Committee for Risk Assessment

RAC

Opinion

proposing harmonised classification and labelling
at Community level of

gallium arsenide

ECHA/RAC/CLH-0000000792-73-03/F

Adopted

25 May 2010

Annankatu 18 | P.O. Box 400 | 00121 Helsinki | Finland
www.echa.eu | Tel.: + 358 9 68.61.80

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

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

Substance Name: ***gallium arsenide***

EC Number: ***215-114-8***

CAS Number: ***1303-00-0***

The proposal was submitted by ***France***
and received by ECHA on 2 June 2009

PROCESS FOR ADOPTION OF THE OPINION

France 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/consultations/harmonised_cl/harmon_cl_prev_cons_en.asp on 12 June 2009. Parties concerned and MSCAs were invited to submit comments and contributions by 27 July 2009.

ADOPTION OF THE OPINION OF RAC

Rapporteur, appointed by RAC: Marianne van der Hagen
Co-rapporteur, appointed by RAC: Normunds Kadikis

The opinion takes into account the comments of MSCAs and parties concerned provided in accordance with Article 37 (4) of the CLP Regulation.

The RAC opinion on the proposed harmonised classification and labelling has been reached on **25 May 2010,** in accordance with Article 37 (4) of the CLP Regulation, giving parties concerned the opportunity to comment. Comments received are compiled in Annex 2.
The RAC Opinion was adopted by ***consensus.***

OPINION OF RAC

RAC adopted the opinion that gallium arsenide should be classified and labelled as follows[1]:

Classification & labelling in accordance with the CLP Regulation:

Classification[2]: Carc. 1A - H350
Repr. 1B - H360F[3]
STOT RE 1 - H372,

Specific concentration limits: None
M-factors: None
Notes: None

Labelling: GHS08, **GHS09; Dgr; H350** May cause cancer, **H360F** May damage fertility, **H372** Causes damage to the respiratory and haematopoietic system and testes through prolonged or repeated exposure.

Classification & labelling in accordance with Directive 67/548/EEC:

Classification[3]: Carc. Cat. 1; R45
Repro. Cat. 2; R60
T; R48/23

Specific concentration limits: None
Notes: Note E

Labelling: T; R45-48/23-60; S45- 53-60

SCIENTIFIC GROUNDS FOR THE OPINION

The opinion relates to those hazard classes that have been reviewed in the proposal for harmonised classification and labelling as submitted by France.

[1] Note that not all hazard classes have been evaluated.
[2] This section should reflect all relevant entries for the C&L: classification, R-phrases, S-phrases, concentrations limits, nota.
[3] It is the view of RAC that hazard statement H360F is the most appropriate, given the available toxicological profile of gallium arsenide, but RAC recognised that H360 could be applied if the available criteria are applied strictly.

Carcinogenicity

None of the epidemiological studies of cancer in the semiconductor industry were informative with regard to GaAs. The dossier submitter has presented robust 105 weeks inhalation studies in rats and mice (NTP, 2000) and a 15 weeks intratracheal instillation study in hamster (Ohyama et al., 1988). Gallium arsenide was carcinogenic only in female rats after inhalation. This was observed as alveolar/bronchiolar adenoma or carcinoma.

The dossier submitter had proposed that gallium arsenide was to be classified as Carc Cat 3 (Directive 67/548/EEC) based on the animal studies. In the public consultation a wish to classify gallium arsenide in agreement to IARC (group 1), proposing Carc Cat 1 instead of Carc Cat 3 (Directive 67/548/EEC) was raised. RAC agreed that an evaluation of carcinogenic effects of gallium arsenide solely based on results from animal studies is insufficient, especially since animals are less sensitive than humans to the carcinogenic effect of arsenic. It was decided to include information from human studies (results of epidemiological studies of carcinogenicity from exposure to arsenic compounds in copper smelters and from drinking water) on arsenic compounds listed as carcinogens in category 1A in CLP Annex VI and apply read-across to GaAs. A read-across approach is further supported by toxicokinetic data describing the formation of similar arsenic metabolites following GaAs exposure as those formed following exposure to classified arsenic compounds. It was agreed that the carcinogenicity of arsenic and arsenic compounds is of relevance to gallium arsenide and must be taken into account.

In conclusion, there is no human data for gallium arsenide per se, but substantial documentation of carcinogenicity in humans of arsenic and arsenic compounds is available, as evaluated by IARC and briefly discussed in the BD. Gallium arsenide is also carcinogenic in female rats after inhalation and would fulfil the criteria for Carc. 2 (CLP), if assessed overlooking carcinogenicity from arsenic and arsenic compounds in humans.

By applying weight of evidence and based on read-across from other arsenic compounds listed as carcinogen category 1A in Annex VI of CLP and with reference to the IARC grouping of Arsenic and arsenic compounds as well as gallium arsenide in group 1 (“carcinogenic to humans”), RAC recommends to classify gallium arsenide as a Carc. 1A – H350 according to CLP.

Germ Cell Mutagenicity

Three genotoxicity studies on gallium arsenide were summarised as supportive information but no classification was proposed. No comments questioning the conclusions on this hazard class were received during the public consultation. Gallium arsenide did not induce mutations *in vitro* in the Ames test or *in vitro* or *in vivo* in the micronucleus test.

As gallium arsenide did not induce mutations in two guideline tests and one non-guideline test it should not be classified as mutagenic to germ cells. RAC is aware of the vast publicly available information on mutagenicity of other arsenic compounds, but this was not presented by the dossier submitter and reviewed by RAC.

Reproductive Toxicity

No multi-generation studies investigating potential effects of gallium arsenide on fertility are available but repeated dose toxicity studies have reported data on reproductive organs. The dossier submitter presented two 8 weeks tracheal instillation studies in rats and hamsters, and two 14 weeks inhalation studies in rats and mice. Several testicular concentration-related modifications, like decreased testis weights, epididymis weights, spermatids counts and spermatozoa motility, have been observed in the whole-body inhalation of gallium arsenide in rats and mice. Similar testicular effects have also been reported in rats and hamster following intratracheal instillations. Histopathologic examination of the testis in rat and hamsters revealed a spermiation failure as spermatid retention was observed at post-spermiation stages for both species.

Comments received agreed to the proposed classification based on the effects in testis and hence the potential reduced male fertility at low doses in animals of two species, provided that the effects found in testis were primary and not secondary to other toxic effects. The effect on testis is considered to be primary, as it is seen as reduced epididymal spermatozoal concentration in mice exposed to 10 mg/m^3 without clinically significant reduction in hemoglobin concentration or reduced body weight.

Clear evidence of effect on fertility at low doses in the absence of other toxic effects warrants classification for reproductive toxicity. Also at higher doses the effects were considered to be primary and not resulting from other toxic effects. Effects on development of the offspring and effects on or via lactation were not evaluated. Due to clear evidence of testicular toxicity in two species the original proposal to classify gallium arsenide as Repr. 1B - H360F (CLP) is supported. This is also supported by the potential of gallium to accumulate in rat testis following inhalation exposure (see toxicokinetics section in the Background Document).

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

In the respiratory tract non-neoplastic effects (e.g. epithelial hyperplasia in larynx and lungs) were observed in two subacute and two subchronic studies in rats and mice. Microcytic anemia was observed in a dose related manner in rats and mice. Microcytic anemia would be consistent with an iron deficiency or iron deficiency-like disorders in which iron is unavailable for the production of heme. For rats, this effect was more pronounced in males than in females. However, the reduction in hemoglobin concentration was considered to be of possible clinical relevance only in male rats (13 % decrease) in the highest dose group, and not in male and female mice. Testis effects were observed as described in the section Reproductive Toxicity above.

In the public consultation as well as in RAC there was a wish for more information on dose-response relationship. Clarity of biological significance of the observed effects, in particular microcytic anemia, was described as missing from the proposal. This was adjusted in the BD.

In rats and mice, lung lesions (non-neoplastic hyperplasia, metaplasia, granuloma, etc minimal at 1 mg/m^3 sufficiently severe at 10 mg/m^3), non-neoplastic lesions in the larynx of male rats and hyperplasia of the tracheobronchial lymph node in mice warrant a classification as T, R48/23. Converting the concentrations to mg/l (10 mg/m^3 :1000 corresponding to 0.01 mg/litre) and applying the guidance value ($C \leq 0.02$) in the table 3.9.2 for particulates in the

CLP guidance this corresponds to classification as STOT-RE 1 – H372: Causes damage to the respiratory and haematopoietic system and testes through prolonged or repeated exposure.

Acute toxicity (and Specific target organ toxicity after single exposure, STOT-SE)

A single administration of gallium arsenide by intratracheal instillation or via the oral route caused delayed specific haematological and immunological toxicity in a reversible manner (when further time point evaluated) but no mortality in rats or mice.

Nobody questioned the conclusion of not classifying gallium arsenide as acute toxic. But in the public consultation it was claimed that there was insufficient detail concerning the magnitude of effects and questioned if the observed toxicity fulfilled classification as STOT-SE. According to the dossier submitter this was however not the case as the effects observed were considered to be adaptative responses of minimal toxicological importance. Both in the public consultation and in RAC the group entry for arsenic compounds in CLP annex VI was raised. In this group entry "arsenic compounds, with the exception of those specified elsewhere in this Annex" is classified as acute toxic category 3.

Due to the fact that a single administration of gallium arsenide by intratracheal instillation or oral route caused no mortality or consistent and significant adverse change in clinical biochemistry, haematology, or urinalysis, neither a specific acute toxicity classification nor a STOT-SE classification is warranted. RAC supports the original proposal not to apply the group entry for arsenic compounds regarding acute toxicity (R23/25, Directive 67/548/EEC; H301, H331, CLP) for GaAs.

Environmental hazard assessment (Aquatic toxicity)

No information on environmental hazards was evaluated in the dossier. However, both in the public consultation and in RAC, the group entry for arsenic compounds in CLP annex VI (Index no. 033-002-00-5) was raised. In this group entry "arsenic compounds, with the exception of those specified elsewhere in this Annex" is classified with regard to aquatic toxicity (acute and chronic).

As no substance specific information is presented, RAC has not evaluated this endpoint and do not propose to carry over the environmental classification from 29th ATP to Directive 67/548/EEC on "arsenic compounds, with the exception of those specified elsewhere in this Annex" (Aquatic acute 1 – H400, Aquatic chronic 1, - H410). However it is understood that industry is conducting relevant studies for the purposes of REACH registration (Eurometaux, pers. Comm.., 2010).

Additional information

RAC raised the need for applying note E to the future CLP entry in annex VI. Note E: "Substances with specific effects on human health (see Chapter 4 of Annex VI to Directive 67/548/EEC) that are classified as carcinogenic, mutagenic and/or toxic for reproduction in categories 1 or 2 are ascribed Note E if they are also classified as very toxic (T+), toxic (T) or harmful (Xn). For these substances, the risk phrases R20, R21, R22, R23, R24, R25, R26, R27, R28, R39, R68 (harmful), R48 and R65 and all combinations of these risk phrases shall be preceded by the word 'Also'."

The Background Document, attached as Annex 1, gives the detailed scientific grounds for the Opinion.

ANNEXES:

Annex 1	Background Document (BD)[4]
Annex 2	Comments received on the CLH report, response to comments provided by the dossier submitter and rapporteurs'comments (excl. confidential information)

[4] The Background Document (BD) supporting the opinion contains scientific justifications for the CLH proposal.