Committee for Risk Assessment

RAC

Opinion

proposing harmonised classification and labelling
at EU level of

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

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

Adopted

3 June 2015

CLH-O-0000001412-86-57/F

Annankatu 18, P.O. Box 400, FI-00121 Helsinki, Finland | Tel. +358 9 686180 | Fax +358 9 68618210 | echa.europa.eu

3 June 2015
CLH-O-0000001412-86-57/F

OPINION OF THE COMMITTEE FOR RISK ASSESSMENT ON A DOSSIER PROPOSING HARMONISED CLASSIFICATION AND LABELLING AT EU LEVEL

In accordance with Article 37 (4) of (EC) No 1272/2008, the Classification, Labelling and Packaging (CLP) Regulation, the Committee for Risk Assessment (RAC) has adopted an opinion on the proposal for harmonized classification and labelling (CLH) of:

Chemical name: **dichlofluanid (ISO); N-[(Dichlorofluoromethyl)thio]-N',N'-dimethyl-N-phenylsulfamide**

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

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

The proposal was submitted by the **United Kingdom** and received by RAC on **25/09/2014**.

In this opinion, all classifications are given in the form of CLP hazard classes and/or categories, the majority of which are consistent with the Globally Harmonized System (GHS).

PROCESS FOR ADOPTION OF THE OPINION

United Kingdom has submitted a CLH dossier containing a proposal together with the justification and background information documented in a CLH report. The CLH report was made publicly available in accordance with the requirements of the CLP Regulation at ***http://echa.europa.eu/harmonised-classification-and-labelling-consultations/*** on **28/10/2014**. Concerned parties and Member State Competent Authorities (MSCA) were invited to submit comments and contributions by **12/12/2014**.

ADOPTION OF THE OPINION OF THE RAC

Rapporteur, appointed by RAC: **Anne-Lee Gustafson**

The opinion takes into account the comments provided by MSCAs and concerned parties in accordance with Article 37(4) of the CLP Regulation. The RAC opinion on the proposed harmonized classification and labelling was reached on **3 June 2015** and the comments received are compiled in Annex 2.

The RAC opinion was adopted by **consensus**.

Existing Annex VI entry (CLP, Table 3.1)

OPINION OF THE RAC

The RAC adopted the opinion on Dichlofluanid that should be classified and labelled as follows:

Classification and labelling in accordance with the CLP Regulation (Regulation (EC) 1272/2008)

	Index No	International Chemical Identification	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors
					Hazard Class and Category Code(s)	Hazard statement Code(s)	Pictogram, Signal Word Code(s)	Hazard state-ment Code(s)	Suppl. Hazard statement Code(s)	
Current Annex VI entry	616-006-00-7	dichlofluanid (ISO); *N*-dichlorofluoromethylthio-*N*',*N*'-dimethyl-*N*-phenylsulfamide	214-118-7	1085-98-9	Acute Tox. 4 * Eye Irrit. 2 Skin Sens. 1 Aquatic Acute 1	H332 H319 H317 H400	GHS07 GHS09 Wng	H332 H319 H317 H400	-	M=10
Dossier submitters proposal	616-006-00-7	dichlofluanid (ISO); *N*-[(Dichlorofluoromethyl)thio]-*N*',*N*'-dimethyl-*N*-phenylsulfamide	214-118-7	1085-98-9	**Modify** Acute Tox. 4 Skin Sens. 1B	**Retain** H332 H317	**Retain** GHS07 Wng	**Retain** H332 H317	**-**	**-**
RAC opinion	616-006-00-7	dichlofluanid (ISO); *N*-[(Dichlorofluoromethyl)thio]-*N*',*N*'-dimethyl-*N*-phenylsulfamide	214-118-7	1085-98-9	**Retain** Skin Sens. 1 **Modify** Acute Tox. 4	**Retain** H317 H332	**Retain** GHS07 Wng	**Retain** H332 H317	**-**	**-**
Resulting Annex VI entry if agreed by COM	616-006-00-7	dichlofluanid (ISO); *N*-[(Dichlorofluoromethyl)thio]-*N*',*N*'-dimethyl-*N*-phenylsulfamide	214-118-7	1085-98-9	Acute Tox. 4 Eye Irrit. 2 Skin Sens. 1 Aquatic Acute 1	H332 H319 H317 H400	GHS07 GHS09 Wng	H332 H319 H317 H400	-	M=10

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.

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>
</table>

<table>
<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 were exposed at this dose level.</td>
<td>Shiotsuka, 1986 (CAR DOC. II-A section 3.2, and CLH dossier).</td>
</tr>
</table>

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.

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 can not 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 RAC is of the opinion that the current harmonised classification Skin Sens. 1; H317 should be retained.

Additional references

Björkner, B., Bruze, M. & Gruvberger, B. (1990). Sensitization to dichlofluanide. Contact Dermatitis 23(4): 246.

ECB (European Chemicals Bureau) (1997). C&L proposal submitted by Austria. ECBI/28/96 - Add. 11.

ECB (European Chemicals Bureau) (1998). Summary record from meeting of the comission working group on C&L of dangerous substances. ECBI/27/98-Rev. 2

Hansson, C. & Wallengren, J. (1995). Allergic contact dermatitis from dichlofluanid. Contact Dermatitis 32(2): 116-117.

ANNEXES:

Annex 1 Background Document (BD) gives the detailed scientific grounds for the opinion. The BD is based on the CLH report prepared by the Dossier Submitter; the evaluation performed by RAC is contained in RAC boxes.

Annex 2 Comments received on the CLH report, response to comments provided by the Dossier Submitter and rapporteurs' comments (excl. confidential information).