the Draize test (Bomhard & Loeser, 1980a) gives an indication that dichlofluanid could be a Skin Sens. 1A sensitiser since intradermal injections of 0.1% sensitised 100% of the animals. There was no specific respose to these latter comments by the DS.

Assessment and comparison with the classification criteria

The result from a pilot study was not reported in the CLH report but was briefly reported in the CAR (Section A6.1.5). The test substance (100, 50, 25 or 12.5% dichlofluanid in Freunds complete Adjuvant (50% solution in water)) was applied to various sites on the flanks of four Guinea pigs. 24 hours after topical application under occlusive dressing, the 12.5% and 25% concentrations were not skin irritants. At the 50 and 100% concentrations slight to moderate skin irritations were reported. The maximum non-irritant concentration was 25%.

Main study

15 Male Pirbright Guinea pigs (15/group) were used to evaluate the skin sensitising properties of dichlofluanid (Bomhard *et al*., 1980) in a GPMT method considered by the DS to be comparable to the OECD TG 406.

Detailed information on induction/challange/scoring schedule and on results from the skin sensitisation test is given in the tables below (data from the CAR).

Induction	Concentration of dichlofluanid (%)	Day of treatment	Application	Post-challenge observations[1] (15 animals/ group)	
				24 hr	48 hr

Induction 1	10	0	Intradermal	-	-
Induction 2	5	7	Topical	-	-
Challenge 1	12.5[2]	21	Topical	0/4 1/9 2/2	0/2 1/7 2/6
Challenge 2	25	21	Topical	0/2 1/6 2/7	0/2 1/4 2/9

1) First number = grade of reaction (0= no reaction, 1= in places slight redness, 2 = moderate to diffuse redness, 3= intensive redness and swelling); second number number of animals with allergic reactions. RAC notes that the scoring system corresponds to that in OECD TG 406 for GPMT. 2) In addition to the maximum non-irritating concentration (25%) a lower test concentration was used but justification for including an additional dose level as well as for choosing this specific dose level was not given in the CLH report.

	Number of animals with signs of allergic reactions (i.e. at least score 1)/number of animals in group	
	Control	Test group
		12.5% dichlofluanid solution
Scored after 24 hr	1/15	11/15
Scored after 48 hr	0/15	13/15
		25% dichlofluanid solution
Scored after 24 hr	0/15	13/15
Scored after 48 hr	1/15	13/15

The intention of the design of a GPMT performed according to OECD TG 406 is to maximize the ability to detect a sensitisation hazard, i.e. the test should be conducted at highest induction dose causing mild–to-moderate skin irritation. In the study by Bomhard et al. (1980) the topical induction dose used (5%) is below the dose identified in the pilot study as the highest non-irritating dose (i.e. 25%). RAC notes that with these deviations from the OECD TG 406 study design, it is likely that the present result (positive response [score ≥ 1] in 13/15 animals) underestimates the sensitising properties of dichlofluanid.

Positive skin reactions were also reported in two non-standard (non-guidline, non-GLP) studies (a Draize test, Bomhard & Loeser, 1980a, and a Klecak open epicutaneous test, Bomhard & Loeser 1980b). RAC concludes that overall these studies support the result of the GPMT study. However, the data cannot be used for subcategorisation since the use of these non-standard tests for subcategorisation is not acknowledged by the CLP guidance (see section 3.4.2.2.3.2.).

The worker surveillance reports provided by the DS (indicating no skin sensitising properties) are contradicted by two positive case reports in the open literature (provided during the PC). However, RAC concludes that the available information provided in the CLH report and in the case studies are not sufficient to be used for subcategorisation.

RAC notes that with the design used in the GPMT study by Bomhard et al. (1980), the inherent skin sensitising properties of dichlofluanid are probably somewhat underestimated. However, the results of the study, i.e. positive response (score ≥ 1) in 13/15 animals at an intradermal induction dose of 10%, fulfil the criteria for identifying a substance with a significant skin sensitising effect (Category 1, if redness (score>1) in ≥ 30% of the test animals, see Table 3.4.2-e in the CLP guidance). RAC concludes that there is no study available that investigates the sensitising properties of dichlofluanid at intradermal induction concentrations needed for subcategorisation (i.e. ≤ 1%). In the absence of such data the CLP Regulation specifies that the skin sensitising substance shall be classified in Category 1 without a subcategory (Annex I: 3.4.2.2.1.1). Thus the RAC is of the opinion that the current harmonised classification Skin Sens. 1; H317 should be retained.

4.7 Repeated dose toxicity

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

Not considered in this report.

4.9 Germ cell mutagenicity (Mutagenicity)

Not considered in this report.

4.10 Carcinogenicity

Not considered in this report.

4.11 Toxicity for reproduction

Not considered in this report

4.12 Other effects

Not considered in this report

5 ENVIRONMENTAL HAZARD ASSESSMENT

5.1 Degradation

Not considered in this report.

5.2 Environmental distribution

Not considered in this report.

5.3 Aquatic Bioaccumulation

Not considered in this report.

5.4 Aquatic toxicity

Not considered in this report.

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

Not considered in this report.

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

Not considered in this report.

6 OTHER INFORMATION

NONE

7. REFERENCES

All references should be viewed as references to the Competent Authority Report – Doc IIIA – Study Summaries for Dichlofluanid (for use in wood preservatives – PT8) - September 2005 and Document IIA – Effects Assessment for the Active Substance – Dichlofluanid (PT8) – finalised January 2007 as prepared by the UK for the review of the active substance under Directive 98/8/EC.

Full references, as reproduced below, are also provided in the document - Directive 98/8/EC concerning the placing of biocidal products on the market - *Inclusion of active substances in Annex I to Directive 98/8/EC* - Assessment Report –DICHLOFLUANID - PT8 - November 2006

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8. ANNEXES

None