Committee for Risk Assessment

RAC

Annex 5

Response to comments document (RCOM)
to the Opinion

on gallium arsenide in relation to toxicity to reproduction

EC Number: 215-114-8
CAS Number:1303-00-0

ECHA/RAC/A77-O-0000001412-86-11/A5

Adopted

23 July 2013

ANNEX 5 - COMMENTS AND RESPONSE TO COMMENTS ON RAC'S DRAFT OPINION ON THE TOXICITY TO REPRODUCTION OF GALLIUM ARSENIDE

COMMENTS AND RESPONSE TO COMMENTS ON RAC'S DRAFT OPINION ON THE TOXICITY TO REPRODUCTION OF GALLIUM ARSENIDE

Comments provided during public consultation are made available in this table as submitted by the webform. ECHA accepts no responsibility or liability for the content of this table.

Substance name: Gallium arsenide
EC number: 215-114-8
CAS number: 1303-00-0

TOXICITY TO REPRODUCTION (effects on sexual function and fertility)

Date	Country	Organisation	Type of Organisation	Comment number
19.06.2013	Germany	HSE Dr. Hofmann GmbH	Academic institution (Consulting company)	1

Comment received

Dear Mr Dancert,
please refer to a separate pdf-document send via email classification@echa.europa.eu and the document is also send via mail. The following is copied from this letter, however please refer to the pdf or the original document only. Thank you very much.
The letter is also send in copy to
BMWi Berlin
Herrn Dr. Philipp Rösler
Scharnhorststr. 34-37
10115 Berlin
Postanschrift: 11019 Berlin
and
European Commission
Enterprise and Industry DG
Director General
Daniel Calleja Crespo
Communication and Information Unit R4
BREY 13/092
B - 1049 Brussels (Belgium).

Invalid RAC Opinion on Gallium Arsenide in Relation to Toxicity to Reproduction (revised draft of May 29, 2013)

Dear Mr. Dancert,

according to your request persuant to Article 77(3)(c) of REACH on 17.04.2012 the committee for risk assessment (RAC) should give scientific advice on Gallium Arsenide in relation to toxicity to reproduction.

The proposed opinion on the reproduction toxicity of gallium arsenide (GaAs) does not meet fundamental demands for a scientific evaluation as requested by REACH and CLP regulation and their ECHA guidance documents and is therefore invalid.

According to the actual scientific standards and also according to REACH and CLP regulation the reliability of a publication/study has to be checked. This has to be the first step of a scientific evaluation.
There is a fundamental difference whether a study was performed according to a validated

and approved study protocol and with an accepted quality assurance system (carried out according to GLP and according to the test methods1 referred to in Article 13(3), REACH) or whether the data come from an experimental study design without validation and with no specific quality assurance system. The REACH and CLP regulation and the respective ECHA guidance documents ask for every single publication and study to be evaluated with respect to its reliability. From the REACH and CLP regulation it is requested to use data of adequate reliability and quality for evaluation and subsequent classification.

The actual RAC opinion does not give any hint that such an evaluation of the cited studies has been performed in sufficient detail. In contrast, data from studies with full reliability were inextricably mixed with data from studies with resticted reliability or even with data from invalid/ not reliable and not assignable studies. With such a procedure a reliable scientific evaluation cannot be achieved.

The opinion and especially the data used in the opinion have to be reevaluated in detail with respect to their reliability according to the legal requirements and recommendations set out in the respective REACH and CLP guidance documents provided for both industry and authorites.

It is quite astonishing that a scientific committee under REACH/ CLP dares to set such a formally incorrect opinion for public comments. Nevertheless one has to keep in mind that with this questionable procedure a future industry with its jobs is set at risk without sufficient evidence.

For details please consider the specific comments in the annex below.

Best regards

Wolfram Hofmann
Dr. med., Dipl. Chem., Facharzt für Pharmakologie und Toxikologie

Thomas Gildemeister
Dr. rer. nat., Dipl. Biol.

Annex

some detailed aspects on the draft RAC opinion (May 29, 2013)

1. The drafted opinion does not give any hint that reliability of the cited studies has been evaluated. This is the first key step within the scientific evaluation, as laid out as follows in the REACH and CLP regulation and respective ECHA guidance documents:

Any new toxicological studies have to be conducted according to GLP (Article 13 (4) REACH, Article 8 (4) CLP) and according to the test methods2 referred to in Article 13(3), REACH and Article 8 (4) CLP)
CLP-regulation requests to use data of adequate reliability and quality for the evaluation and subsequent classification of a substance: "... adequate reliability and quality of data ..." is requested for animal and human data in Article 7 paragraph 1 of CLP-regulation.
If data from studies other than performed under GLP and according the to test methods referred to in Article 13(3) REACH is used then the study must be adequate and reliable with regard to covering key parameters as well as "... adequate and reliable documentation of the study is provided." The "adequacy for the purpose of classification and labelling

and/or risk assessment" must be given (only an selection is provided, see Annex XI of REACH).
The same applies to key studies that are used within the concept of „Grouping of substances and read-across approach". The quality assessment of a study/ publication should follow the criteria laid out in Klimisch et al. (1997) (see guidance for REACH and CLP e.g. on „data sharing" and „on information requirements and chemical safety assessment"). Each study used for substance evaluation must be reviewed even if the information is from assessments carried out under other international and national programmes. The reliability has to be assessed (see Guidance on the preparation of dossiers for harmonised classification and labelling (ECHA, 05/2010)).

For the cited references of the draft RAC opinion of May 29 2013 and RAC opinion of 2010 regarding studies with GaAs the reliability is given in the disseminated (robust) study summaries submitted within the REACH registration dossier by the respective registrants. These data should have been available to the RAC and it seems that these publicly available summaries were completely ignored. A summary of the reliability (copied from the disseminated information at ECHA's web page) is given below for some of the cited studies of RAC. For further information and complete (robust) study summaries on all the cited references and also on proposed classification and labelling by the Registrants we request RAC to look at http://echa.europa.eu/information-on-chemicals.

Some of the references cited in draft RAC opinion of May 29 2013 and their reliability:

Tanaka et al (2000): not reliable (Klimisch 3)
Rationale for reliability incl. deficiencies (see published / disseminated information at http://echa.europa.eu/information-on-chemicals): No standard study design. Incomplete report of results, no data on animal number, no single values reported.

Cross references: Omura 1996, Hirata 1997
In a first series of publications only data on reproduction toxicity of the male animals were published (Omura 1996, Hirata 1997).

Tanaka et al. (2000): The missing data on systemic toxicity were published, showing slight to severe inflammatory responses in the lung and slight to mild lesions in the convoluted tubules of the kidney. These results might indicate that the testicular changes are a consequence of a systemic impairment of the animals by the inflammatory reactions to GaAs in the lung.

Nowadays the incomplete report of study results would be a severe deviation from GLP.

Conclusion:
Because the study is not reliable the study is disregarded and not helpful in assessing the effects of Gallium arsenide.

Omura et al. (1996a), Rat: not reliable (Klimisch 3)
Rationale for reliability incl. deficiencies (see published / disseminated information at http://echa.europa.eu/information-on-chemicals): No standard study protocol used, methods not validated. No instillation volume given. All in all relevant data are missing. The documentation is insufficient for assessment. ITherefore, the study is not reliable.
GaAs was mechanically pulverized to a fine powder – not representing the marketed substance, which is to be evaluated rather than a mechanically destroyed material.
- Impurities (identity and concentrations): 0.02% (wt%) of zirconium and a trace amount of yttrium (comment: this is in contrast to the reprorted purity, probably contaminated during

pulverisation process)

In a previous publication (Omura et al., j. Occup. Health 1995;37;165-166) as far as the data are comparable, exactly the same numbers are published for a group of 8 GaAs treated animals. This finding does not support the reliability of the study.
Although the authors stated that an intratracheal instillation of GaAs damages the lung they did not check the systemic toxicity: no clinical observations, no organ weights other than testes and epididymides, no other histopathology than with testes and epididySome of the references cited in draft RAC opinion of May 29 2013 and their reliability:

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Conclusion:
Because the study is not reliable the study is disregarded and not helpful in assessing the effects of Gallium arsenide.

Omura et al. (1996b), Hamster: not reliable (Klimisch 3)
Rationale for reliability incl. deficiencies (see published / disseminated information at http://echa.europa.eu/information-on-chemicals): No standard study protocol used, methods not validated. The documentation is insufficient for assessment therefore the study is not reliable.

- pulverisation was performed at the testing laboratory
- Analytical purity: 99.9999% (before pulverisation)
- Impurities (identity and concentrations): 0.02% (wt%) of zirconium and a trace amount of yttrium (comment: this is in contrast to the given purity, probably contaminated during pulverisation process)

concentrations of Arsenic and Gallium were determined using ICP-MS. (However, No data are given on detection limit and limit of quantification, which does not contribute to the reliability of the study).
Relevant data are missing: no check of systemic toxicity. Only one dose level examined. Although it is known that an intratracheal instillation of GaAs damages the lung the authors did not check neither the systemic toxicity nor the lung: no clinical observations, no organ weights other than testes and epididymides, no other histopathology than with testes and epididymides. It is not assignable whether the testicular changes are an effect of a specific toxicity or a consequence of a systemic impairment of the animals, which of course may also affects the testicular functions. All in all relevant data are missing.

Conclusion:
Because the study is not reliable the study is disregarded and not helpful in assessing the effects of Gallium arsenide.

2. Insufficient justification of inadequate READ across from studies with other substances (As2O3, NaAsO2 and InAs).

In the RAC draft opinion (29 May 2013) studies of Chiou et al. (2008), Li et al. (2012), Pant et al. (2001 and 2004), Omura et al. (2000) and Yamazaki et al. (2000) with the substances As2O3, NaAsO2 and InAs were described to justify potential reprotoxic effects from GaAs. A justification for this read across from apparent structural analogues is completely missing. Further, the requirement to evaluate the reliability of these studies seems to be not fulfilled based on the information in the draft RAC opinion. This procedure not to justify the read across and to perform read across even if reliable high quality data are available is in our opinion not conform with the REACH and CLP regulation and the respective ECHA guidance documents.

A read across from As2O3 and NaAsO2 is not needed because very high quality data are available to assess the reprotoxic effects of GaAs. According to our understanding of the REACH and CLP-regulation studies from apparent structural analogues shall not be used for the evaluation of a substance if adequate and reliable data are available for GaAs itself.

The NTP studies were the first reliable studies that characterise the toxic effects of GaAs particles of respirable size in a reproducible way (under GLP and according to validated standardised study protocol). These NTP studies deliver sufficient data for the evaluation of

the toxicity of Gallium arsenide particles.

3. Distinction between GaAs as manufactured in form of an Ingot as a massive form and fine dust:

Generally it should be distinguished between the massive form of GaAs and the very fine dust of respirable size that was used in the cited studies with GaAs. However the material which was used in the tests was a mechanically destroyed material of a very fine particle size not representing the manufactured or marketed material, which is to be evaluated rather than a mechanically destroyed material. GaA is manufactured as an ingot (shape of a cylinder). GaAs is marketed as a wafer, fulfilling the criteria for articles according to the definitions of REACH (Article 3 (3)) and CLP (Article 2 (9)). These forms of GaAs are considered massive forms.

GaAs in its massive form is not to be classified with respect to toxicity to reproduction. This procedure to distinguish particle sizes is common practice within the CLP classification procedure:
Examples are:
Powders of metals: e.g.
magnesium: only powder (pyrophoric) and powder or turnings are classified (see index no. 012-002-00-3 and 012-002-00-9). Magnesium in its massive form is not classified.
Aluminium: only powder is classified (see index no. 013-002-00-1013-001-00-6), Aluminium in its massive form is not classified.
Nickel: nickel powder; with particle diameter < 1 mm is additionally classified as Aquatic Chronic 3 (see index number 028-002-01-4) in comparison to its massive form
Crystalline Silicon dioxide leading to silicosis among others if inhaled as very fine dust. However the massive form, rocks can not be inhaled and are thus not to be classified.

4. Additionally RAC seemed to have committed one of the "deadly sins of toxicology" (Zbinden, 1987: Zbinden G: Predictive value of animal studies in toxicology. Centre for Medicines Research, Woodmansterne Road, Carshalton, Surrey SM5 4DS CMR Annual Lecture;1987: ppl-12) - they described a toxic effect but underestimated its importance!

With respect to the proteinosis in the lungs after inhalative exposure to GaAs in the RAC draft opinion is noted, that "extensive lung toxicity" was observed in the fully reliable NTP-studies. However RAC modified these clear lung effects with the results of not reliable studies (which are Tanaka et al. (2000) and Omura (1996a and 1996b) and came to the conclusion that "There are signs of lung toxicity, but they are not very severe at the concentrations where signs of testis toxicity start to appear (e.g., mild alveolar proteinosis in mice and mild to moderate inflammatory changes in the lungs of hamsters)." suggesting that the lung effects are mild toxic effects.This is not true!

According to Manzzone et al., Cleveland Clinic Journal of Medicine, Volume 68, Number 12, Dezember 2001 "pulmonary alveolar proteinosis (PAP) is an uncommon disorder (with humans)... today well over 300 cases have been documented. The natural history of PAP is variable. From 54% to 75% of patients undergo at least one lavage procedure."

Although human lung proteinosis has so far no connection to chemicals it is nevertheless clear, that this is a severe illness. Therefore, the PAP Foundation declares on its homepage: "Pulmonary Alveolar Proteinosis is a life-threatening disorder that affects men, women and children."

The NTP studies are the first fully reliable studies demonstrating in a clear and reproducible way the toxic effects of GaAs particles. Until today a lot of publications and studies with questionable reliability have caused a lot of confusion with respect to the toxic effects of GaAs particles. From the NTP studies it is clear that fine GaAs particles cause a severe toxic reaction in the lungs after inhalation exposure at relatively low concentrations. This leads to a lot of toxic consequences in the body: reduced uptake of oxygen into the body, reduced elimination of CO2 from the blood, increased arteriovenous shunts in the lung and a number of further patho-physiological reactions following in the lung and in the body. RAC did not evaluate the systemic toxicity of GaAs in an adequate manner.

For GaAs dust of respirable size RAC should set up an evaluation according to the actual scientific standards and according to the legal regulations, especially according to REACH and CLP and the respective guidance. The actual proposal does not meet at all these self-evident requirements and is therefore not an acceptable basis for a scientific/toxicological discussion.

RAC's response

1. The respective studies/robust study summaries which form the basis for the RAC opinion were provided either in the original CLH report submitted by France in June 2009, during the public consultation on carcinogenicity of gallium arsenide held from 11 March to 27 April 2011, or in the Additional Information Report (AIR) submitted by industry in December 2011. All these documents are annexed to the RAC opinion, were subject to consultation and have been properly considered by the Committee.

The overall assessment of the reproductive and other toxicity, such as lung toxicity, of GaAs is based on a weight of evidence assessment of "*all available information*" as required under Article 9(3) of the CLP Regulation. Sections 1.1.1 and 3.7.2.3.1 of Annex I provide explicit instructions in this regard and have been rigorously followed by the Committee in its opinion. It should be underlined that although "*both positive and negative results are assembled together into the weight of evidence determination*", "*a single positive study performed according to good scientific principles and with statistically or biologically significant positive result may justify classification*" according to the criteria in section 3.7.2.3.1. Furthermore testicular toxicity is present in three different species, including mice and rats in the NTP-studies.

2. There is no formal read across performed between the arsenic-containing substances and GaAs. The studies are cited to show that arsenic as such can cause testicular toxicity, which is a possible alternative MoA also for arsenic released from GaAs.

3. According to CLP (Article 23(d) and 1.3.4.1 and 2, Annex I), metals in massive form, alloys, mixtures containing polymers and mixtures containing elastomers need not be labeled

> *"if they do not present a hazard to human health by inhalation, ingestion or contact with skin ….in the form in which they are placed on the market, although classified as hazardous in accordance with the criteria* " [in Annex I, CLP]. *"Instead, the supplier shall provide the information to downstream users or distributors by means of the SDS".*

In its opinion on the carcinogenicity of GaAs (1 December 2011), the RAC was of the view that the same provisions should apply to the massive form of gallium arsenide (being a semi-metal/metalloid) as to the particulate form.

In the RAC opinion on carcinogenicity (RAC opinion No. ECHA/RAC/A77-O-0000001412-86-05/F adopted on 1 December 2011) it was concluded that GaAs is bioavailable and it is underlined that also larger particles of GaAs are shown to release As under physiological conditions. In the same opinion, RAC concludes with regard to crystalline and/or amorphous

form that "*upon mechanical stress, the crystalline structure of gallium arsenide may be disrupted at the particle surface. The information provided by IND indicates that the release of As ions is low or negligible from intact single crystals (e.g. wafers) in physiological solutions. Thus the bioavailability observed in the experimental studies is likely to be related to a partial disruption of the crystalline structure at the particle surface. A similar disruption of the crystalline structure is assumed to be present at the surface of dust particles generated in the occupational setting.*"

It should be noted that according to CLP (Article 5(1), 8(6) and 9(5)) and CLP guidance (section 1.2.2), the forms or physical states of a substance in which the substance is placed on the market and in which it can be reasonably be expected to be used should be considered when data are evaluated for the purpose of classification. Humans may be exposed to particles of GaAs in e.g. occupational settings, which justifies testing of GaAs in particulate form. In general, small particles are used in inhalation studies in line with the provisions in the test guidelines (MMAD usually between 1-4 µm), to ensure that they reach the alveoli.

It is stated in the comment that it is common practice in CLP to distinguish particle sizes in classification. As indicated above, this is not the case. Furthermore, in the list of substances referred to in the comment, only "nickel" has an EU harmonised classification, and that classification is the same as for "nickel powder (particle diameter < 1 mm)" for the health hazards (although the environmental classification differ) (Annex VI of the CLP Regulation). The other substances are lacking an EU harmonised classification and are therefore subject for self-classification.

4. The RAC has evaluated all effects as objectively as possible, and we are of the opinion that the proteinosis is not underestimated. The effects on the testis, considered also in relation to other toxicity, have been carefully compared with the criteria in CLP, considering also the relevant CLP guidance.

Date	Country	Organisation	Type of Organisation	Comment number
19.06.2013	United States	General Electric	Company-Importer	2

Comment received

Comments on ECHA Committee for Risk Assessment (RAC) opinion on gallium arsenide (GaAs) in relation to toxicity to reproduction – classification as category 1B (Presumed human reproductive toxicant)

General comments on the opinion of the RAC

The RAC Opinion shows that there is uncertainty regarding the effects of GaAs on the testes of mice, rats and hamsters. However, according to the criteria for classification category 1B, set out in the Guidance on the Application of the CLP criteria for reproductive toxicity (the Guidance), "[s]uch data shall provide clear evidence of an adverse effect on sexual function and fertility or on development in the absence of other toxic effects, or if occurring together with other toxic effects the adverse effect on reproduction is considered not to be a secondary non-specific consequence of other toxic effects." The RAC Opinion does not establish that the effects seen on the reproductive organs are totally in the absence of other toxic effects or not considered a secondary non-specific consequence of lung toxicity. Indeed, according to the RAC Opinion itself, "the effects [of GsAs] are likely to cause reduced male fertility, although functional fertility has not been studied." This statement shows that there is not enough data currently to provide clear evidence of an effect on sexual function and fertility, particularly since the RAC itself has stated that the functional fertility has not been studied. Therefore, given the absence of "clear evidence" of an adverse effect in regards to both sexual function and fertility, the RAC categorization of

GaAs as a 1B reproductive toxicant is not warranted.

Furthermore, in regards to testicular toxicity, the Opinion relies on a study where a portion of the data lacks statistical significance.

This study, cited on page 2, first paragraph of the Opinion states that "studies in mice, rats and hamsters have all shown testicular toxicity…include decrease in epididymis weights". However, the study in which there was a 13% decrease in the relative weights of the epididymis between the control and test groups that was found to be significant (Omura, et. Al. J. Occup. Health, 37, 165-166, 1995) was not significant when a different statistical method was applied by the same research group (Omura, et. Al. Fundam. Appl. Toxicol. 32, 72-78, 1996). Therefore, given the lack of statistical significance related to some of the data within the study, which forms a foundation for the RAC Opinion, the effects of the study are not necessarily "clear" as initially stated.

Potential retention/accumulation of gallium and/or arsenic in the testes

• The Opinion seems to rely on a study that shows an absence of accumulation in organs besides the lungs, which does not support the distribution of these ions to contribute to the toxicity in the testes. On page 3, the opinion states that "also at higher concentrations, the effects on the testes were not considered to be the result of other toxic effects. This was supported by the potential of gallium to accumulate in the rat tests following inhalation exposure." However, there is no mention of any accumulation of arsenic in the testes. In fact, on page 4, the opinion states that for this study "the arsenic concentrations varied highly and did not seem to clearly accumulate during the exposure period". Also, in the NTP study, the concentration of gallium was only detectable at the higher doses and at the later time points in the study and was relatively low compared to the levels seen in the lungs. Furthermore, the absence of arsenic accumulation in this 2-year inhalation study argues against arsenic having a direct effect on the testes. In fact, the authors of the study stated that these relatively low levels indicated that there was no accumulation of either gallium or arsenic other than in the lungs. Since this NTP study is one of the major studies that the RAC is basing their opinion on, this lack of accumulation in other organs besides the lungs does not support the distribution of these ions to contribute to the toxicity in the testes.

Testis toxicity as a secondary non-specific consequence of other toxicity

• The RAC Opinion states that "the lungs are a more sensitive target organ, and signs of lung toxicity are noted at lower GaAs concentrations than those causing testicular toxicity." If the lung is the more sensitive tissue/organ, then that is where the initial primary toxic effects of GaAs inhalation would be seen. On page 7, the opinion states that there "are signs of lung toxicity, but they are not very severe at the concentrations where signs of testis toxicity start to appear", but since these studies did not look at hematology or blood gas concentrations, the RAC cannot completely discount this hypothesis. In fact, the RAC states that "the design of the available studies does not permit a firm conclusion on the possible relationship between lung toxicity and testicular toxicity" so there is a possibility that the testis toxicity is a secondary effect of the lung toxicity.

• On page 8, the RAC concludes that "some contribution of the lung toxicity to the testis toxicity cannot be fully excluded". With this statement the RAC acknowledges that hypoxia can affect the testicular function and even cause testicular toxicity, but that currently there is not enough data to offer a quantitative dose response relationship. From the NTP study (NTP TR492, 2000), the RAC is of the opinion that there is no evidence for hypoxemia because there was no increased vascularization of the testes tissue at the exposure levels that caused testis toxicity, but other clinical signs of hypoxemia such as decreased blood gas concentration or oxygen tension were not looked at in the study, so it is difficult to assume that there was no hypoxemia without looking at other effects. It is not speculative to hypothesize that even mild lung toxicity and decreased lung function can lead to a

hypoxic state. As the RAC stated, there is not enough data to offer a dose response relationship so just as it cannot currently be shown that the lung toxicity had an effect on the testes toxicity, it cannot also be summarily dismissed by the RAC as not having an effect on the testes either.

• On page 10, the RAC states that the effects on the testes could be caused by a direct action of As. However, in the IARC monograph on the carcinogenicity of As in drinking water (IARC monograph 84, 2004), there is absolutely no evidence of reproductive toxicity for arsenic in both human and animal studies.

All of these comments lead to the conclusion that there are some questions regarding the effects of GaAs on the testes of mice, rats and hamsters and therefore, there is not "clear evidence" that these effects seen on the reproductive organs are totally in the absence of other toxic effects or considered to not be a secondary non-specific consequence of lung toxicity. Therefore, the categorization of GaAs as a 1B reproductive toxicant is not warranted.

RAC's response

Classification for reproductive toxicity does not require data from multi-generation studies when there is convincing histopathological data from repeated dose toxicity studies showing testicular toxicity.

Regarding the MoA for the testicular effects, it is correct that RAC acknowledge that there are different possible MoAs, and that there is not sufficient evidence for any specific MoA. Besides hitherto unknown MoAs, possible MoAs include an involvement of lung toxicity and a direct effect of arsenic and/or gallium ions in the testis. The potential accumulation of arsenic in the testis is in the NTP-studies only studied at low exposure levels. Higher concentrations of arsenic in the testis at higher exposure levels is possible, and even likely. However, no MoA is proven and in the absence of data clearly showing that the testicular effect is a secondary *non-specific* consequence of other toxic effects, according to the criteria the substance should be classified.

Date	Country	Organisation	Type of Organisation	Comment number
18.06.2013	Sweden		MemberState	3

Comment received

The Swedish CA supports the draft opinion (May 29, 2013) of the committee for risk assessment on gallium arsenide in relation to toxicity to reproduction.

RAC's response

Thanks for the support.

Date	Country	Organisation	Type of Organisation	Comment number
18.06.2013	Germany	WirtschaftsVereinigung Metalle	Industry or trade association	4

Comment received

WirtschaftsVereinigung Metalle (WVM), the German Non-Ferrous Metals Association, represents the German non ferrous (NF) metals industry towards politics and economy. We support our members in regulatory, occupational health & safety affairs in order to maintain and establish measures at a very high level. In addition WVM is manager of the REACH Arsenic and Arsenic Compounds Consortium covering GaAs as well.

WVM observed closely the decision process at RAC regarding GaAs and – more specifically – on the reprotox endpoint. We as well noted that this consultation is dedicated to the draft

opinion agreed by RAC and considering the exceptional nature of the request. This is why WVM would like to address only very briefly the following aspects in the context of this consultation:

1) WVM (ad personam Martin Wieske) is part of the German subcommittee III of the committee on hazardous substance (AGS). This tripartite group is dealing with hazard risk assessment of substances and considered in 2011 already the classification of GaAs. Based on the existing data and aligned on the criteria of the CLP directive this group came after intensive discussions (deepened in a specific expert group on reprotoxicity) to the conclusion that a reprotox cat 2 is warranted. The rational was described in a summary paper and fed into the RAC process via the German Federal Ministry of Labour and Social Affairs at that time. We are astonished that this vote (cited below) is note taken into account:

Thema Reproduktionstoxizität

Nach hoher Galliumarsenid-Exposition wurden Effekte auf die männlichen Geschlechtsorgane (Hodeneffekte) beobachtet. Eine Beeinträchtigung der Fertilität wurde allerdings nicht nachgewiesen, da keine Generationen-Studie vorliegt. Es ist bekannt, dass ein Effekt im Hoden bei der Ratte erst nach stärkerer Schädigung funktionell evident wird. Die beobachteten Hoden-Effekte werden jedoch im Fall von Galliumarsenid im Vergleich zur Lungentoxizität als Hochdosiseffekte und als nicht so gravierend eingeschätzt, als dass sie alleine zur Einstufung in Kategorie 1B führen würden.

Da insgesamt nur begrenzte Daten vorliegen und unter Berücksichtigung des Effektausmaßes im Dosisbezug, der quantitativen Bioverfügbarkeit vom löslichem Arsen aus Galliumarsenid, der tierexperimentellen Daten zur Hodentoxizität löslicher Arsenverbindungen und da ein sekundärer Einfluss auf die Hodentoxizität durch die Anämie nicht ausgeschlossen werden kann wird vorgeschlagen Galliumarsenid in die Reprotox Kategorie 2 (CLP) einzustufen.

Der UAIII stimmt dem Vorschlag einer Einstufung von Galliumarsenid in Reprotox Kat. 2 (CLP) zu.

2) WVM regrets that the RAC minority position on the classification of GaAs will be only made available in a separate document after the public consultation. It should be subject of this consultation and part of the further discussion as well. The minority opinion is supported by industry and a number of independent toxicologists. In conformity with the position of the German subcommittee III of the committee on hazardous substance it is concluded that the adverse effects on male reproduction parameters have to be considered as secondary and non-specific consequence of other toxic effects. We are convinced that the submitted data give sufficiently good evidence showing that a classification as reprotoxic category 1B should not been applied.

RAC's response

The RAC has noted the AGS document, but the RAC is required to make an independent assessment of the data, and that has been done.

Date	Country	Organisation	Type of Organisation	Comment number
18.06.2013	Belgium		MemberState	5

Comment received

Belgium thanks the rapporteurs for the excellent detailed analysis. We support the RAC opinion to maintain the classification of gallium arsenide as Rep. 1B H 360 F (CLP).

Studies in more than one species have demonstrated the testicular toxicity after exposure to GaAs by inhalation and/or via intra-tracheal instillation. In rat, mice and hamster, a

decreasing testis weights, epididymis weights, spermatid counts, spermatozoa motility and testis atrophy (in rats and mice) have been observed. Those effects are reported as clear-cut and clearly adverse.

We further consider those adverse fertility effects as non-specific secondary consequence of other toxic effects. Studies provided in the AIR cannot allow concluding on the MoA responsible for testicular toxicity. No evidence of hypoxaemia in the animals has been observed (no clinical signs as pallor of mucous membranes, poor general health status, weakness, laboured breathing,…). No increase vascularisation of the testis tissue has been reported in the histopathological study of the testes at the exposure levels causing testis toxicity. In mice and hamster, the alveolar proteinosis as well as inflammatory changes in the lungs are mild and/or moderate at the dose levels were testis effects start. In rat, the marked alveolar proteinosis were observed at concentration which do not produce any statistically significant testicular toxicity (testis atrophy), reduced Hb, body weight gain or any clinical symptoms. Therefore, we agree with RAC that no correlation between the occurrence /severity of the lung toxicity and testis toxicity can be shown. Besides, we support the following rationale: "the expected physiological of alveolar proteinosis as a dominant effect of systemic GaAs toxicity would be increased haematocrit and haemoglobin levels and, not the microcytic anaemia observed."

With the given studies, we agree on the lack of evidence to consider the testis toxicity solely as a secondary consequence of the combination of alveolar proteinosis and microcytic anaemia.

Regarding the CLP criteria, we support the classification Rep.1 B H 360F "… based on the clear adverse effects observed on fertility in animal studies …which is not a secondary non-specific consequence of other toxic effects…"

RAC's response

Thank you for the support.

Date	Country	Organisation	Type of Organisation	Comment number
18.06.2013	Germany	VDMA- German Engineering Association	Industry or trade association	6

Comment received

The German Engineering Association (VDMA) is the largest association representing the capital goods industry in Europe. The VDMA- Working Group on Innovative Materials for sustainable high tech electronics and photonics represents companies throughout the entire supply chain of innovative materials from the III-V materials (main group periodic system). We closely followed the Opinion making process and we would like to state the following:

<u>Executive Summary</u>

While acknowledging the effort that has been put into the latest Opinion, Industry remains convinced that RAC has not properly considered the data gathered and submitted by Industry showing that adverse effects on male reproduction parameters have to be considered as secondary non-specific consequences of other toxic effects. Our position is based on the following arguments:

• GaAs particles (at least those used in the referred experiments very small, mechanically treated with a partly destroyed crystal lattice) affect -like other particular substances- the lungs and blood after inhalation/intra-tracheal instillation. These effects are dose- and time-dependent, i.e. the longer the treatment the lower the doses with lung effects and the higher the degree the more pathologic effects in the lungs are observed.

• Subchronic GaAs inhalation exposure is associated with effects on the lungs in rats (≥ 0.1 mg/m3) and mice (≥ 1.0 mg/m3) initially in the form of an alveolar proteinosis, which is characterized by abnormal accumulation of surfactant occurring within the alveoli, thereby interferring with gas exchange.

• High-dose (≥ 10 mg/m3), subchronic inhalation exposure to GaAs is associated with effects on the blood/blood-forming tissues (haemolysis/hypochromic microcytic anaemia) by an as yet unknown mode of action.

• High-dose (≥ 10 mg/m3), subchronic inhalation exposure to GaAs is associated with effects on the germinal epithelium of the testes. The effects observed show close similarities to those after episodes of oxygen undersupply/hypoxaemic states of various causes.

• Under these experimental conditions, some dissociation into Ga and As ions occurs with resulting measurable albeit low Ga and As concentrations in blood and tissues. In human workplace conditions the data available up to now do not indicate bioavailability of Ga/As from GaAs. In addition, the GaAs used in optoelectronic industry is very poorly soluble and the exposure at production and processing is very low (± 10 µg/m3).

• Systemically available Ga ions are not known to possess a potential for primary testicular and haemolytic effects in experimental animals and/or humans (oral, subcutaneous, intravenous, inhalational exposure) even after comparatively high doses of Ga ions from soluble inorganic compounds. Whether occasional observations of hypochromic microcytic anaemia (generally in the presence of other systemic toxicity such as nephrotoxicity) in cancer patients treated intravenously with high doses of soluble Ga compounds can be used to hypothesize identical underlying mechanisms is highly questionable. In whole-body scintigraphs of patients treated with 67Ga isotopes no specific affinity of Ga for testicular tissues has been observed.

• Systemically available AsIII or AsV ions are not known do possess a potential for primary testicular and haemolytic effects in experimental animals and/or humans (oral, subcutaneous, intravenous, inhalational/intratracheal exposure) even after comparatively high doses of As ions from soluble inorganic compounds. A number of studies in rodents with oral, subcutaneous or intraperitoneal administration, using mostly doses of soluble As compounds in ranges with significant systemic toxicity (other than testicular), revealed effects on male fertility parameters/testicular toxicity. The scope of investigations in these studies do not allow to answer the question whether these effects were primary or secondary. The bioavailable As concentrations (rarely documented) must have been much higher and the toxicokinetics entirely different than those after intratracheal/inhalational GaAs exposure.

• Subacute (12 exposures within 16 days) inhalation exposure to extremely high concentrations of GaAs (up to 150 mg/m3) as well as chronic inhalation exposure for 2 years to concentrations of GaAs still about 50- to 100-fold higher than occupational exposure did not indicate testicular toxicity and/or haemolytic activity in rats and mice. The only organ affected in these quite extensive studies was the lung.

• Up to date there is noone case available where exposure to GaAs has been associated with effects in humans that could support the classification as....

Overall, there is neither a real hazard of male fertility effects in humans under occupational exposure conditions. The fact that a combination of certain degree of lung toxicity, haemolysis and anaemia is necessary to induce these effects essentially precludes human relevance.

One should keep in mind, that the exposure scenario in the experimental animal studies is rather artificial. Whole-body exposure to GaAs samples massively treated by mechanical stress (damaging parts of the crystal lattice), with a particle size distribution dissimilar to

that measured in Ga production, where male fertility effects occurred only at levels at least 1000-fold higher than workplace air concentrations and only in the presence of lung effects, anaemia and haemolysis.

Introduction

In its revised draft on the "Opinion on gallium arsenide in relation to toxicity to reproduction„ from May 29, 2013 the Committee for Risk Assessment (RAC) maintained "its view to classify gallium arsenide (CAS No 1303-00-0) as toxic to reproduction, Cat. 1B, H360F, according to the CLP Regulation." and further states that

"The RAC is of the opinion that there is not sufficient evidence to support the mode of action (MoA) for the testicular toxicity proposed in the AIR (i.e. "lung effects being the primary effects of GaAs exposure leading to haematological changes and hypoxaemia triggering the testicular effects")."

In a recent paper, submitted to RAC, the arguments supporting/not supporting a primary/specific effect of GaAs have been quite extensively evaluated (Bomhard et al., 2012). A further paper has demonstrated that a number of hypoxaemic states caused by hypobaric conditions/diseases/lung toxicity are capable of inducing effects on male fertility similar to those observed after GaAs inhalation/intratracheal instillation (Bomhard and Gelbke, 2013). A third paper extensively deals with the questions of bioavailability of arsenic and gallium ions from GaAs in relation to the mechanical treatment of GaAs crystals (Bomhard et al. 2013).

In the view of industry these comprehensive evaluations demonstrate sufficient evidence for a secondary non-specific mode of action.

General comments

The bulk of data available on the toxicology, bioavailability and toxicokinetics of GaAs whose reliability and validaity can be questioned may cause confusion about the relevant facts. Therefore, a brief summary of the most relevant studies is here below presented ahead of more specific comments on the Opinion.

What are the relevant studies?

The 16-day, 14-week and 2-year NTP studies (with a few toxicokinetic data from the Mast et al. 1990 studies) are those on which the evaluation should be based. Despite some data gaps those studies allow to draw most relevant conclusions.

Facts from the relevant studies

The 16-days NTP studies demonstrate that concentrations up to 150 mg/m³

- do not cause testicular toxicity in rats and mice,
- did not give indications for haemolysis and increased haematopoesis
- induced a dose-dependent alveolar proteinosis of minimal (1 mg/m³) to moderate degree (150 mg/m³) accompanied by minimal hystiocytic alveolar cell infiltration (at 10 mg/m³ and above) in rats,
- induced a dose-dependent alveolar proteinosis of minimal (10 mg/m³) to moderate degree (150 mg/m³) accompanied by minimal hystiocytic alveolar cell infiltration and minimal to mild alveolar epithelial hyperplasia in mice
- which caused a dose-dependent increase in relative lung weights of 19 to 40 % in male rats and 35 to 74 % in male mice.

The Mast et al. 1990 studies with subacute inhalation exposure of male (12 consecutive days) and female rats (16 consecutive days) show

- a dose-dependent increase in Ga and As concentrations in male rat whole blood and testes (10 – 75 mg/m³),

- no detectable (with 1 exception) Ga and As concentrations in male mouse testes (1 – 37 mg/m³),
- a dose-dependent increase in whole blood Ga and As concentrations of female rats with a steady-state achieved with Ga ions after 10 days, while As concentrations increased over time due to the known strong binding of As to haemoglobin.

Conclusion on the data from subacute studies: Despite extremely high concentrations (up to 500000-fold the current US TLV) and "substantial„ bioavailability (due to the particle characteristics), there is no indication of systemic toxicity. Therefore there is no indication for a primary toxicity of either Ga or As ions on the testes or the blood.

The 14-weeks NTP studies demonstrate

- that concentrations of 0.1 up to 75 mg/m³ induced a dose-dependent alveolar proteinosis of minimal (0.1 mg/m³) to marked degree (≥ 10 mg/m³) accompanied by minimal hystiocytic alveolar cell infiltration (at 0.1 mg/m3 and above) in rats,
- that concentrations of 1.0 up to 75 mg/m³ induced a dose-dependent alveolar proteinosis of minimal (1 mg/m³) to moderate degree (≥ 37 mg/m³) accompanied by minimal (1 mg/m³) to mild (≥ 10 mg/m³) hystiocytic alveolar cell infiltration, minimal (1 mg/m³) to moderate alveolar epithelial hyperplasia (≥ 37 mg/m³) mild suppurative inflammation (≥ 10 mg/m³) and minimal granuloma formation (≥ 10 mg/m³) in mice,
- a dose-and time-dependent effect on the red blood with highly significant and partly marked effects on e.g. erythrocyte/reticulocyte count (increase up to 66/91 %), mean cell volume/haemoglobin (decrease up to 52/45 %), haematocrit (decrease up to 24 %) in male rats,
- bone marrow hyperplasia characterized by hypercellularity due to increased numbers of erythropoietic cells was present in groups of male rats exposed to 10 mg/m³ or greater,
- haemosiderosis in the liver of male rats exposed to 37 or and the occurrence of schisto- and keratinocytes in blood smears of male rats exposed to 10 - 75 mg/m³ indicate haemolytic processes,
- Testicular atrophy and epididymal hypospermia were observed in all male rats exposed to 37 (minimal degree) or 75 (moderate to marked degree) mg/m³, as well as in male mice at 10 mg/m³ (minimal) and 37 or 75 mg/m³ (moderate severity).
- total spermatid heads per testis and per gram testis and spermatid counts were significantly decreased in male rats exposed to 75 mg/m³ and in male mice exposed to 37 or 75 mg/m³. In male rats exposed to 10 mg/m³ or greater, the motility of epididymal spermatozoa was decreased, this was the case in mice at ≥ 37 mg/m³. Epdidymal sperm concentration was significantly decreased in male rats at 75 mg/m³ and in mice at ≥ 10 mg/m³.

The 2-year NTP studies demonstrate

- no effects on the testes at concentrations up to 1mg/m³,
- no indications of increased haematopoiesis or haemolysis,
- but clearly affected the lungs by chronic inflammation, alveolar proteinosis etc.

<u>Specific comments on statements within the Opinion</u>

III. Opinion of the RAC p.2, § 2:

Citation: "Also, marked alveolar proteinosis is observed in rats at concentrations which do not produce any significant testicular toxicity (such as testis atrophy), reduced Hb, body weight gain or any clinical symptoms. Thus, no correlation between occurrence and severity of the lung toxicity and testis toxicity is shown. There is therefore no evidence for the testicular toxicity being secondary to other toxic effects in these studies."

Comment: This assessment is based on the results of subjective, semiquantitative scoring/grading of alveolar proteinosis on presumably one or two 5 µm slices of the lung

(details not given in the NTP report), which does not allow to support the conclusions drawn by RAC.

A quantitative and objective description of the degree of alveolar proteinosis can be derived from the lung weights, which were (rounded) in male rats of the 14-week study in ascending order of dosing i.e.

control – 0.1 – 1.0 – 10 – 37 – 75 mg/m³:

1.5 – 2.0 – 2.4 – 2.9 – 3.8 – 4.2 g absolute;

4.4 – 5.9 – 6.9 – 8.7 – 11.5 – 13.3 mg/g bw relative.

In male mice, the respective lung weights were:

0.24 – 0.24 – 0.27 – 0.36 – 0.48 – 0.52 g absolute;

6.4 – 6.6 – 7.0 – 10.3 – 13.4 – 15.5 mg/g bw relative.

In rats, all lung weights of the dosed rats differed very significantly ($P < 0.01$) from controls, in mice they differed very significantly from controls at 10 mg/m³ and above; the absolute weight at 1.0 mg/m³ differed significantly ($P < 0.05$)

Since this lung weight increase can almost exclusively be explained by the increase in alveolar proteinosis in rats, as well as to a large extent in mice, there is a clear-cut association between the degree of alveolar proteinosis and the degree of testicular effects. In mice, probably/possibly the combination of alveolar proteinosis, alveolar epithelial hyperplasia and suppurative inflammation, (eventually with other species-specific properties of lung function, oxygen transport capacity by the blood, and reaction to hypoxaemic states at the germinal epithelium) might well explain that seemingly less severe effects on the lungs have somewhat more severe effects on the testes.

Page 4, § 4+5:

Citation: „Chiou et al. (2008) studied the effects of 15 subcutaneous administrations (during a period of 3 weeks) of As2O3 in mice, and observed a dose-dependent increase in As concentrations in the testes (40, 64 and 182 ppb As at 0, 0.3 and 3 mg As2O3/kg/day) as well as in testicular toxicity (inhibition of spermatogenesis). Pant et al. have studied testicular toxicity and accumulation of As after administration of soluble sodium arsenite (NaAsO2) to mice via the drinking water for 35 days (0-534 µmol NaAsO2/l) (Pant et al., 2001) or for 365 days (53 µmol NaAsO2/l) (Pant et al., 2004). After 35 days the concentration of As in the testes increased to 5.3 mg/kg in the highest dose group. In the 1-year study the concentration of As in the testes was 6.5 mg/kg. In both studies, evidence of testicular toxicity was observed at these concentrations of As in the testes."

Comment:By referring to papers of Chiou et al. (2008), Pant et al., (2001, 2004); (and Li et al. 2012, cited on page 10) papers, RAC obviously tries to demonstrate a possible contribution of As ions to the observed testicular toxicity after GaAs exposure. Indeed, there are meanwhile quite a number of similar publications showing testicular/sperm effects in rodents after exposure to As (list of further references available). Besides their mostly questionable validity, they all use highly soluble As compounds at dose levels known to exert a number of other systemic adverse effects. Also in several cases, only one dose level is used, and (adequate) histopathology is often lacking (e.g. in Chiou et al. 2008; Pant et al. 2001, 2004). The Chiou et al. (2008) paper is obviously used to demonstrate testicular effects already at extremely low tissue concentrations. However, these data are meaningless without knowledge of the kinetics of As elimination.

Elimination of As from oral or parenteral treatment of rodents or humans with soluble inorganic arsenic compounds like As2O3, NaAsO2, Na2AsO5, is very rapid: after 2 to 3 days about 90 to 99 % of the dose is excreted (e.g. Brunet et al. 1982; Hughes et al. 1999,

2003; Lindgren et al. 1982; Marafante and Vather 1987; Shen et al. 1997). The half-lives of the predominant alpha-phase has been estimated to be in the range of a few hours. This rapid elimination is entirely different from that after inhalation/intratracheal instillation exposure to very poorly soluble GaAs/other As compounds like lead arsenate or calcium arsenate (Inamasu et al. 1982; Marafante and Vahter, 1987; Pershagen et al. 1982), thus suited to be used in this context. However, the lung-clearance half-lives in male rats of the NTP studies ranged from 16 days (10 mg/m³/14 week) to 100 days (0.1 mg/m³/2 years), thereby indicating some kind of overload at the high concentrations used in the 14-week studies.

The NTP-2year-inhalation study in rats shows that there is no accumulation of As from GaAs in the

testes (anyhow not to be expected due to the binding of As to haemoglobin). The NTP-mouse study of Mast et al. (1990) with subacute inhalation exposure of mice to concentrations up to 37 mg/m³ shows that there is even no As detectable in the testes. The studies of the Omura/Tanaka group show that there is no As "accumulation" in the testes of rats and hamsters after subacute intratracheal instillation in the testes (Hirata et al. 1997). In both species the serum concentrations were higher than those in the testes.

Page 4, § 6:

Citation: „The studies by Engelstad et al. (1982), Ishii et al. (2011) and Jonkhoff et al. (1995) describe scintigraphic results from humans injected intravenously with a single dose of radiolabelled gallium citrate. However, the testes are not mentioned in these studies, and the RAC is of the opinion that these scintigraphs are not helpful in determining potential (lack of) distribution to, and accumulation of gallium in the testes."

Comment: The major reason for the absence of specific mention to the testes in these studies (and in a more recent study including 14 male patients by Ishii et al. 2013) is obviously the lack of any noteworthy Ga concentration in the testes. The whole-body scintigraphs of male patients, depicted in these papers demonstrate that the testes are not a localisation of Ga accumulation (no special anatomical expertise necessary).

Page 4, § 6:

Citation: „The overall view of these studies is that both gallium and arsenic ions are distributed to the testes, but that neither ion is retained or accumulated in the testes to a higher extent than to some other organs. The RAC concludes that these ions are distributed to the testes, where they potentially could directly contribute to testis toxicity."

Comment: This qualitative conclusion is neglecting the many literature data on the lack of testicular toxicity/male fertility effects of soluble As and Ga compounds at much higher dose levels/much higher bioavailability (Collery et al. 1996; Colomina et al. 1993; Golub et al. 1998). In addition, it must be considered that the toxicity of soluble Ga and As compounds differs by one to two orders of magnitude: comparable data on acute to subchronic toxicity in experimental animals demonstrate that the systemic toxicity of As compounds is in the mg/kg range or even lower, whereas it is in the 100 mg/kg range for Ga. In humans, the relations are quite similar. Thus, it is highly unlikely that the traces of Ga ions detected in the testes „directly contribute to testis toxicity".

A comparison of the results of Ga and As measurements in testes of rats and mice exposed to GaAs for 12 consecutive days 6 hours/day (same GaAs sample as in 14-week NTP studies) (Mast et al. 1990) with those on the testicular effects in the 14-week studies is presented in the following table.

Rat Mouse

Exposure (mg/m3) As (µg/g) Ga (µg/g) Testicular

atrophy* Hypospermia* As (µg/g) Ga (µg/g) Testicular

atrophy* Hypospermia*

0 < 0.15 < 0.10 0 0 < 0.15 < 0.10 0 0

1 n.t. n.t. 0 0 < 0.15 < 0.10 0 0

10 0.19 0.24 0 0 < 0.15 < 0.10 1.3 2.0

37 0.56 1.02 1.1 1.8 < 0.15 < 0.10** 3.2 4.0

75 0.82 1.70 3.4 3.9 n.t. n.t. 3.1 4.0

*average severity grade from 14-week NTP inhalation study (maximum 4.0); ** 1 value 0.88 µg/g contaminated?; As + Ga concentration: n = 3 (except 37 mg/m3 mouse: n = 2); n.t. = not tested.

The essential conclusion from these analytical data is:

there is no association/correlation between As and Ga concentrations in the testes of rats and mice and the degree of male "fertility„ effects in the 14-week NTP studies. Thus, supporting the hypothesis that neither As nor Ga are responsible for these effects but hypoxaemia in combination with haematological effects. The higher severity degree and broader effect constellation in the lung of mice (except alveolar proteinosis) might explain the higher sensitivity of mice with regard to testicular atrophy and hypospermia.

Page 5 §4:

Citation: „The RAC concludes that although several organs were affected by intratracheal exposure to GaAs, only mild to moderate lung effects were reported and hypoxaemia was not measured after GaAs exposure in hamsters by Tanaka et al. (2000). Accordingly, the new information from this study does not support the notion that the animals suffer from severe lung toxicity and hypoxia at exposure levels causing testis toxicity."

Comment: However, on page 25 of their paper Tanaka et al. (2000) report that "foci of mild to severe inflammatory responses were present in the lungs of all groups....". The comparison to indium arsenide, which was highly toxic to the lungs (causing even lethality in 3/8 hamsters) might have influenced the grading of GaAs lung effects.

Drawing attention to this paper (as well as to those of Webb et al., 1984, 1986, 1987; Goering et al. 1988; see §3 on this page) by industry was intended to put the Omura et al. 1996 a,b publications into perspective, since in the forementioned papers effects on other organs were not reported, and the RAC Opinion of 25 May 2010 emphasized the „clear evidence of effects on fertility....in the absence of other toxic effects...". Since no haematological/adequate histopatology investigations have been performed within these studies to answer the question of effects on/degree of haematotoxicity they are not suited to reject the mechanism of action proposed by industry.

Page 5 §5:

Citation: "It was proposed that data from a study with indium arsenide could be helpful in clarifying the relationship between lung and testis toxicity."

Comment: This "proposal„ was brought into discussion by RAC members in an attempt to reject the mechanism of action proposed by industry saying that InAs causes severe lung toxicity but no testicular toxicity. Industry drew the attention to studies by Yamazaki et al (2000) and Omura et al. (2000) demonstrating testicular effects in the presence of lung effects in hamsters after intratracheal instillation after exposure to InAs (4.0 mg/kg body weight/day twice weekly for eight weeks). However, the lung effects were qualitatively different i.e. severe inflammation, no alveolar proteinosis. Thus it fulfills one of the prerequisites postulated by Bomhard and Gelbke (2013) for a potential of secondary effects

on male fertility/testicular toxicity due to hypoxaemia by lung toxicity (i.e. lung affection sufficient to impair gas exchange).

Since InAs (as well as other In compounds) have different effects on the rodents' lungs (and blood, see NTP studies with InP) than GaAs, their use in supporting or rejecting the proposed mechanism of action in the case of GaAs (which by the way includes effects on the blood i.e. haemolysis, anaemia) requires more careful consideration.

InAs and indium phosphide (InP) cause very severe lung toxicity (citation from Yamazaki et al. 2000): "Histopathologically, severe pulmonary inflammation and localized lesions with bronchioloalveolar cell hyperplasia were present in both InAs and InP groups from just after the last administration. The localized lesions gradually transformed to proteinosis like lesions with periodic acid Schiff reagent positive exudation after 16 weeks." Since this points to some comparability between InAs and InP it is of interest to check in this context, how InP compares with GaAs when tested in studies under comparable inhalation conditions and including the same spectrum of haematological and reproductive tissue evaluation as reported by NTP 2001 (TR 499). Histopathology at the end of the 14-week studies revealed a spectrum of lesions in the lungs of all exposed groups of mice and rats consisting of alveolar proteinosis, chronic active inflammation, interstitial fibrosis, and alveolar epithelial hyperplasia and was thus different from those in the GaAs studies. Reproductive tissue evaluations revealed no effects in rats and mice. Haematological evaluations in rats and mice revealed a pattern of effects significantly different from those with GaAs: no indications for haemolytic effects, clear indications for increased haematopoiesis, with an increase in haematocrit, no decrease in haemoglobin, much less decrease in cell volume compared with GaAs in rats and increased haematocrit, increased haemoglobin, less strong effects on mean cell volume and haemoglobin. This indicates that rats and mice were in a state of compensated hypoxaemia and thus corroborates the proposed MoA that the blood has a decisive role in the development of hypoxaemic sequels.

(The occurrence of large degenerating cells (degeneration) of testicular germinal epithelial origin within seminiferous tubules of the testes and within the epididymis of all males, flattened glandular epithelium and reduced secretory material (atrophy) within the prostate and seminal vesicles in 100 mg/m³ rats were considered secondary to debilitation. No effects on male reproductive organs were found in mice.)

References

Page 6,§1

Citation: „It has been proposed by the submitter of the AIR and by Bomhard and Gelbke (2013) that the testis toxicity of GaAs is secondary to alveolar proteinosis. For InAs, testis toxicity occurs before any signs of alveolar proteinosis are observed. Later (e.g. week 16), the testis toxicity has become very severe while alveolar proteinosis is characterised as mild. The involvement of alveolar proteinosis in the testis toxicity of InAs is therefore not immediately apparent."

Comment: Reducing the proposed mechanism of actionto „testis toxicity of GaAs is secondary to alveolar proteinosis" is an unacceptable shortcut of what has been extensively elaborated in the papers by Bomhard et al. (2012) and Bomhard and Gelbke (2013). Careful reading of these publications in international journals of high reputation is adviced.

References:

Bomhard EM, Cohen SM, Gelbke HP, Williams GM. Evaluation of the male reproductive toxicity of gallium arsenide. Regul Toxicol Pharmacol. 2012 Oct;64(1):77-86.

Bomhard EM, Gelbke HP. Hypoxaemia affects male reproduction: a case study of how to differentiate between primary and secondary hypoxic testicular toxicity due to chemical

exposure. Arch Toxicol. 2013 Feb 21. [Epub ahead of print]

Page 6, end of §4

Citation: „Thus, at the dose where testis toxicity started to appear (10 mg/m³), the relative lung weight was doubled and the lung pathology (alveolar proteinosis) marked. These results suggest that testis atrophy and hypospermia occur independently of alveolar proteinosis since at 10 mg/m³ marked alveolar proteinosis was observed in the absence of testis atrophy and hypospermia. In the rat, the lungs are clearly more sensitive than the testes."

Comment: The logic of this argumentation is not clear and might be too simplistic. Our proposed mechanism of action is the following: at lung effects (in this case alveolar proteinosis, but it may also include severe inflammation, etc.) gas exchange is impaired. This is a non-specific consequence. The resulting reduction in oxygen supply is, in the case of a healthy organism, intact blood forming tissues, lack of interfering processes, ameliorated/compensated mainly by increased haematopoiesis (as can be seen by increased numbers of erythrocytes, by haematopoietic cell proliferation in spleen, bone marrow). In cases of sufficient compensation no effects on male fertility are to be observed. In cases of insufficient compensation, however, effects on male fertility parameters can occur, because the seminiferous epithelium operates on the verge of hypoxia. In the case of GaAs haematological and histopathological results from the NTP studies clearly indicate effects (haemolysis, anaemia), which are suited to conclude that there was insufficient compensation of the oxygen depletion. In this case, it is obvious that male fertility effects might not be detectable even in case of rather severe lung effects, especially when there is sufficient time for compensation (which is mostly the case when investigations are at the end of 13/14-week studies). The cases of InP (see above) and nickel subsulphide (see Bomhard and Gelbke 2013) are illustrating the latter.

Page 6, end of §5

Citation: „The reduction in haemoglobin concentration is considered by the RAC to have clinical relevance only in male rats at the highest dose (-13% Hb), and not in mice (only 5.6% reduction of Hb at the highest dose)."

Comment: The biological consequences/clinical relevance of the complex dose- and time-dependent changes in the blood can in our opinion not just be orientated on the reduction in haemoglobin concentration at one timepoint, at which obviously the organism heavily struggling to overcome a serious deficiency, thereby producing erythrocytes containing up to 36/24 % less haemoglobin and up to 40/38% less mean cell volume than control rats/mice.

Page 8, §2

Citation: „The microcytic responsive anaemia could be an effect of an inhibition

of delta-aminolevulinic acid dehydratase (ALAD), an enzyme involved in the heme

biosynthesis pathway and shown to be inhibited by GaAs (Goering et al., 1988)..."

Comment: Goering et al. (1988) administered single intratracheal doses of 50, 100 or 200 mg/kg to male CD rats and determined ALAD activity in blood, liver and kidneys as well as ALA excretion with the urine 6 days (after administration of 100 mg/kg also 3, 6, 12 and 18 days) after treatment. ALAD activity was not affected in blood, liver and kidneys at 50 mg/kg but dose-dependently decreased in blood and kidneys, in liver only at 200 mg/kg. At these doses lung weights were dose-dependently and massively increased, kidney toxicity was observed at 100 mg/kg (other dose levels not reported).

To put these results into perspective the following aspects shall be considered:

a) the preparation of the GaAs sample that was used: the GaAs sample was „initially ground in a cryogenic mill... and subsequently placed in a rotary grinder". The majority of particles was less than 1µm diameter. The consequences of such treatment and the incomparability of such a GaAs with that occurring at the workplaces has been recently explained in detail by Bomhard et al. (2013)

b) how dose levels of ≥ 50 mg/kg compare with the dose levels after inhalation of ≥ 50 mg/m³: the almost cumulative (due to the long half-life in the lungs) concentrations of 70 x 6h exposures to GaAs in the lungs of male rats of the 14-week NTP study (measured as Ga and As) were about 600 – 1500 – 2000 µg/lung at 10, 37.5 and 75 mg/m³ respectively. The mean body weight of the animals was 334 – 328 – 314 g, thus the „cumulative" dose was in the range of 1.8 – 4.5 – 6.0 mg/kg. There is thus a factor of more than 50 between the dose producing first ALAD effects in blood and kidneys and the dose at the concentration of 10mg/m3, at which already significant blood effects occurred.

No such data are available for mice.

Page 8, §2

Citation: „As gallium binds to transferrin and it is known that microcytic anaemia may develop in patients treated with gallium nitrate (Chitambar, 2010), the RAC considers the occurrence of a mild microcytic anaemia at the 10 mg/m³dose to be indicative of systemic toxicity."

Comment: It is highly questionable that the observation of microcytic anaemia sometimes observed in patients treated with intravenous infusions of comparably very high doses of the soluble gallium nitrate (200 – 1000 mg/m²/d, resulting in peak serum levels of up to 50 µg Ga/ml; see e.g. Krakoff et al. 1979) is relevant to assigning gallium as the cause of microcytic anemia in the rat study. Haemolysis as observed in animal experiments, has not been reported in humans after high-dose intravenous treatment with soluble gallium and arsenic compounds! Renal toxicity also observed in human as well as animal studies using relatively high doses of soluble Ga compounds have not bin observed in any of the studies with GaAs.

Page 8, last §

Citation: „The RAC is of the opinion that there is no evidence for hypoxaemia in the animal studies on GaAs (e.g., no clinical signs such as pallor of mucous membranes, poor general health status, weakness, laboured breathing, or signs of hypoxia in other vulnerable organs). No increased vascularisation of the testis tissue has been reported in the histopathological study of the testes in the NTP study (no increase in number of blood vessels or decrease in vessel diameter in the testes) at the exposure levels causing testis toxicity. This proposed mechanism of action therefore seems rather speculative for GaAs."

Comment: To our knowledge there is very little data which would demonstrate that some or all these findings should be observed under conditions comparable to those in the GaAs studies. Whole-body 6hours exposure to relatively high concentrations of greyish particles may have masked some subtle changes. Quantitation of increases in blood vessels or decreases in vessel diameter in the testes would require special studies/evaluations, which have not been performed. Since, for reasons presented before as well as in the paper by Bomhard et al. (2012), neither the bioavailable Ga nor As concentrations can explain the pattern of effects, the proposed mechanism of action is the only plausible one.

Page 9, §3

Citation: „However, the RAC notes that 'free' Ga3+ has a low solubility in most aqueous solutions, and readily hydrolyses to various hydroxide species (e.g., Ga(OH)4-) limiting the absorption. Since gallium has been used therapeutically there is quite some experience on how to present it under physiological conditions to avoid problems with precipitation and to

improve absorption. A review by Bernstein (2005) describes how gallium in saline will hydrolyse into Ga(OH)4-, which with a pHdependent rate is transformed into insoluble Ga(OH)3, that will precipitate, and then form crystalline GaO(OH). The review concludes that there is low oral absorption of gallium salts, "likely due in large part to the formation of poorly soluble gallium hydroxides in the gastrointestinal tract".“

Comment: There are quite a number of toxicological and clinical studies available (e.g. Adamson et al. 1975; Gomez et al. 1992; Hart and Adamson 1971; Hart et al. 1971; Keller et al. 1986; Krakoff et al. 1979; Samson et al. 1980) which have used gallium nitrate in aqueous solutions over a broad range of concentrations for parenteral (subcutaneous, intraperitoneal: animal experiments; intravenous: animal experiments and clinical studies). The occurrence of dose-dependent effects and the absence of any reports on precipitations during these studies make these justifications/elaborations for the purpose of devalidating the Colomina et al. (1993) study more than questionable. The results of the Colomina et al. (1993) study are well in line with other studies showing rather low toxicity of soluble Ga compounds in experimental animals and humans.

The Colomina et al. (1993) study is remarkable in that very special and specific investigations on the testes were performed: e.g. the diameters of 50 tubules of each testicle were measured in a Videoplan Kontron morphometer and the mean tubular diameters were calculated. The tubules were evaluated for the existence of complete spermatogenesis and for focal or diffuse atrophy. Sertoli cells were classified as normal, atrophic, or with cytoplasmic vacuolization. The existence of multinucleated cells within the tubular lumen or among spermatogenic cells was assessed. The existence of degenerative changes in interstitial Leydig cells was also studied. Sperm count, motility and morphology were investigated.s

Pages 7 and 10ff

Comment: Many repetitions of positions mentioned before and already commented. No really new arguments besides referring to definitions about specific vs non-specific. In our opinion laid down and explained in the papers/documents mentioned there is sufficient and convincing information that raises doubt about the relevance of the effect for humans and therefore classification in Category 2 is more appropriate.

The most likely sequence of events may be helpful in deciding whether the male fertility effects are specific:

1. High intratracheal doses/inhalation concentrations of poorly soluble GaAs particles cause more or less massive lung effects (inflammation/alveolar proteinosis), sufficient to suppose an effect on gas exchange/oxygen diffusion. These lung effects following particle exposure are non-specific, although vary depending on particle size/surface/charge etc..

2. The result is a decrease in blood oxygen levels, which again is non-specific (admittedly this decrease is rearly measured in toxicological studies, but indirectly to be seen in haematological parameters).

3. In an attempt to overcome the oxygen depletion, the organism produces or tries to produce more haemoglobin by increased haematopoiesis. This is irrespective of the cause of the oxygen depletion and thus again a non-specific reaction.

4. Testicular effects in case of reduced oxygen supply are to be seen in a variety of cases, including high altitude (hypobaric) conditions/lung diseases/blood disorders. Thus, they are a non-specific consequence of oxygen depletion. The reason is that the germinal epithelium operates at the verge of hypoxia.

5. The fact that testicular effects have not been demonstrated in other cases of lung toxicity can have various explanations: degree of oxygen depletion, rapid amelioration/compensation by haematopoiesis, lack of haemolysis, timepoint of testicular

investigations too late, insensitive methods etc., but is not a valid argument for excluding a non-specific sequence of events.

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RAC's response

Thank you for the very detailed comments. As also stated in the comments, there are few new data, and the arguments for and against classification have been discussed repeatedly. The RAC agrees that from a risk assessment perspective, lung toxicity occurs at a lower exposure level than testis toxicity, but such considerations are not relevant for classification and labelling (CLP Regulation (EC) 1272/2008). The overall assessment is a weight of evidence evaluation, and we can only conclude that there are different views on the data base when it comes to how 'proven' we consider the relationship between the lung toxicity and the testicular toxicity. The RAC has also noted that no other lung toxicant seems to exert secondary testicular toxicity, and has taken this observation seriously when concluding that there is not sufficient evidence for the testicular toxicity of GaAs being a secondary non-specific effect of lung toxicity.

Date	Country	Organisation	Type of Organisation	Comment number
17.06.2013	France		Individual	7

Comment received

as an individual worker in micro electronics I have been surged from 3 skin carcinomas. This disease is currently studied by french social security to be in relation with arsenic exposure in GaAs manufacturing tool maintenance.

I found a bit estonishing such regulations are taking in a such non mature industries with new substrate and processes where the disease can occur 40 years after exposure. Be carefull in your final view. Arsenic is known since the 40/50s as a poison.

Please read carefully on arsenic effects on humans.

http://docnum.univ-lorraine.fr/public/SCDMED_T_2002_BOURNIQUEL_CHRISTINE.pdf

This medical thesis work expressaly says that people exposed to arsenic should be followed for sexual organs in particular

my little contribution as a potential victim of AsGa

RAC's response

Thank you for your contribution and your information.

Date	Country	Organisation	Type of Organisation	Comment number

ANNEX 5 - COMMENTS AND RESPONSE TO COMMENTS ON RAC'S DRAFT OPINION ON THE TOXICITY TO REPRODUCTION OF GALLIUM ARSENIDE

14.06.2013	Norway		MemberState	8
Comment received				
Norway would like to thank ECHA for the opportunity to comment on the draft opinion by RAC concerning the toxicity to reproduction of gallium arsenide, cas no. 1303-00-0. We support the proposal to maintain the previously agreed classification of gallium arsenide for reproductive toxicity with Repr. 1B - H360F. We are of the opinion that the information submitted by Industry during the last public consultation are not changing the previously agreed classification. We agree with RAC's conlusion on the fact that there is not enough evidence to consider the testis toxicity as a secondary effect of lung toxicity. No correlation between occurrence and severity of lung toxicity and testis toxicity is shown, and the classification for reproductive toxicity with Repr. 1B - H360F should therefore be maintained.				
RAC’s response				
Thank you for the support.				

Date	Country	Organisation	Type of Organisation	Comment number
11.06.2013	France		MemberState	9
Comment received				
FR supports the draft opinion.				
RAC’s response				
Thank you for the support.				