ANNEX 2 - 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

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

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	1

Comment received

Dear Mr Dancet,
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. Dancet,

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 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 cause may also effects 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.

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.

(...)