Committee for Risk Assessment

(RAC)

Annex 5

Response to comments document (RCOM)

RAC response to comments received during the public consultation of 11 March to 27 April 2011 on the proposed harmonised classification and labelling as carcinogenic of

gallium arsenide

ECHA/RAC/A77-O-0000001412-86-05/F

Adopted

1 December 2011

Comments recived during public consultation on gallium arsenide (11 March until 27 April 2011) and RAC response to comments

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

Date	Country/ Person/ Organisation/ MSCA	Comment	RAC response
08/04/2011	Italy / Individual	Possible substitution: Ga2Se3···As (Crystal Glass) VPE 3 AsCl3 (g) + Ga2Se3 (s) → Ga2Se3···As + 3/2 Cl2↑ + 2 AsCl3↑ Redox: 3 x (1 As3+ + 1 e- → 1 As2+) 1 x (3 Cl1- → 3 Cl0 + 3 e-)	Unclear message
13/04/2011	France / Thomas Pearsall / European Photonics Industry Consortium / Industry or trade association	*ECHA comment: same comment was included in the attached document (EPIC_Comments on GaAs_ECHA.pdf)* To: ECHA From : Tom Pearsall Subject: Risk Assessment Committee concerning Gallium Arsenide: Opinion proposing harmonised classification and labelling at Community level of gallium arsenide ECHA/RAC/CLH-0000000792-73-03/F To the ECHA and its Risk Assessment Committee On behalf of EPIC and its Board of Governors, I am writing to request a reopening of the recommendation procedure for classification of gallium arsenide. Although we were not made aware of the original opinion which was adopted on 25 May 2010, we feel strongly that the procedure used by the Risk Assessment Committee (RAC) of ECHA to determine the CLP classification for gallium arsenide is not appropriate to determine whether or not gallium arsenide represents a biological risk. In particular, the “read-across” approach that assigns to gallium arsenide the toxicity of related compounds like arsenic or arsenic oxides is not relevant. Using the same procedure, table salt would have the same toxicity as chlorine, one of its constituent chemicals. The testing protocol used on rats appears to be flawed as well. Aspiration of finely ground powders is known to lead to lung disease and cancers, regardless of the underlying materials. Prolonged breathing of glass powders and fibres leads to silicosis, yet there is no action to classify glass as a toxic agent.	Thank you for your comments. Regarding comments on read-across, please see point 1) of the Annex to RCOM (Additional response to comments). The comparison with table salt is not relevant. The test protocol in the NTP study in rats (NTP, 2000) followed OECD test guideline 451, with minor deviations. Regarding fine particulate matter-considerations, please see point 3) of the Annex to RCOM (Additional response to comments). Your comments on use of gallium arsenide are

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		We support the REACh initiative of the European Commission and its classification of biologically hazardous materials, provided of course that each classification be determined by a rigorous and scientifically supported testing procedure. The two examples cited above demonstrate that it is critical that these tests measure the innate toxicity of the material being cited, not its form or its apparent relationship to some other material that may be toxic. Gallium arsenide is present in our daily environment as a solid and inert material. It is used to make transistors and lasers. The transistors are required for every mobile telephone. There is a gallium arsenide laser in every CD player, and also in every industrial solid-state laser. These are used to cut and weld steel on automobile assembly lines and in critical surgical operations on the eye. Gallium arsenide lasers are widely used for amplification in modern optical fiber telecommunications. Gallium arsenide is a basic part of high-efficiency photovoltaic modules. In the opinion of EPIC, it would be very hard to imagine a world without mobile telephones, fiber-optic telecommunications, CDs, and key surgical procedures. We do not know of any other material that could serve as a substitute. It is a material of such importance that recommendations about its continued use should be made carefully, using contemporary scientific standards that are relevant both to gallium arsenide and to the way it is used in various applications. Such a procedure may be more costly and time-consuming, but would be easily justified by the economic and technological importance of this material. We are pleased by the decision of the Commission to review the RAC opinion on the CLP classification of gallium arsenide with respect to the endpoint carcinogenicity. We regard it necessary however, that the RAC opinion on the CLP classification of gallium arsenide be also reviewed with respect to all endpoints and in particular with respect to the endpoint fertility. Best regards, Thomas P. Pearsall Secretary General	noted. However use of a substance is not relevant for the classification which is a result of assessment of intrinsic properties of the substance. Assessment of the hazard properties of GaAs as a substance and risk assessment from exposure related to usage of GaAs in the microelectronic industry are different things. In accordance with the mandate from the ED this consultation did not concern other effects than carcinogenicity. Still many comments were received on toxicity to reproduction. This issue was discussed in RAC-16 and the following conclusion was reached: "RAC confirms that its conclusion regarding the classification of gallium arsenide for reproductive toxicity in its opinion of 25 May 2010 was based upon a proper evaluation of the data."
18/04/2011	Germany / Christian Eckert / ZVEI / Industry or trade association	*ECHA comment: The document attached (2011_Jan_28_GaAs_ZVEI-Position.pdf) is copied below.* Gallium Arsenide Position of ZVEI – German Electrical and Electronic Manufacturers' Association	Thank you for your comments. We understand your

Date	Country/ Person/ Organisation/ MSCA	Comment	RAC response
		On "Opinion of the Committee for Risk Assessment (RAC) proposing harmonized classification and labelling at Community level of Gallium Arsenide, adopted 25th May 2010" **Executive Summary** The Committee for Risk Assessment (RAC) has adopted an opinion on the proposal for reclassification of Gallium Arsenide (see ECHA/RAC/CLH-0000000792-73-03/F, adoptet 25 May 2010). ZVEI and its member companies have serious concerns about the process of classification and labelling of Gallium Arsenide that is currently pursued by the ECHA Committee for Risk Assessment. There is evidence that the results of referenced toxicological studies have been misinterpreted and even have been falsely cited. A scientifically sound evaluation of the classification proposal should consider inputs of all stakeholders and in this case should be aligned with the dossier generation for the registration process. ZVEI and its member companies highly recommend to correct the RAC opinion on classification and labelling of GaAs carefully using good scientific sense and to release the political pressure on pushing quickly SVHC substance on the REACH candidate list for the benefit of keeping the high tech industry chemical supply chain within Europe. **Importance of Gallium Arsenide for Electronic Industries:** Gallium arsenide is a fundamental compound semiconductor material and forms a core substrate for semiconductor technology. Its properties recommend GaAs circuitry, inter alia, in mobile phones, satellite communications or microwave point-to-point links. GaAs also demonstrates potential in opto-electronics for application in medical systems and especially in high brightness light emitting diodes (LED) and laser diodes. In summary, Gallium Arsenide is used in many high tech applications because of its unique characteristics. Due to the unique characteristics of arsenic doping chemistry there are currently no replacement elements for arsenic. **Classification of Gallium Arsenide** Substance Name: Gallium Arsenide (GaAs) EC Number: 215-114-8 CAS Number: 1303-00-0 **Classification:** **France Draft Dossier** from 2nd June 2009: Carc. 2 - H351; STOT Rep. 1 - H372; Repr. 1B - H360F **RAC oppinion** from 25th May 2010: Carc. 1A - H350; STOT Rep. 1 - H372; Repr. 1B - H360F **Please find below our serious concerns described in detail:**	concern for a possible future inclusion of gallium arsenide on the candidate list and Annex XIV, eliciting the authorisation regime in REACH. However identification of substances of very high concern (SVHC) and proposals for the candidate list is not within RACs portfolio. Regarding your comments on use please see response to France / Thomas Pearsall / European Photonics Industry Consortium / Industry or trade association in the beginning of this document. Assessment of the hazard properties of GaAs as a substance and risk assessment from exposure related to usage of GaAs in the microelectronic industry are different things. Regarding your comments on read-across and threshold, please see points 1) & 2) of the Annex to RCOM (Additional response to comments). We agree that there are

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		1) Procedure of RAC process: RAC did not fully conduct the review task as they required (e.g. they did not verify the conclusions falsely quoted or referred to in the report of the French CA). RAC did not extend its review sufficiently to come to an independent opinion. The Read-Across was applied without sufficient proof of the appropriateness of the Read-Across approach. The Read-Across was used to overrule the toxicological test findings despite strong evidence that the carcinogenicity of arsenicals is likely to have a threshold below which there is no carcinogenic activity.1 **2) Content of RAC opinion:** The outcome of the NTP study was only superficially reviewed and not put into a perspective. The negative genotoxicity data were not adequately considered and also not put into a perspective on the likelihood of a threshold/NOEL of the arsenic carcinogenicity. The supportive value of the epidemiological studies in the semiconductor industry was not recognized, thereby ignoring the existence of exposure data in this industry.2 The two claims that supported the rationale for the repro/fertility classification (absence of other toxic effects and accumulation in rat testis) were not checked and a wrong conclusion was taken. A plausible toxicological mode of action of the fertility effects in experimental animals at high dose levels was not recognized.3 **Availability, performance characteristics and substitution of GaAs substrates:** Gallium arsenide is a compound of the two elements, gallium and arsenic. It is a fundamental compound semiconductor material and forms a core substrate for semiconductor technology. GaAs substrates for semiconductor devices have many technical advantages compared to Silicon based semiconductor components. GaAs circuitry offers higher efficiencies and output power at lower voltages and allows better high frequency performance. GaAs devices generate ultra low noise when operated at high frequencies thus ensuring improved signal reception. They can also be operated at higher power levels than the equivalent silicon device because they have higher breakdown voltages. GaAs have a direct band gap, which means that it can be used to emit light. GaAs also demonstrate potential in opto-electronics for application in medical systems and especially in high brightness light emitting diodes (LED) and laser diodes. LED (light emitting diodes) producers use GaAs as a substrate. Due to the unique characteristics of arsenic doping chemistry there are no replacement elements for arsenic. **End applications and markets for GaAs compound semiconductor substrates:** LED's are the current and future lighting sources of most display technologies and are a key alternative to less energy efficient alternatives. The electronic properties of GaAs circuitry enable its use in most mobile phones for power amplifiers and switches. GaAs is also commonly used in satellite communications, microwave point-to-point links. All these specific technical aspects of GaAs ensure improved material and energy efficiency, whilst ensuring quality and high performance products for the final consumer. GaAs devices are also inevitable for modern sensor systems based on radar and/or radiometer principles. Such systems are used in automotive and other transport environments to increase safety for passengers and other traffic participants. Furthermore, many future security systems are based on such GaAs components. **Consequences for Semiconductor Industry** It would be a serious competitive disadvantage for the German and European GaAs manufacturers to be obliged to	relevant occupational epidemiological studies that were not submitted by the dossier submitter or assessed by RAC in the opinion adopted 25 May 2010. These are now included in the opinion. Regarding your comment on toxicity to reproduction, please see response to France / Thomas Pearsall / European Photonics Industry Consortium / Industry or trade association in the beginning of this document. Several companies submitted comments in the public consultation describing the low risk in the affected industry. Classification is based on assessing the intrinsic properties of the substance, not the risk during use. For considerations on risk versus intrinsic properties please see the opinion.

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		eventually apply for an authorization for the use of GaAs based on an incorrect classification of GaAs as a CMR Substance and its inclusion in the REACH candidate list. Being aware of the ultimate goal to sunset the manufacture and use of SVHC substances in Europe this would result in a practical unavailability of GaAs substrate for the electronics, defense and military industries from European sources. The European high tech industry would be solely dependant on ready made products with GaAs inside deriving from sources like Japan and China. **Arsenic is rigorously managed in the semiconductor manufacturing environment and there is no consumer exposure** The use of arsenic as a component of GaAs in semiconductor manufacturing does not pose a threat to the human health or the environment due to the closed system manufacturing and the stringent manufacturing controls in place in semiconductor factories using GaAs. The use of GaAs as a semiconductor wafer material is stringently monitored and highly regulated. There is no arsenic exposure potential for the consumer during the use phase of the electronic product, e.g. the mobile phone. The end of life phase of the mobile phones and other electronic products are covered by the EU WEEE directive and therefore potential environmental exposure is minimized. The amount of arsenic in a semiconductor product is typically very low. Furthermore, the tiny amounts of arsenic present in the semiconductor pose no exposure risk to the consumer of the final electronic product. The arsenic is chemically bound in a crystal of GaAs or silicon. The semiconductor device is further encapsulated in a final package to both physically protect the device and to create a practical means of attaching the device to a printed circuit board. **About ZVEI** The "ZVEI - German Electrical and Electronic Manufacturers' Association" promotes the industry's joint economic, technological and environmental policy interests on a national, European and global level. The ZVEI represents more than 1,600 companies, mostly SMEs, with round about 815,000 employees in Germany in 2010, plus 600,000 employees all over the world. In 2010 the turnover was Euro 162 billion. The electrical and electronics industry is the most innovative and the second largest industry sector in Germany. 1 Dr. Ernst M. Bomhard, Comments on the RAC Opinion on Gallium Arsenide, Jan. 2011 2 Dr. Ernst M. Bomhard, *Derivation of a DNEL (Inhalation local and systemic) for Gallium Arsenide* 15 November 2010 3 Dr. Ernst M. Bomhard, *Classification of Gallium Arsenide regarding Reprotoxicity (Fertility)* 19 November 2010	
19/04/2011	Belgium / Shane Harte / European Semiconductor Industry Association (ECCA-ESIA_ / Industry or trade association	ESIA input on the proposed harmonised classification and labelling of Gallium Arsenide of carcinogenicity category 1A 19/4/2011 Please find enclosed European Semiconductor Industry Association's (ESIA) new and relevant information to the ECHA public consultation on the proposed harmonised classification and labelling of Gallium Arsenide (GaAs) of carcinogenicity category 1A. ESIA would like to underline the imperative to have a thorough and scientifically based harmonized classification and labelling assessment process for GaAs and for any other substance that undergoes this process under the new REACH regulation. ESIA has concerns on the methods used by the committee for risk assessment (RAC) to come to the	Thank you for your comments. RAC is aware that gallium arsenide is the only arsenic compound tested in a long term animal study by inhalation. Available animal data on gallium

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		opinion of carcinogenicity category 1A for GaAS on May 25th 2010. The use of the 'read across' method in this instance would appear to be applied without clear evidence of the adequate nature of the read across approach. The specific substance properties for gallium arsenide outlined in the US National Toxicology Programme study dossier were essentially overlooked in favour of a 'read across' method to to a well-known carcinogenic Arsenic (As) species. The RAC opinion appears to have failed to have comprehensively evaluated the complete dataset on GaAs and the issue of the carcinogenicity of As. The RAC opinion mentions that the "evaluation of carcinogenic effects of gallium arsenide solely based on results from animal studies is insufficient, especially since animals are less sensitive than humans to the carcinogenic effect of arsenic." Therefore the RAC decided to include information from human studies on arsenic compounds listed as carcinogens in category 1A in CLP Annex VI and apply read-across to GaAs. It was further stated that "a read-across approach is further supported by toxicokinetic data describing the formation of similar arsenic metabolites following GaAs exposure as those formed following exposure to classified arsenic compounds" and it was agreed "that the carcinogenicity of arsenic and arsenic compounds is of relevance to gallium arsenide and must be taken into account." ESIA would like to raise the following comments with regard to the issues above; animal data on GaAs exists but this information was not utilized and appears to have been overlooked by RAC; inorganic arsenicals other than GaAs have never been tested adequately for carcinogenesis, and never by the inhalation route ; the genotoxic effects of GaAs do not seem totally comparable with other arsenicals limiting the validity of the read-across and recent evaluations pointing towards a threshold for the carcinogenic effects of As were not considered by RAC. ESIA would also like to comment on the consideration of the endpoint of reprotoxic by the RAC and the process by which this view was apparently reached.Gallium arsenide was also classified for Reprotox effects based on an opinion of the French Competent Authority. This opinion does not appear to have been fully checked for validity and accuracy by the RAC committee. The original references referred to in the French submission were presumably accidentally misquoted by the submitting country. This led inadvertently to the opposite classification as that which was being indicated by the data. The issue here relates to an apparent deficiency in the assessment procedures by which the RAC committee has proofed the original evidence and papers as submitted by the competent authority. The opinion formed by the RAC for classification of GaAs into Reprotoxicity 1B – H360F are not supported by the available data. All toxicological end points must be taken into account: the reprotoxic as well as the carcinogenic end points. ESIA supports the scientific assessment and comments made by Dr. Ernst M. Bomhard.on the RAC Opinion on Gallium Arsenide Additional Relevant Supplementary Information ESIA is fully aware that this consultation relates to GaAS in the context of the RAC opinion. However in an effort to assist the ECHA authorities and the various committees in their assessment and decision making roles now and going forward in the future, the semiconductor industry feels it is important to give a clear background and a context as to how and why gallium arsenide is used by the semiconductor industry and as to why an accurate classification of GaAS is such a key issue for the semiconductor industry. Gallium arsenide is a fundamental compound semiconductor material and forms a core substrate for semiconductor technology and therefore is a major issue for the wider	arsenide was not overlooked by RAC in the opinion of 25 May 2010. However when assessing gallium arsenide RAC also took account of widely available data on carcinogenicity in humans from arsenic and arsenic compounds. Regarding your comments on read-across, please see point 1) of the Annex to RCOM (Additional response to comments). Regarding your comments on genotoxicity, please see point 2) of the Annex to RCOM (Additional response to comments). Regarding your comment on toxicity to reproduction, please see response to France / Thomas Pearsall / European Photonics Industry Consortium / Industry or trade association in the beginning of this document. Please find the response to the comments from Dr. Ernst M. Bomhard later in this document. Regarding your comment on the candidate list and

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		electronics industry. Why would a potential inaccurate classification of GaAS in the EU be such a crucial issue for the European semiconductor industry? If GaAs was to be classified as a CMR substance based on an inaccurate classification that did not consider all the relevant specific data of the substance this would inadvertently and unnecessarily restrict the sale of many GaAS based electronic products in Europe and present a serious distortion of the free movement of goods within and importation of goods into the European Union. An inaccurate classification and labeling of the substance would lead to a disproportionate administrative burden, unjustified technical measures and ultimately lead to an inadvertent deselection from the European supply chain. Electronic equipment manufacturers in many cases maintain restricted substance list and ultimately restrict CMR substances from being used and being present in semiconductor products supplied to them. An inaccurate CMR classification for GaAs would trigger a significant number of the key aspects of the REACH regulation such as a listing on the REACH candidate list based on REACH art. 59 and ultimately may lead to inclusion in REACH Annex XIV. Candidate listing will trigger communication requirements for articles (Art. 33) consisting of at least 0.1% of the substance and provision of SDS (above 0.1%). Also, if the substance is not registered by 2010, SVHCs in articles above 0.1% must be notified to ECHA as from June 1, 2011 six months after listing (Article 7 (2) REACH). The CLP process for GaAs must review and consider carefully all scientific data available today so that appropriate risk management measures can be taken along its life cycle to guarantee safe handling and disposal of the products GaAs is a part of. CLP classification should be performed on the basis of internationally recognized toxicological standards and consider the latest results of toxicological research. ESIA remains confident that the reopened consultation on GaAs will review and take into account all the relevant scientific data and trusts a scientific and transparent CLP process for GaAs will be achieved. How are GaAS used in the compound semiconductor manufacturing process? The use of arsenic as a component of GaAs in semiconductor manufacturing does not pose a threat to the human health or the environment due to the closed system manufacturing and the stringent manufacturing controls in place in semiconductor factories using GaAs. The use of GaAs as a semiconductor wafer material is stringently monitored and highly regulated. There is also no arsenic exposure potential for the consumer during the use phase of the final electronic product, e.g the mobile phone. The concentration of GaAs components in a semiconductor chip is very small The European semiconductor industry association (ESIA) was the first industry grouping to cooperate with ECHA under a joint project to outline the exposure scenarios that could potentially exist from the production of semiconductor devices (microchips). This joint report has been officially published in August 2010 and is posted under the guidance section of the ECHA website. http://guidance.echa.europa.eu/docs/other_docs/es_project_document_v5.pdf This detailed report outlines the typical semiconductor manufacturing environment in which the temperature, humidity	triggering of communication requirements please see the response to Germany / Christian Eckert / ZVEI / Industry or trade association earlier in this document. Regarding your comment on use please see response to France / Thomas Pearsall / European Photonics Industry Consortium / Industry or trade association in the beginning of this document. Assessment of the hazard properties of GaAs as a substance and risk assessment from exposure related to usage of GaAs in the microelectronic industry are different things.

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		and airborne particle contamination are strictly controlled and gives a good overview of the reference points and detailed engineered risk management measures that exist in semiconductor factories. The Fab (factory) environment is, typically thousands of times cleaner than a hospital operating room. Chemical vapors and gases are stringently controlled. In Fabs a large number of engineered Risk Management Measures (RMM) are used to prevent and control chemical release to the environment and exposure of workers. Chemical dispensing may be totally contained, equipment is enclosed and extraction removes fumes and vapors to air abatement systems such as water scrubbers or thermal oxidizers. In many cases secondary and even tertiary redundancy to controls ensure that, in the event that one control fails, other will continue to provide the necessary protection. Why are GaAs used as a core technology for a range of modern day communication applications including current and next generation mobile handsets and Wi-Fi applications, opto-electronics, and control systems? GaAs have many technical advantages which ensure a high volume demand for advanced communication systems and wireless applications in particular..The lower knee voltage of GaAs circuitry offers higher efficiencies and output power at lower voltages. It has a higher saturated electron velocity and higher electron mobility, allowing better high frequency performance. GaAs devices generate ultra low noise when operated at high frequencies thus ensuring improved signal reception. They can also be operated at higher power levels than the equivalent silicon device because they have higher breakdown voltages. GaAs have a direct band gap, which means that it can be used to emit light. GaAs also demonstrate potential in opto-electronics for application in medical systems and especially in high brightness light emitting diodes (LED) and laser diodes. LED (light emitting diodes) producers use GaAs as a substrate. LED's are the current and future lighting sources of most display technologies and are a key alternative to less energy efficient alternatives. These electronic properties of GaAs circuitry enable its use in most mobile phones for the power amplifiers and switches. GaAs are also commonly used in satellite communications, microwave point-to-point links, and some defence and radar systems. All these specific technical aspects of GaAs ensure improved material and energy efficiency, whilst ensuring quality and high performance eletronic products for the final consumer. The European semiconductor industry is always ready to outline further the risk management measures employed in our industry on the process substances used and the benefits to wider society from the use of some substances in the technologies which we create. i The European Semiconductor Industry Association's mission (ESIA) is to represent, promote and defend the vital interests of the European-based semiconductor industry and to ensure its competitiveness in the global market. The semiconductor industry provides the key enabling technologies at the forefront of the development of the Information Society. In Europe, the sector supports over 115,000 direct jobs and up to 500,000 induced jobs. With membership covering companies, national sector associations and research institutes, ESIA is the voice of the semiconductor industry in Europe. ii NTP Technical Report on the Toxicology and Carcinogenesis of Gallium Arsenide in F344/N Rats and B6C3F1 Mice (Inhalation studies), NTP TR 492, Sept. 2000	

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		iii Huff et al. Toxicol Sci 55, 2000, 17-23.	
21/04/2011	United States / Steve Aden / Avago Technologies Wireless (U.S.A.) Manufacturing Inc. / Company-Downstream user	Dr. H. Vasken Aposhian of the Department of Molecular and Cellular Biology of the University of Arizona, USA, is an internationally recognized expert in arsenic toxicology and metals toxicology whose bibliography includes over 130 published papers. Dr. Aposhian co-authored two of the papers referenced by the RAC in the background document to the RAC opinion. Dr. Aposhian prepared the attached critique of the background document to the RAC opinion. Dr. Aposhian's critique challenges the use of read across for classification of GaAs and points to serious problems in using animal data from rats. Dr. Aposhian has provided references for 16 papers which are relevant to the carcinogenicity of gallium arsenide and its metabolic products. Fifteen of the references provided by Dr. Aposhian are not listed in the references for the background document to the RAC opinion. These references have apparently not been assessed by the RAC and therefore should be considered as new information. (The original document has been uploaded to the ECHA web site for comments on the carcinogenicity of gallium arsenide, see attachment; "Reactions to and recommendations for modifying The Background document to the Opinion proposing harmonised classification and labelling at Community level of gallium arsenide"). (Filename = Dr_HV_Aposhian_Critique_of_ECHA_Background_Document.pdf) *ECHA comment: The attached document (Dr_HV_Aposhian_Critique_of_ECHA_Background_Document.pdf) is copied below.* **Reactions to and recommendations for modifying** The Background document to the Opinion proposing harmonised classification and labelling at Community level of gallium arsenide ECHA/RAC/CLH-0000000792-73-03/A1 Which was adopted 25 May 2010 **For submission to The European Chemicals Agency's, Committee for Risk Assessment, (ECHA / RAC),** Prepared by **H. Vasken Aposhian, PhD** Emeritus Professor of Molecular and Cellular Biology (active) Emeritus Professor of Pharmacology (active) Department of Molecular and Cellular LSS Bldg. RM 444 University of Arizona Tucson, AZ 85721 Office Telephone (520) 621-7565 Home Telephone (520) 299-2462 also present address until at least May 1, 2011 is 87 Atlantic Rd. Unit # 4 Gloucester, MA 01930 Home Telephone (978) 283-0961 Submitted April 18, 2011 **Table of Contents** **Page 3** Executive summary **Page 4** 1- Qualifications of H. V. Aposhian, PhD, to write this report: **Page 5** 2- The discussion of the bio-transformation of inorganic Arsenic, in the ECHA background document, (section 5.1 Toxicokinetics, including figure 3) & (section 5.7.5 Summary and discussion of carcinogenicity), does not adequately justify their use of the read across method which effectively equates GaAs to As and other As compounds. **Page 6** 3- There is published information which provides evidence that GaAs acts differently than As relative to carcinogenicity. The citations are included.	Thank you for your comments and references for 16 papers. Assessment of the hazard properties of GaAs as a substance and risk assessment from exposure related to usage of GaAs in the microelectronic industry are different things. Regarding your comments on read-across, please see point 1) of the Annex to RCOM (Additional response to comments). For RAC evaluation of Carter et al. (2003) please see point 6) of the Annex to RCOM (Additional response to comments). Regarding your comment on occupational epidemiological studies please see response to Germany / Christian Eckert / ZVEI / Industry or trade association in the beginning of this document. In addition to epidemiological studies on carcinogenicity from drinking water, references were made to

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		Page 7 4- There is published information concerning the carcinogenicity of GaAs, which is not adequately considered in the background document. The citations are included. **Page 7** 5- The rat is an atypical and very poor mammalian model for humans in As or GaAs toxicity. It is an atypical model for how the human body processes or metabolizes inorganic arsenic. The published evidence is presented and cited. **Page 9** 6- There are other factors, not considered in the ECHA background document, which should be considered for proper classification of GaAs with respect to carcinogenicity. The citations are included. **Page 9** 7- Summary of Reactions and Recommendations for modifying the ECHA/RAC Background document on GaAs**.** **Page 10** References **Page 12** APPENDIX - CURRICULUM VITAE of H. V. Aposhian, PhD. **Executive Summary** 1- The purpose of this report is to request the Committee to reconsider its May 25, 2010 report on gallium arsenide. Suggestions and recommendations are respectfully offered. 2- **The present author believes that published statements in peer-reviewed articles from various highly-regarded arsenic experts that are quoted in this present report indicate that the read across method should not be used for gallium arsenide. There is insufficient evidence to equate the different arsenic compounds.** 3- There is published information which provides evidence that GaAs acts differently than As relative to carcinogenicity. We doubt that total arsenic in all environmental arsenic exposures is representative of risk when there appear to be several different "most toxic arsenic compounds." 4- Gallium arsenide is not found in nature and should not be judged by the same drinking water exposure scenarios that are used for the inorganic arsenic oxides. 5- The rat is an atypical and very poor mammalian model for inorganic As or GaAs toxicity in humans. The published evidence is presented and cited**. Yet, the RAC Background document appears to inappropriately use the rat data especially in the example of the carcinogenicity in female rats.** 6- There are other factors, not considered in the ECHA background document, which need to be considered for proper classification of GaAs with respect to carcinogenicity. **7- Summary of Reactions and Recommendations. It appears that the RAC is completely disregarding major points cited in the Carter et al (2003) paper which is a widely quoted classic in the field of arsenic and GaAs metabolism and toxicity. Since GaAs behaves differently from other arsenic compounds, and since rats are a poor model for how the human processes arsenic, the change to a 1A recommendation is not scientifically warranted and needs to be reconsidered.** ***1- Qualifications of H. V. Aposhian, PhD, to write this report. (A complete Curriculum Vitae is in the Appendix):*** My laboratory has studied arsenic and mercury toxicology at the basic animal and cellular level as well as in human populations in rural areas of Chile, Inner Mongolia, Mexico, Romania, China and the United States. My research on arsenic and mercury during this 33 year period at the University of Arizona was supported, financially and generously by competitively awarded grants from the Department of Defense (DOD), National Institutes of Health (NIH) and various private foundations. The results of this extensive research have been published in international peer-reviewed scientific journals. One of my publications has been designated as the most downloaded paper of the month by the	occupational epidemiological studies from smelters (via inhalation) in the RAC opinion adopted 25 May 2010. In both drinking water and in smelters, exposure would ultimately lead to similar metabolites as following exposure to gallium arsenide. The read-across was based on this, please see point 1) of the Annex to RCOM (Additional response to comments). You question the RAC conclusion of the NTP study from 2000. A recent paper by Tokar et al. (2010) was also submitted in the public consultation. This paper supports the conclusions from the rat study (NTP, 2000) and consequently strengthens our previous conclusion on the NTP study in the RAC opinion of 25 May 2010. The relevance of data from animal studies on arsenic and arsenic compounds is further discussed in the Tokar paper (Tokar et a., 2010).

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		pre-eminent Toxicology journal, Chemical Research in Toxicology. At any given time, my laboratories usually had as many as 12 people who were predoctoral students, postdoctorals, research assistants, senior investigators and/or Institute heads from the United States, Mexico, Austria, Czechoslovakia, China, the Soviet Union, Egypt, Romania and other countries. They were in my lab group for educational and/or research purposes dealing with heavy metal toxicology. I have been a consultant for the NIH, EPA, FDA, and various multinational pharmaceutical organizations. In 1959, I was awarded the first United States Public Health Senior Research Fellowship to work with Nobel Laureate Dr. Arthur Kornberg, Professor and Chairman of the Department of Biological Chemistry, Stanford University College of Medicine. The purpose of this competitively awarded fellowship was to give me the opportunity to learn modern approaches to research and to utilize them by doing research under Professor Kornberg's direction. I did this with him for 3 years. I have been Associate Professor of Microbiology, Tufts University Medical School, and Professor (and for a number of years Head) of the Pharmacology Department at University of Maryland Medical School. From 1975 to 2008, I was Professor in the Department of Molecular and Cellular, College of Science and Professor in the Pharmacology Department of the College of Medicine of the University of Arizona including a stint as Department Head. A Curriculum Vitae is in the appendix of this report. A recent review article *Arsenic toxicology: five questions* has been well received and extensively quoted (Aposhian H.V., and M.M. Aposhian. 2006.) . **The following comments regard the *ECHA background document on Gallium Arsenide.*** Authoritative statements written by arsenic research experts in articles published in first-rate peer-reviewed international journals have been included and quoted to support the major points the author wishes to bring to the attention of the Committee. There is some redundancy in the present report since published statements from the peer-reviewed literature have been requoted in subsequent sections to support the main statements of that section. ***2- The discussion of the bio-transformation of inorganic Arsenic, in the ECHA background document, (section 5.1 Toxicokinetics, including figure 3) & (section 5.7.5 Summary and discussion of carcinogenicity), does not adequately justify their use of the read across method which effectively equates GaAs to As and other As compounds.*** The three major research laboratories dealing with the metabolism of inorganic arsenic for at least the last 10 years have been the Aposhian lab at University of Arizona, the Vahter lab at the Karolinska Institute, and the Thomas,EPA –Styblo, University of North Carolina collaborating labs. A major contention of the present report is that **the ECHA background document, (section 5.1 Toxicokinetics, including figure 3) & (section 5.7.5 Summary and discussion of carcinogenicity), does not adequately justify their use of the read across method. The evidence for this contention is as follows:** As an established expert in human arsenic metabolism (please see publication list in CV Appendix) it is my opinion that the read across method is not appropriate for gallium arsenide. It is pertinent to note that Figure 3 of the ECHA background document was as stated "adapted from Zakharyan et al (2001)". The Zakharyan et al (2001) paper was from the present author's laboratory. The present author points this out to assure the readers that he is very knowledgeable about inorganic arsenic metabolism, especially as far as the human is concerned. The present author would also like to note that the late Professor D. M. Carter, was the pre-eminent authority on gallium arsenide toxicology and was the first author of the Carter et al. (2003) paper that is quoted extensively in this report and elsewhere.	

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		Carter et al. (2003) in Abstract on page 309 state that "The urinary metabolites after GaAs exposure were the same as excreted by arsenic oxides but the chemical compounds responsible for the toxic effects of GaAs are different from the arsenic oxides. The review concludes that **there is insufficient evidence to equate the different arsenic compounds."** *[bold type added by present author]* Carter et al (2003) on page 326 states that The toxicity of gallium appears to be limited by its solubility and by the solution composition of materials that could bind or solubilize gallium. The toxicity of arsenic appeared to depend on the species formed during dissolution: arsine, arsenious acid, or arsenic acid. **It is clear that highly insoluble arsenide semiconductors were less acutely toxic than equal amounts of arsine or their more soluble arsenious acid products.** *[bold type added by present author]* In the" Derivation of a DNEL (Inhalation local and systemic) for Gallium Arsenide" prepared by Dr. Ernst M. Bomhard that has been submitted to the ECHA, it is stated on page 16 In GaAs production both Ga and As internal exposure is generally very low owing to the generally low ambient air concentrations (sophisticated technical installations, low level of respirable particles and personal protection measures). There are only a few workplaces or operations where the mean air concentrations have exceeded the limit of 10 µg As/m3, the Threshold Limit Value in the US since 1993. As yet no clinical signs, neither respiratory symptoms nor skin changes, reportedly the most sensitive and early indicators of As exposure in the low dose range (Ahsan et al. 2006; Parvez et al. 2010) have obviously been observed at these exposure conditions. The lack of clinical symptoms in workers exposed for many years argues against an accumulation potential of As or Ga in people involved in GaAs production and processing. Several large epidemiological studies in the semiconductor industry did not reveal increased cancer risks attributable to the As exposure despite the fact that the As exposure there is usually higher than in GaAs production and use (Bender et al.2007; Beall et al. 2005; Boice et al. 2010; Darnton et al. 2010; Nichols und Sorahan.2005). With one exception exposure to Ga has not been measured. In these studies clinical findings are not mentioned suggesting that at least obvious findings such as skin changes were absent. Carter et al (2003) on page 323 states that "……arsine and gallium arsenide, [that] are in widespread use in the microelectronics industry. These two arsenic compounds are not found in nature and **should not be judged by the same drinking water exposure scenarios that are used for the inorganic oxides**." *[bold type added by present author]* **Thus the present author believes that the above quotes from various highly regarded authorities indicate the use of the read across method should not be used for gallium arsenide.** ***3- There is published information which provides evidence that GaAs acts differently than As relative to carcinogenicity.*** Carter et al. in Abstract on page 309 state that "The urinary metabolites after GaAs exposure were the same as excreted by arsenic oxides but the chemical	

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		compounds responsible for the toxic effects of GaAs are different from the arsenic oxides. **The review concludes that there is insufficient evidence to equate the different arsenic compounds."** *[bold type added by present author]* Also Carter et al., in page 310 state that "There is one major question that should be asked before the standards for industrial exposure are revised. Can the results used for the drinking water standards of environmental arsenic compounds be extrapolated to industrial inhalation exposures for the important arsenic compounds used in industry? The drinking water standard did not analyze individual arsenic compounds separately. **We doubt that total arsenic in all environmental arsenic exposures is representative of risk when there appear to be several different "most toxic arsenic compounds."** *[bold type added by present author]* **The present author believes that the above quotes from various highly regarded authorities provide evidence that GaAs acts differently than As relative to carcinogenicity.** ***4- There is published information concerning the carcinogenicty of GaAs, which is not adequately considered in the background document.*** The reader is referred to Section 5.7.4. Carcinogenicity: human data of the RAC's Background Document on Gallium Arsenide. Page 31 of the report states In March 2009 IARC reconfirmed the classification of arsenic and inorganic arsenic compounds as "carcinogenic to humans" (group 1). The working group made the overall evaluation on a group "arsenic and inorganic arsenic compounds" rather than on some individual arsenic compounds, based on the combined results of epidemiological studies, carcinogenicity studies in experimental animals, and data on the chemical characteristics, metabolism and modes of action of carcinogenicity. **BUT** **Again the above are in direct disagreement to clear statements in the widely quoted GaAs review article by Carter et al., (2003).** Carter et al. (2003) in Abstract on page 309 state that "The urinary metabolites after GaAs exposure were the same as excreted by arsenic oxides but the chemical compounds responsible for the toxic effects of GaAs are different from the arsenic oxides. The review concludes that **there is insufficient evidence to equate the different arsenic compounds."** *[bold type added by present author]*. Thus, the statement from the RAC report "The working group made the overall evaluation on a group "arsenic and inorganic arsenic compounds" rather than on some individual arsenic compounds." is certainly not what authors of the major, widely-acclaimed review article *The metabolism of inorganic arsenic oxides, gallium arsenide and arsine: a toxicochemical review (*Carter et al., 2003) have emphasized and stated very clearly and what experts in arsenic toxicology believe In addition the RAC report states its decision on carcinogenicity is "based on the combined results of epidemiological	

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		studies, carcinogenicity studies in experimental animals, ……arsine and gallium arsenide, ... " Again Carter et al (2003) clearly state "These two arsenic compounds [arsine and gallium arsenide] are not found in nature and **should not be judged by the same drinking water exposure scenarios** *that are used for the inorganic oxides." [bold type added by present author]*. The majority if not all the epidemiological data on arsenic carcinogenicity is based on drinking water. The RAC report does not indicate that. Finally, as shown in the next section acknowledged experts in arsenic research do not use the rat to study arsenic toxicology since the rat is an atypical and a very poor mammalian model for humans when considering As or GaAs toxicity. Yet, the RAC report on page 30 states there is clear evidence for carcinogenicity based on the rat studies. **The present author believes that the above quotes from various highly regarded authorities provide evidence that there is published information concerning the carcinogenicity of GaAs, which is not adequately considered in the background document.** ***5- The rat is an atypical and very poor mammalian model for humans in As or GaAs toxicity.*** ***The published evidence is presented and cited:*** **The rat is an atypical model for how the human body processes or metabolizes inorganic arsenic. (**Please see below for literature citations.) Thus, it is surprising that the rat was used exclusively in 8 of the 11 examples on pages 8 to 11 of Section *5.1* "Toxicokinetics (absorption, metabolism, distribution and elimination) of the Committee for Risk Assessment RAC Annex 1, Background document to the Opinion proposing harmonised classification and labelling at Community level of gallium arsenide." It seems unwise to ignore the opinions of highly recognized experts in the areas of arsenic metabolism and toxicology. Some of them are the late Dr. Dean Carter, of The University of Arizona, the world's preeminent authority on gallium arsenide toxicology and biology; Dr. Marie Vahter of the Karolinska Institute a pioneer in modern inorganic arsenic toxicology; Dr. H. Vasken Aposhian of the University of Arizona. The latter two investigators were major contributors and wrote a number of the chapters to the 1999 monograph *Arsenic in Drinking Water* published in 1999 by the National Research Council/the U.S. National Academy of Sciences. Other experts are Dr. David Thomas, EPA, and Dr. Allan H Smith of the University of California at Berkeley. As stated in *Arsenic in Drinking Water* published in 1999 by the National Research Council/the U.S. National Academy of Sciences: Page 155 "The rat also methylates inorganic arsenic efficiently, but a major portion of the DMA produced is retained in the erythrocytes (Odanaka et al. 1980; Lerman et al. 1983), giving rise to a slow urinary excretion of DMA and **a tissue-distribution pattern that is different from that in most other species** (Vahter et al. 1984). **In addition, the rat shows an extensive biliary excretion of arsenic, about 800 and 37 times more than the dog and rabbit, respectively** (Klaassen 1974)." (bold type made by present author) Page 160 **"In the rat, arsenic is retained in the blood considerably longer than in other species** because of the accumulation of DMA in the red blood cells, apparently bound to hemoglobin (Odanaka et al. 1980; Lerman and Clarkson 1983; Vahter 1983; Vahter et al. 1984). The accumulation of arsenic in the rat erythrocytes was first reported	

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		more than 50 years ago (Hunter et al. 1942)." (bold type made by present author) Carter et al. 2003 clearly state on Page 315- "*Human data and animal data* **"It is not possible to use animal data as a model for humans or for the rat to serve as a model for other laboratory animals.** It was a surprise when the results from long- term animal studies did not model humans. …… **The problem with early data from animals was that rats were used.** Previous scientific committees have stated that they did not recommend rats for arsenic oxide disposition studies." (bold type made by present author) Carter et al. 2003 page 325 state that "The 2-year exposure showed increased alveolar/ bronchiolar neoplasms in female rats. This finding is important and the lung appears to be acting as a point of contact toxicant for particles. **Unfortunately, the rat is not recommended for arsenic studies;** only the females responded and there were no other As or Ga species tested for comparison." (bold type made by present author.) The reader is also referred to *Vahter, M. 1994. Species differences in the metabolism of arsenic compounds. Appl. Organomet. Chem. 8: 175-182.* **All of the above are some of the reasons why acknowledged experts in arsenic research do not use the rat to study arsenic toxicology and why the rat is an atypical and a very poor mammalian model for humans when considering inorganic As or GaAs toxicity.** ***6- There are other factors, not considered in the ECHA background document, which should be considered for proper classification of GaAs with respect to carcinogenicity.*** The ECHA background document quotes epidemiology data concerning the carcinogenicity of inorganic arsenic – mainly arsenite in drinking water. GaAs is not naturally occurring and as Toxicology experts in the arsenic area believe **GaAs should not be judged by the same drinking water exposure scenarios that are used for the inorganic oxides in drinking water.** Carter et al (2003) on page 323 states that "……arsine and gallium arsenide, [that] are in widespread use in the microelectronics industry. These two arsenic compounds are not found in nature and **should not be judged by the same drinking water exposure scenarios** *that are used for the inorganic oxides* [font made bold by current author]. Carter et al. on page 310 state that "There is one major question that should be asked before the standards for industrial exposure are revised. Can the results used for the drinking water standards of environmental arsenic compounds be extrapolated to industrial inhalation exposures for the important arsenic compounds used in industry? The drinking water standard did not analyze individual arsenic compounds separately. **We doubt that total arsenic in all environmental arsenic exposures is representative of risk when there appear to be several different "most toxic arsenic compounds."** [font made bold by current author].	

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		Carter et al. 2003 page 325 state that "The 2-year exposure showed increased alveolar/ bronchiolar neoplasms in female rats. This finding is important and the lung appears to be acting as a point of contact toxicant for particles. Unfortunately, the rat is not recommended for arsenic studies; **only the females responded and there were no other As or Ga species tested for comparison**." [font made bold by current author]. ***7- Summary of Reactions and Recommendations for modifying the ECHA/RAC Background document on GaAs.*** **When all the points made in this paper are considered together, the logical conclusion would be to delay a premature classification of GaAs since it is not supported by solid scientific knowledge. Finally, it seems as though the RAC is completely disregarding major points cited in Carter et al (2003). The paper is a widely quoted classic in the field of arsenic and GaAs metabolism and toxicity. Since GaAs behaves differently from other arsenic compounds, and since rats are a poor model, the change to a 1A recommendation needs to be reconsidered.** **References** Ahsan et al. Arsenic exposure from drinking water and risk of premalignant skin lesions in Bangladesh: baseline results from the Health Effects of Arsenic Longitudinal Study. Am J Epidemiol 163, 2006, 1138-1148. Aposhian H.V., and M.M. Aposhian. 2006. Arsenic toxicology: five questions. Chemical. Research in Toxicology 19: 1-15. Beall et al. Mortality among semiconductor and storage device-manufacturing workers. J Occup Environ Med 47, 2005, 996-1014. Bender et al. Cancer incidence among semiconductor and storage device workers. Occup Environ Med 64, 2007 30-36. Boice et al. Cancer mortality among US worker employed in semiconductor wafer fabrication. J Occup Environ Med 52, 2010, 1082-1097. Carter, D. E., Aposhian, H. V., and Gandolfi, A. J. (2003). The metabolism of inorganic arsenic oxides, gallium arsenide and arsine: a toxicochemical review. *Toxicol and Applied Pharmacol*, *193*, 309-334. Darnton et al. A further study of cancer among the current and former employees of National Semiconductor (UK) Ltd., Greenock. Health and Safety Executive, UK 2010. Hunter F.T., A.F. Kip, and J.W. Irvine. 1942. Radioactive tracer studies on arsenic injected as potassium arsenite. J. Pharmacol. Exp. Ther. 76:207220 Klaassen, C.D. 1974. Biliary excretion of arsenic in rats, rabbits and dogs. Toxicol. Appl. Pharmacol. 29: 447-457. Lerman, S., and T.W. Clarkson. 1983. The metabolism of arsenite and arsenate by the rat. Fundam. Appl. Toxicol. 3:309-314. Nichols und Sorahan. Cancer incidence and cancer mortality in a cohort of UK among semiconductor workers. Occup Med 55, 2005, 625-630. Odanaka, Y., O. Matano, and S. Goto. 1980. Biomethylation of inorganic arsenic by the rat and some laboratory animals. Bull. Environ. Contam. Toxicol. 24: 452-459. Parvez et al. A prospective study of respiratory symptoms associated with chronic arsenic exposure in Bangladesh: findings from the Health Effects of Arsenic Longitudinal Study (HEALS). Thorax 65, 2010, 528-33.	

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		Vahter, M. 1983. Metabolism of Inorganic Arsenic in Relation to Chemical Form and Animal Species. Doctoral Thesis. Karolinska Institutet, Stockholm. Vahter, M., E. Marafante, and L. Dencker. 1984. Tissue distribution and retention of 74As-dimethylarsinic acid in mice and rats. Arch. Environ. Contam. Toxicol. 13:259-264 Vahter, M. 1994. Species differences in the metabolism of arsenic compounds. Appl. Organomet. Chem. 8: 175-182. **APPENDIX** CURRICULUM VITAE November 2011 **H. Vasken Aposhian, PhD** **Emeritus Professor of Molecular and Cellular Biology (active), College of Science** **University of Arizona** **Emeritus Professor of Pharmacology (active), College of Medicine University of Arizona** ***Addresses*** **LSSB Rm 444** **The University of Arizona** **PO BOX 210106** **Tucson, AZ 85721-0106** **Telephone: 520-621-7565 (Tucson, AZ)** **Also:** **Tucson, AZ home** **Telephone 520-299-2462** **and** **87 ATLANTIC RD, Unit # 4** **GLOUCESTER, MA 01930** **Telephone: 978-283-0961** Place of Birth: Providence, RI **Education** M.S. University of Rochester, 1950 (Physiological Chemistry) Ph.D. University of Rochester, 1953 (Physiological Chemistry) Advanced Training: Department of Biochemistry, Stanford University School of Medicine (with Nobel Laureate Dr. Arthur Kornberg), 1959-1962 Department of Biology, Massachusetts Institute of Technology (with Dr. Paul Schimmel) -- six-month sabbatical, January 1-June 30, 1983 Department of Biology, University of California, San Diego -- six-month sabbatical as Visiting Scholar, June 1-	

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		December 30, 1990 **Positions Held** 1954-56 Instructor, Department of Pharmacology, Vanderbilt University School of Medicine 1956-59 Assistant Professor, Department of Pharmacology, Vanderbilt University School of Medicine 1959-62 USPHS Senior Research Fellow, with Nobel Laureate Arthur Kornberg Department of Biochemistry, Stanford University School of Medicine 1962-67 Associate Professor, Department of Microbiology, Tufts University School of Medicine 1966-72 Professor and Head of Department, 1966-72, Department of Cell Biology and Pharmacology, University of Maryland School of Medicine. 1972-75 Professor, Department of Cell Biology and Pharmacology, University of Maryland School of Medicine. 1975-2008 Professor, Department of Pharmacology, College of Medicine, University of Arizona 1975-83 Professor, Department of Cellular and Developmental Biology, College of Liberal Arts, University of Arizona. (Head of Department, 1975-79) 1983 Visiting Professor, Department of Biology, Massachusetts Institute of Technology (January 1, 1983-June 30, 1983) 1983-2008 Professor, Department of Molecular and Cellular Biology, College of Science, University of Arizona 1990 Visiting Scholar University of California, Sa Diego 2008 Emeritus Professor of Molecular and Cellular Biology (active), College of Science, University of Arizona Emeritus Professor of Pharmacology (active), College of Medicine, University of Arizona **Research Interests** 1. Arsenic detoxification and intoxication: molecular mechanisms, human and animal studies. 2. Metal toxicity and mechanisms of intoxication of arsenic, mercury, lead, and manganese, polymorphisms involved; human and animal studies. 3. Biological chelation: Use of chelating agents DMPS and DMSA as a challenge test for mercury, arsenic and lead. 4. DNA and gene delivery systems for mammalian cells and intact animals. 5. Pseudovirions. 6. Autism **Professional Societies** Society for Toxicology American College of Toxicology American Society of Biological Chemistry and Molecular Biology American Society of Microbiology American Society for the Advancement of Science, Fellow New York Academy of Sciences American Society for Pharmacology and Experimental Therapeutics (resigned 1976) American Academy of Microbiology	

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		American Association of University Professors **Awards or Honors** 1959-64 USPHS Senior Research Fellowship (resigned 1962) 1959 Jane Coffin Child Fellowship (declined) 1972 Sigma Xi Annual Award for Scientific Achievement, Maryland Chapter 1974 Student Council Award for Excellence in Teaching, University of Maryland School of Medicine 1977 Invited Guest, Soviet Academy of Science, June, 1977 1977 Invited Lecturer, Al-Hazen Research Institute, Baghdad, Iraq, May, 1977 1981 Invited Speaker, Korean Biochemical Society 1985 National Academy of Science (U.S.) - Soviet Union Academy of Science Exchange Fellow for September, 1985, in Soviet Union 1985 Official Guest of Peoples' Republic of China, Academy of Science, Lecture Tour, October, 1985 1996 Official Guest of Peoples' Republic of China, Academy of Science, Evaluation of arsenic problem in Guizhou Province, November, 1996 1998 Official Guest of Peoples' Republic of China, Academy of Science, Evaluation of arsenic problem in Autonomous Region of Inner Mongolia, November, 1996 1999 Official Guest of Peoples' Republic of China, Academy of Science, Treatment of arsenic problem in Guizhou Province. **National Service (only a few are listed)** 1968-2004 Member of various ad hoc study sections, National Institutes of Health especially for the National Institute for Environmental Health Sciences. 1970-78 Member of ad hoc committees for cancer programs and cancer construction programs of the National Cancer Institute. 1971 Consultant to National Cancer Institute Planning Session, Airlie Conference Center. 1972 Advisor on gene technology to U.S. Senator J.V. Tunney. U.S. Environmental Protection Agency, Mercury Advisory Committee. 1971-73 American Cancer Society, Maryland Division - Member, Board of Directors. 1971-72 American Cancer Society, Maryland Division -Chairman Grants Committee. 1989- Consultant For Various Multinational Pharmaceutical, Consumer-Goods And Life Science Companies. 1990 Lecturer - Continuing Education Committee, Society of Toxicology. 1993 Councilor - Metal Section, Society of Toxicology. 1993 Super Fund - Agenda Workshop for Biodiversity Toxicology of Children, for the National Institute for Environmental Health Sciences. 1995 WAARF Arsenic Research Priority Planning Meeting,-- Mechanisms Section Chairman. 1995 WAARF Arsenic Grant Application Study Section. 1997-98 National Research Council, Committee on Toxicology, Subcommittee on Arsenic in Drinking Water, member. Author and coauthor of a number of chapters in *Arsenic in Drinking Water*- NRC monograph 1997 EPA Working Committee on Arsenic Carcinogenesis. 1998 NIEHS Methylmercury evaluation group.	

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		1998 Mercury toxicity. Presentation to Committee On Government Reform, House of Representatives, Congress of the United States 1998 Cure Autism Now, Research Grant Committee 1999-2000 National Research Council, Committee on Toxicology, Committee on Mercury Toxicity, member. Author of toxicology chapter on methyl mer-cury in *Toxicology Of Methyl Mercury* - NRC monograph 2004 Invited presentation to Vaccine Committee of Institute of medicine, NRCOM entitled: *A Toxicologist's View of Autism and Thimerosal* 2005-2006 EPA, Arsenic Study Committee June 2007 Invited Testimony as expert witness before the US Federal Vaccine Court on first trial dealing with Thimerosal and Autism May 2008 Invited Testimony as expert witness before the US Federal Vaccine Court on second trial on Thimerosal and Autism I have been engaged as an expert witness for a number of legal cases. Most of them were settled out of court. The most recent testimony before a court was in Nova Scotia during April 2009 dealing with heavy metal poisoning of a dental surgeon exposed during major hospital renovations. **The above is not a complete list** *International Service* 1992-2006 Research and Scientific Evaluations of Arsenic, Mercury and Other Toxic Chemicals for National Governments. 1992 Metal Toxicology Workshop for Physicians, Taipei Veterans Hospital Center, Taiwan. 1993 Superfund Workshop, Campaigne de Madonna, Italy. 1993 Mercury Levels in Mexican Dental and Tampico Factory workers. 1994 German Government Metal Toxicology Workshop. 1994 Arsenic Toxicity in Chile. 1994 Hg Toxicity in Denmark. 1996 Arsenic toxicity in China. 1998 Arsenic toxicity in Inner Mongolia. 1999 Arsenic toxicity in China. 1999 Arsenic toxicity in Romania 2000 Lead, cadmium and arsenic toxicity in children in Torreon, Mexico 2003 WHO workshop on Child Health in Southeast Asia (Bangladesh) 2003 US-Japan meeting on arsenic (by invitation only) 2006 International Conference of Chelating Agents, Advisory Board **The above is not a complete list** **University of Arizona Service** 1976-79 University Advisory Committee on Promotion and Tenure. 1975-79 Biomedical Support Research Grants Committee.	

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		1975-77 Executive Committee, Cancer Center. 1979 Search Committee, Biochemistry Head. 1977-85 University Committee to review DNA recombinant research. 1978 Toxicology Program - Member of Executive Committee. 1979-85 Graduate Council - Chairman, Student Affairs Subcommittee; Petitions Subcommittee. 1987 Toxicology Faculty Search Committee, College of Pharmacy. 1988 Molecular and Cellular Biology Faculty Search Committee, College of Arts and Sciences. 1991-95 Chairman, Biomedical Group for Superfund Center. 1992 Member of committee to review College of Medicine Molecular and Cellular Biology course. 1993 Chairman of committee for five-year review of Department Head. 1994 Environmental Quality Committee. 1995 Medical School Neurosciences Review Committee. 1995 Chairman, Departmental Promotion and Tenure Committee. 1998 College of Science, Promotion and Tenure Committee. **State of Arizona Service** 1989-92 Commissioner, Structural Pest Control Commission, State of Arizona. *Grant Support the year immediately before retirement in 2008* NIEHS Superfund Project, *In vivo* and *in vitro* metabolism of arsenic. Autism Research Institute, Autism Biomarkers. Wallace Research Foundation, Mercury and arsenic toxici**ty** **Other** Paid consultant at various times for various multinational pharmaceutical or consumer product companies. **Bibliography** GaAs (Does not include over 100 abstracts of papers presented at international or national meetings or seminars and lectures given at various institutions.) Chowdhury UK, and Aposhian, HV. Protein Expression in The Livers and Urinary Bladders of Hamsters Exposed to Sodium Arsenite Using Fluorescence Difference In Gel Electrophoresis. Submitted Aposhian M. M.; I. Koch; M. D. Avram; U. K. Chowdhury; P. G. Smith; K. J. Reimer; H. V. Aposhian. Arsenic in Ironite fertilizer: The absorption by hamsters and the chemical form.Toxicological & Environmental Chemistry, 91, 1115 – 1124, 2009, Chowdhury UK and Aposhian HV Protein expression in the livers and urinary bladders of hamsters exposed to sodium arsenite., Ann N Y Acad Sci, Oct 2008; 1140: 325-34. Aposhian HV and Aposhian MM. Arsenic Toxicology: Five Questions**.** Chem Res Toxicol 19:1-15 (2006). (**Most downloaded paper of the year for this journal)** . Chowdhury, U.K. , Zakharyan, R.A., Hernandez, A. *et al.* 2006. Glutathione-S-transferase-omega [MMA(V) reductase] knockout mice: Enzyme and arsenic species concentrations in tissues afterarsenate administration. Toxicol. Appl. Pharmaol. **216:** 446-457. Zakharyan RA, Tsaprailis G, Chowdhury UK, Hernandez A, and Aposhian HV. Interactions of Sodium Selenite,	

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21/04/2011	United States / John Sharp / TriQuint Semiconductor, Inc. / Company-Manufacturer	*ECHA comment: The attached document (TriQuint Comments on GaAs Carc Classification_20-Apr-2011.pdf) is copied below.* European Chemicals Agency Annankatu 18, P.O. Box 400 Fl-00121 Helsinki, Finland Greetings: TriQuint Semiconductor, Inc. is pleased to offer the following comments on the Proposal for Harmonised Classification and Labelling of Gallium Arsenide submitted by France. TriQuint Semiconductor designs, develops and manufactures advanced high-performance RF solutions with Gallium Arsenide (GaAs), Gallium Nitride (GaN), Surface Acoustic Wave (SAW) and Bulk Acoustic Wave (BAW) technologies for customers worldwide. We are a leader in market diversity serving customers in mobile devices, 3G and 4G cellular base station, WLAN, WiMAX, GPS, defense and aerospace markets. An important part of the electronics supply chain is the semiconductor industry, which provides all printed boards and electronics assemblies with components needed for a product to function properly. Gallium arsenide is an essential chemical used in the manufacture of component chips that are necessary for all electronics products. We understand that gallium arsenide is a toxic chemical, however, the studies used to justify the classification of gallium arsenide as carcinogenic category 1A (CLP Regulation) are out-of-date and utilize exposure scenarios that are unrealistic and unlikely to occur. Herewith, we offer our comments on the Carcinogenicity classification and the “read across” method that was used to reach the Carcinogenicity classification. Signed for and on behalf of TriQuint Semiconductor, Inc.: Date: 20-Apr-2011 John Sharp Corporate Product Compliance Manager **Gallium Arsenide** **Position of TriQuint Semiconductor, Inc. on the Opinion of the Committee for Risk Assessment proposing harmonized classification and labeling at the EU level for GaAs adopted 25 May 2010**	Thank you for your comments. RAC agrees with IND who claims that the spontaneous incidence of mononuclear-cell leukemia (MCL)1 in Fischer F344 rats is so high that this effect should be disregarded. Please see the opinion (of 1 December 2011). Regarding your comments on no threshold, please see point 1) of the Annex to RCOM (Additional response to comments). EPA guidelines for carcinogen risk assessment (2005) apply the Margin of Exposure approach. Classification is an assessment of the intrinsic properties of the substance, not the risk at use. For considerations on risk versus hazard please see BD to the opinion. Regarding your comments on read-across, please see point 1) of the Annex to

[1] synonyme LGLL (Large Granular Lymphocyte Leukemia)

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		Executive Summary TriQuint Semiconductor, Inc., based on scientific and legal advice, submits that the Opinion of May 25, 2010 of the Risk Assessment Committee on the proposal for the classification of Gallium Arsenide (GaAs) as Carc. Cat. 1A is not supported by the most recent scientific data. TriQuint urges RAC to correct its opinion on the classification and labeling of gallium arsenide. Specifically, TriQuint requests the RAC to respond to the following with supporting data: 1. The most recent papers cited in the IARC monograph (with the exception of the NTP (2000) study), unequivocally state that the various arsenic species with their different valence states need to be considered separately. It is not possible to extrapolate from one species of arsenic compound to another, without a detailed review of the chemistry. 2. The NTP (2000) study shows incidence of carcinogenicity only to female Fischer F344 rats and not to male Fischer F344 rats, nor to mice (male or female), nor to male hamsters. Detailed studies have shown that the F344 strain of rat is especially sensitive to spontaneous incidence of MCL, and that rate of incidence has steadily increased since the 1970s to levels that are shown in the NTP (2000) study. Studies that show evidence of MCL to only female rats of this strain are not sufficient evidence of carcinogenicity. 3. The most recent research does not support a linear extrapolation relating arsenic exposure to carcinogenic potential. There is no basis for the rapporteurs' contention that because gallium arsenide can presumably be metabolized to DMAV, gallium arsenide should be classified as a Carcinogen 1A. There is also no data supporting the rapporteurs' contention that there is no threshold level for gallium arsenide exposure or exposure to DMAV. The studies cited by the rapporteurs are out of date, as EPA has now changed to using a Margin of Exposure (MOE) process, which shows that DMAV is highly unlikely to be of toxicological concern at plausible human exposures. 4. The rapporteurs did not perform a proper "read across" process. They did not analyze the physicochemical characteristics of the analogues they chose to compare to gallium arsenide. They did not perform any of the subsequent steps to properly use the readacross method that are recommended in the OECD (2007) guidance document on the grouping of chemical substances. In addition, the papers that are being cited by the rapporteurs as evidence that gallium arsenide is carcinogenic do not support such a classification. The authors of these papers uniformly think that gallium arsenide is much less toxic than the inorganic arsenic oxide compounds that the rapporteurs have chosen to read-across from. **Part I: The RAC opinion and its basis** The RAC has adopted the opinion that gallium arsenide should be classified and labelled as follows: **Classification & labelling in accordance with the CLP Regulation:** Carc. 1A - H350 Repr. 1B - H360F3 STOT RE 1 - H372, **Specific concentration limits:** None	RCOM (Additional response to comments). This includes referral to the approch in the OECD Guidance on Grouping of Chemicals that you applied in your comments. Regarding your comments on the Carter paper (Carter et a., 2003), please see point 6) of the Annex to RCOM (Additional response to comments). Regarding your comments on the IARC classification on DMA in Group 2B, please also note that IARC has classified gallium arsenide in Group 1 (carcinogenic to humans). Response to comments from Dr. H.V. Aposhian is given above in the response to United States / Steve Aden / Avago Technologies Wireless (U.S.A.) Manufacturing Inc. / Company-Downstream user. Regarding your comments to the BD and the semiconductor industry in 1981, we agree that the numbers were out of date

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		M-factors: None **Notes:** None **Labelling: GHS08**, **GHS09; Dgr; H350** May cause cancer, **H360F** May damage fertility, **H372** Causes damage to the respiratory and haematopoietic system and testes through prolonged or repeated exposure. From the RAC Opinion: None of the epidemiological studies of cancer in the semiconductor industry were informative with regard to GaAs. The dossier submitter has presented robust 105 weeks inhalation studies in rats and mice (NTP, 2000) and a 15 weeks intratracheal instillation study in hamster (Ohyama et al., 1988). Gallium arsenide was carcinogenic only in female rats after inhalation. This was observed as alveolar/bronchiolar adenoma or carcinoma. The dossier submitter had proposed that gallium arsenide was to be classified as Carc Cat 3 (Directive 67/548/EEC) based on the animal studies. In the public consultation a wish to classify gallium arsenide in agreement to IARC (group 1), proposing Carc Cat 1 instead of Carc Cat 3 (Directive 67/548/EEC) was raised. RAC agreed that an evaluation of carcinogenic effects of gallium arsenide solely based on results from animal studies is insufficient, especially since animals are less sensitive than humans to the carcinogenic effect of arsenic. It was decided to include information from human studies (results of epidemiological studies of carcinogenicity from exposure to arsenic compounds in copper smelters and from drinking water) on arsenic compounds listed as carcinogens in category 1A in CLP Annex VI and apply read-across to GaAs. A read-across approach is further supported by toxicokinetic data describing the formation of similar arsenic metabolites following GaAs exposure as those formed following exposure to classified arsenic compounds. It was agreed that the carcinogenicity of arsenic and arsenic compounds is of relevance to gallium arsenide and must be taken into account. In conclusion, there is no human data for gallium arsenide per se, but substantial documentation of carcinogenicity in humans of arsenic and arsenic compounds is available, as evaluated by IARC and briefly discussed in the BD. Gallium arsenide is also carcinogenic in female rats after inhalation and would fulfil the criteria for Carc. 2 (CLP), if assessed overlooking carcinogenicity from arsenic and arsenic compounds in humans. By applying weight of evidence and based on read-across from other arsenic compounds listed as carcinogen category 1A in Annex VI of CLP and with reference to the IARC grouping of Arsenic and arsenic compounds as well as gallium arsenide in group 1 ("carcinogenic to humans"), RAC recommends to classify gallium arsenide as a Carc. 1A – H350 according to CLP. **Part II: Background Document on Gallium Arsenide** In the French Dossier to classify gallium arsenide, the strength of the rapporteurs' proposal rests on the following points: *1. There is a desire by the French rapporteurs to harmonize the CLP Classification of gallium arsenide with the IARC opinion. The IARC Working Group decided that gallium arsenide was carcinogenic to humans (Group 1) based on the fact that gallium arsenide releases a "small amount of its arsenic" once it is in the body, which behaves as inorganic arsenic (pages 37 & 38 of BD).*	and covered a larger sector than the gallium arsenide-using industry. The more suitable recent occupational epidemiological studies that you mention have been included in the opinion and BD.

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		2. Animal studies on DMA, a metabolite of inorganic arsenic, have demonstrated carcinogenicity (page 37 of BD). *3. Based on using the "read across" method, the French rapporteurs have classified gallium arsenide using the classification of other inorganic arsenic compounds (pages 37 & 38 of BD).* **Part III: TriQuint response to the Background Document** TriQuint would like to respond to these points in order. *1. There is a desire by the French rapporteurs to harmonize the CLP Classification of gallium arsenide with the IARC opinion. The IARC Working Group then decided that gallium arsenide was carcinogenic to humans (Group 1) based on the fact that gallium arsenide releases a "small amount of its arsenic" once it is in the body, which behaves as inorganic arsenic.* If the IARC monograph on gallium arsenide was based on the most recent scientific studies of the carcinogenicity of gallium arsenide, it would make sense to harmonize the CLP classification with the IARC grouping. However, the IARC monograph is not based on the most recent data regarding the toxicity of arsenic compounds. TriQuint has analyzed the citations used in the IARC monograph and sorted the approximately 121 citations in the IARC document into categories regarding how the citations were used in the monograph. (The term "approximately" is used because some papers are cited within the text, but the citation is not shown at the end of the monograph, such as Elliot et al (1999)). The papers were segregated into the following categories, again depending on which section of the monograph the papers were cited in: • Carcinogenicity • Gallium as a cancer drug • Gallium, Arsenic, Gallium Arsenide in Industry • Gallium, Arsenic, Gallium Arsenide Metabolism • Methods of Analysis Selecting the Carcinogenicity and Ga, As, GaAs Metabolism categories, we can see that the cited papers range from 1949 to 2003, with the majority of the papers being written from 1984 to 2000.  The most recent Carcinogenicity paper cited is the Carter et al (2003) paper. It is interesting that the IARC monograph on gallium arsenide cites the Carter et al (2003) paper, but only does so in section 4.4 *Genetic and related effects*.	

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		However, the IARC group did not include the conclusion of the Carter et al (2003) paper on page 332: It is concluded that only arsenic compounds or solution species in the same oxidation state should be compared. Further, the arsenic compounds in an exposure should be measured before use in dose–response and risk assessment determinations. The Petrick et al (2000) and Petrick et al (2001) papers were also co-authored by authors of the Carter et al (2003) paper, so the opinions of the authors of those papers are the same as Carter et al (2003). The Styblo et al (2000) paper is reviewed in the Carter et al (2003) paper, where it says on page 311: The MMAsIII formed was more toxic than arsenious acid or DMAsIII when tested using the same cytotoxicity experiments (Petrick et al., 2000; Styblo et al., 2000). Conclusion 1. The AsIII and the AsV levels should not be combined but should be analzyed separately. The current preferred method of analysis that converts the arsenic compounds to the arsines followed by analysis using atomic absorption spectrophotometry should be changed. In the Lancet (2009) article, only one other paper regarding arsenic exposure is cited – the IARC (2004) article. No new studies have been considered in the 2009 update. **Therefore, the most recent papers cited in the IARC monograph (with the exception of the NTP (2000) study), unequivocally state that the various arsenic species with their different valence states need to be considered separately. It is not possible to extrapolate from one species of arsenic compound to another, without a detailed review of the chemistry.** The only other paper from 2000 or later cited in the IARC monograph is the NTP (2000) study, which forms the bulk of the data in the French dossier to classify gallium arsenide. In the NTP (2000) study, only female F344 rats showed any evidence of carcinogenicity. In the Background Document (on page 37), the rapporteurs make the following assertion: Significantly increased incidences of alveolar/bronchiolar neoplasms, benign pheochromocytoma of the adrenal medulla and mononuclear-cell leukaemia were observed in female rats exposed to the highest concentration. There was no evidence of carcinogenic activity in male rats, nor in male or female mice. No carcinogenic response was revealed in the gallium arsenide instillation study with male hamsters. One possible reason for sex specificity might be a higher retention and lower clearance of gallium arsenide particles from the lung of female rats compared to males (Nikula, 2000). In Thomas, et al (2007), the spontaneous incidence of mononuclear-cell leukemia (MCL) is examined in the Fischer F344 rat strain. In the Thomas, et al (2007) paper, MCL is referred to as LGLL (Large Granular Lymphocyte Leukemia). This paper evaluates the problems with using this particular rat strain in assessing human cancer risk. Quoting extensively from the Thomas, et al (2007) paper (please see citations in original paper for more information): (Pages 7-8) - Table 2 [*see below*] documents how the background incidence of LGLL in F344 rats has steadily	

Date	Country/ Person/ Organisation/ MSCA	Comment	RAC response
		increased over time. In addition, Haseman et al. (1985) reported a mean background LGLL incidence 26.5% (range 10–46%) in untreated male F344 rats and 17.3% (range 6–38%) in untreated females. Although, the reasons for the increased LGLL prevalence over time and the high study-to-study variability are unknown, Rao et al. (1990) suggested that changes in diagnostic criteria and a combination of genetic and experimental variables over at least 30 generations may have contributed to the time-related increase in LGLL. Haseman et al. (1998) summarized the spontaneous incidences of neoplasia from 27 feeding studies and 18 inhalation studies whose pathology evaluation had been finalized as of 1 January 1997. In this study, the range of LGLL in untreated male F344 rats varied from 32% to 74% with an average of 50.5% in the feeding studies and 34% to 70% with an average of 57.5% in the inhalation studies. In the females, it varied from 14% to 52% with an average of 28.1% in the feeding studies and 24% to 54% with an average of 37.3% in the inhalation studies. The latest background incidence of LGLL as of writing this review was reported again by Haseman et al. (2003) and is summarized in Table 2. In this study, for the feed studies, these authors reported control LGLL incidences of 59% and 32% for males and females, respectively, given one diet (NIH-07) and 52% and 24% in males and females, respectively, given another diet (NTP-2000). There was a slight reduction of LGLL incidence in the control males from the inhalation studies with an average of 46% (NIH-07) and 47% (NTP-2000), but the incidences in the females were 36% and 35% given NIH-07 and NTP-2000, respectively. These findings illustrate that the background incidence of LGLL in F344 rats has been highly variable and has more than doubled during the two decades since the report of Haseman et al. (1985), the reason(s) for which is (are) not well understood.	

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TABLE 2
Time-Related Changes in Leukemia Incidence (%) in Untreated Male and Female F344 Rats from 2-Year NCI/NTP Studies

Study start dates	Males	Females	Source
1971	7.9	2.1	Tables 3 and 4, Haseman and Rao, 1992
1972	10.5	7.3	
1973	16.3	11.6	
1974	19.7	13.2	
1975	34.0	19.0	
1976	31.5	19.0	
1977	29.2	18.8	
1978	28.9	14.9	
1979	28.1	19.2	
1980	47.5	26.9	
1981	52.7	25.1	
1982	47.7	26.3	
1983	45.0	27.0	
1984–1991 (approx)	50.5	28.1	Table 1, Haseman *et al.*, 1998
1990–1994[a]	59.4	31.7	Table 5, Haseman *et al.*, 2003
1995–1998[b]	52.5	24.2	

[a]NIH-07 diet (used by the NTP until 1995).
[b]NTP-2000 diet (used by the NTP after 1995).

The rats and mice in the NTP (2000) study were fed the NIH-07 diet (Appendix K, page 300 of NTP (2000) study), which results in a higher spontaneous rate of MCL incidence. Using the data from the table on page 30 of the Background Document, the incidence rate of MCL for female F344 rats is:

- 0 mg/m3 GaAs exposure – 22 out of 50 = 44%
- 0.01 mg/m3 GaAs exposure – 21 out of 50 = 42%
- 0.1 mg/m3 GaAs exposure – 18 out of 50 = 36%
- 1.0 mg/m3 GaAs exposure – 33 out of 50 = 66%

Overall, 94 out of 200 (47%) female rats had incidences of MCL, which doesn't seem to be related to exposure levels. While the highest incidence of MCL occurred at the highest concentration of gallium arsenide, the lowest incidence of MCL occurred at the second-highest concentration of gallium arsenide. It is difficult to make any assertion about increasing gallium arsenide content causing increased carcinogenicity risk, using this data.

Quoting again from Thomas, et al (2007):

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		(Page 16) - It is also noted that LGLL effects were more often than not confined to one sex, whereas for most tumors evaluated in NTP studies, similar effects are frequently seen in males and females (with of course, the exception of reproductive system neoplasms). Since there are modulating factors known to affect leukemia in one sex only (corn oil), and the majority of carcinogenic effects appear to be sex-specific for this neoplasm, it seems plausible to speculate that there may also be as yet unidentified factors/modes of action that are unique to one sex or the other for inducing LGLL in the F344 rat. Given the potential relevance of the F344 rat LGLL to the rare human NK-LGLL and in light of the factors that complicate definitive interpretation of chemicalinduced increases in LGLL (i.e., that spontaneous LGLL in F344 rat occurs at a high and variable incidence, is capable of being modulated by dietary factors such as corn oil, and has little evidence to support a mode of action [MOA]), it is proposed, like other reported recommendations (MacDonald, 2004) to adopt a ‘‘weight-of-evidence’’ approach when statistically identified increases in LGLL occur with exposure to a given compound. The ‘‘weight-of-evidence’’ approach, similar to the NTP’s rigorous evaluation approach, should include assessment of the nature of dose–response curve in terms of incidence and/or severity, appropriate historical control data, reduction in latency time, reproducibility, or lack thereof when exposed through different routes, reproducibility, or lack thereof when tested in another strain or species, involvement of both sexes or only one, comparative species metabolism of the administered compound, genotoxicity, cytotoxicity, and any other relevant information. Most importantly, is there a biological plausible reason for tumor induction, or increased incidence? Does the chemical have toxic or carcinogenic effects on LGLs or their precursors? In addition, increasing the stringency of statistical analysis to further reduce the identification of false positives is also recommended. Moreover, detailed analyses of LGLL ‘‘associated’’ chemicals in NTP bioassays along with their genotoxicity and subchronic toxicity data may reveal a ‘‘model’’ LGLLinducing chemical which could be used for future studies aimed at determining a MOA for LGLL in the F344 rat. Quoting again from Carter et al, (2003): It is not possible to use animal data as a model for humans or for the rat to serve as a model for other laboratory animals. It was a surprise when the results from long-term animal studies did not model humans. … The problem with early data from animals was that rats were used. Previous scientific committees have stated that they did not recommend rats for arsenic oxide disposition studies. **The NTP (2000) study shows incidence of carcinogenicity only to female Fischer F344 rats and not to male Fischer F344 rats, nor to mice (male or female), nor to male hamsters. Detailed studies have shown that the F344 strain of rat is especially sensitive to spontaneous incidence of MCL, and that rate of incidence has steadily increased since the 1970s to levels that are shown in the NTP (2000) study. Studies that show evidence of MCL to only female rats of this strain are not sufficient evidence of carcinogenicity.** *2. Animal studies on DMA, a metabolite of inorganic arsenic, have demonstrated carcinogenicity.* This is taken from the Lancet 2009 article on Monograph 100 (IARC, 2009), which contains an update on Arsenic. On	

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		page 31 of the Background Document, the rapporteurs make the statement: The common metabolic pathway of elemental and inorganic arsenic species was underlined: arsenate _ arsenite _ methylarsonate _ dimethylarsenite (IARC, in press; Lancet, 2009). On page 37 of the Background Document, the rapporteurs make the statement: However animal studies on DMA, a metabolite of inorganic arsenic, has demonstrated carcinogenicity (Lancet, 2009). The Lancet article states: On the basis of sufficient evidence of cancer caused by DMA in experimental animals, and because MMA is extensively metabolised to DMA, both compounds are classified as “possibly carcinogenic to humans” (Group 2B). Arsenobetaine and other organic arsenic compounds that are not metabolised in humans are “not classifiable” (Group 3). It is not logical that DMA is only a Group 2B carcinogen, but because gallium arsenide can presumably metabolize to DMA, it is proposed to be classified as a Group 1 carcinogen. Again on page 37 of the BD, the rapporteurs make the comment that: No threshold has been identified for the carcinogenic effect of arsenic and it is assumed that the risk of cancer increases linearly with the dose. This is why EPA has applied linear models when estimating lifetime risk (http://www.epa.gov/ncea/iris/subst/0278.htm). This is an old study on the IRIS system (April 1998, based on data from the 1980s). More recently (see Cohen et al, 2006), EPA has changed to using a Margin of Exposure (MOE) approach rather than linear extrapolation (see U.S. EPA, 2005). To quote from Cohen et al, (2006) in their use of the MOE calculation for bladder cancer from methylated arsenicals: To calculate the MOE for DMAV, the no-observed-effect level (NOEL) from the 2-year feeding study (Arnold et al., submitted; van Gemert and Eldan, 1998) should be compared to a plausible human exposure. We have selected the value of 0.79 mg/kg/day for the NOEL. This preneoplastic endpoint is based on bladdercell necrosis and hyperplasia in the female rat and is conservative because it is approximately 10 times lower than the tumorigenic dose (van Gemert and Eldan, 1999). To quantify a plausible human exposure we used the U.S. EPA chronic dietary estimate of 2 ×10−7 mg DMAV/kg/day for the U.S. population combined with a hypothetical estimate of 2 × 10−6 mg DMAV/kg/day for the maximum dose of DMAV consumed in drinking water. This yielded a hypothetical human daily dose of 2.2 × 10−6 mg DMAV/kg/day. Based on this dose and the NOEL from the 2-year rat bioassay, the resulting MOE is about 360,000, which is sufficiently large to demonstrate that DMAV is highly unlikely to be of toxicological concern at plausible human exposures.	

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		Further statements in Cohen et al (2006) regarding the linear dose response: • Page 111 – "These two bioassays are consistent with the hypothesis that the dose response relationship of the DMAV-induced carcinogenicity in rats is nonlinear; tumors occur only at relatively high doses." • Page 118 – "In addition, Kligerman et al. (2003) present figures showing that DMAIII-induced genotoxicity has a linear dose-response. However, scatter in the data at low doses does not appear to support linearity. On the contrary, their data strongly support a threshold response in each of the presented assays. They suggested positive results in some assays at concentrations less than 1 μm, based on a linear extrapolation of the experimental data. However, statistically significant results at tested doses occurred only at doses higher than 2 μ*M*. The actual results at lower doses were not statistically significantly different from controls." • Page 123 – "In summary, although there are data gaps pertaining to the actual mechanism of action of the DMAV-induced rat bladder tumors, the weight of evidence is clearly sufficient to support the mode of action of cytotoxicity and regenerative cell proliferation, and there are no inconsistencies. The key observation with all of the proposed mechanisms, including effects related to indirect genotoxicity, is that the dose response is nonlinear, as is the tumor response." To again quote from Cohen et al, (2006) In terms of the overall risk assessment of arsenic compounds, it is imperative to recognize that important toxicological and metabolic differences exist between inorganic arsenic, MMAV, and DMAV. Differences in the in vivo metabolism, cellular uptake, and in vitro cytotoxicity distinguish inorganic arsenic from methylated arsenic compounds. To the extent possible, risk assessment and risk management decisions should rely on the best available science. Sufficient chemical and toxicological information is available to justify and enable the assessment of MMAV and DMAV using chemical-specific data. Giving each arsenic compound separate toxicological consideration in risk assessments is scientifically sound and consistent with evaluations of other compounds that exist in multiple forms and exhibit distinct toxicological and chemical characteristics. Based on differences in toxicity, the U.S. EPA has developed distinct risk assessment criteria for different forms of chromium (recognizing different valence states), as well as mercury, tin, and lead (recognizing differences in inorganic vs. organic forms) (U.S. EPA, 1997, 2004). **Thus, the most recent research does not support a linear extrapolation, and a threshold level for DMAV exposure does exist. There is no basis for the rapporteurs' contention that because gallium arsenide can presumably be metabolized to DMAV, gallium arsenide should be classified as a Carcinogen 1A. There is also no data that supports the rapporteurs' contention that there is no threshold level for gallium arsenide exposure or exposure to DMAV. The studies cited by the rapporteurs are out of date, as EPA has now changed to using a Margin of Exposure (MOE) process, which shows that DMAV is highly unlikely to be of toxicological concern at plausible human exposures.** *3. Based on using the "read across" method, the French rapporteurs have classified gallium arsenide using the classification of other inorganic arsenic compounds.* The proper use of the "read across" method is outlined in the OECD document *Guidance on the Grouping of Chemicals* (2007).	

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		This document mentions two main approaches – the chemical category approach or the analogue approach. The purpose of using either of these two approaches is to identify a group of similar substances to the substance of concern, and then "read across" the data at issue from the "group" of chemicals to the substance of concern. The chemical category approach is to be used when there are a large number of chemicals that fit within the category that is being defined, while the analogue approach is for smaller groups of chemicals. In our reading of the BD, we have assumed that the rapporteurs have used the analogue approach, as the number of chemicals they are comparing is rather limited, and do not contain any joint characteristics other than containing arsenic as an element in the molecular structure. The approach for using the analogue approach is given in Chapter 4 of OECD (2007) and consists of 6 steps: 4.2.1 Step 1: Identification of potential analogues 4.2.2 Step 2: Data gathering for the analogues 4.2.3 Step 3: Evaluation of available data for adequacy 4.2.4 Step 4: Construct a matrix of data availability 4.2.5 Step 5: Assess the adequacy of the analogue approach and fill the data gap 4.2.6 Step 6: Document the analogue approach We will work through the BD document to see if this guidance has been followed by the rapporteurs: Step 1: Identification of potential analogues The rapporteurs have identified the following potential analogues on page 31 of the BD: • Diarsenic trioxide (CAS # 1327-53-3) • Diarsenic pentoxide (CAS # 1303-28-2) • Arsenic acid and its salts (no CAS #) • Triethyl arsenate (CAS # 15606-95-8) • Trinickel bis (arsenate) (CAS # 13477-70-8) • Lead hydrogen arsenate (CAS # 7784-40-9) The rapporteurs have duplicate entries for triethyl arsenate. Clearly, the organoarsenic compounds and the lead compounds should not be used as analogues, as these compounds are not inorganic arsenic oxides, which is the claim of the IARC and the rapporteurs. This reduces the list of potential analogues to: • Diarsenic trioxide (CAS # 1327-53-3) • Diarsenic pentoxide (CAS # 1303-28-2) • Arsenic acid and its salts (no CAS #) Step 2: Data gathering for the analogues The OECD (2007) document lists several physicochemical characteristics that should be evaluated to determine whether the chemicals chosen are acceptable analogues, such as: • physical state	

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		• MW • logKow and other partition coefficients (e.g. the Henry's Law coefficient • soil organic-carbon partition coefficient) • aqueous solubility • particle size and structure • vapour pressure • melting point • boiling point We can construct a table of these 3 analogues and gallium arsenide and their readily available physicochemical properties. These properties are widely available, but in this case the CRC Handbook (63rd edition) was used:	

Characteristic	Gallium Arsenide	Diarsenic Trioxide	Diarsenic Pentoxide	Arsenic Acid
Molecular weight	144.64	197.84	229.84	141.9
Melting point, °C	1238	312.3	315 (decomposes)	35.5
Density, g/cm^3	5.32	3.738	4.32	2.0 - 2.5
Water solubility, g/100 cm^3	<0.1	3.7 @ 20 °C 10.14 @ 100 °C	150 @ 16 °C 76.7 @ 100 °C	302 @12.5 °C
Valence state of Arsenic in molecule	-3	3	5	5
Physical State	Gray cubic crystals	White cubic crystals	White hygroscopic powder	White tetrahedral hygroscopic powder

It is clear from this table, that there are significant physicochemical differences between these chosen analogues, specifically in the melting temperatures, solubility and valence states. However, as the BD rapporteurs did not perform this evaluation, they did not recognize that these are very different substances.

Also, since the BD rapporteurs did not accomplish Step 2 of the Guidelines, they did not accomplish any of the subsequent steps. They did not evaluate the available data for adequacy, construct a matrix of data availability, assess the adequacy of the analogue approach and fill the data gap, and finally document the analogue approach.

Since the correct "grouping" guidance was not followed, it is difficult to understand how the rapporteurs were able to identify adequate information to be "read across" to gallium arsenide.

It is interesting that on page 11 of the BD, the rapporteurs cite the Carter et al. (2003) document, by saying that the Carter et al. (2003) document reviewed the data of the Yamauchi (1986) and Rosner and Carter (1987) papers. Stated in this manner, it would seem that the Carter et al (2003) paper supported that the gallium and arsenic moieties were released from gallium arsenide in dangerous amounts.

It would have been more accurate if the rapporteurs had cited the Carter et al (2003) paper's conclusions. On page 326 in Carter et al (2003), the authors state:

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		Summary of biological responses to GaAs The biological activity of GaAs was in the lung because it was a deposition site and in the liver, testis, and immune system because it could cause systemic effects after absorption. These effects occurred from a combination of changes caused by the GaAs in the particulate form, by the insoluble compounds formed after reaction with water, and from the soluble species that formed after dissolution. The toxicity of gallium appears to be limited by its solubility and by the solution composition of materials that could bind or solubilize gallium. The toxicity of arsenic appeared to depend on the species formed during dissolution: arsine, arsenious acid, or arsenic acid. It is clear that highly insoluble arsenide semiconductors were less acutely toxic than equal amounts of arsine or their more soluble arsenious acid products.[emphasis added] In addition, even the Yamauchi (1986) paper states that "The low solubility and poor oral absorption may make this compound [gallium arsenide] less toxic that other inorganic arsenic compounds." On page 332 in Carter et al. (2003), the authors conclude by stating: **Conclusions for arsenic oxides, gallium arsenide, and arsine** An enormous number of arsenic compounds can be made because arsenic can bind to carbon atoms like nitrogen, it can change between a number of oxidation states, +V, +III, 0, -III, and it can bind to organic thiol compounds like metals to form complexes. It is a metal(loid) and can participate in many different kinds of reactions. … Unfortunately, it is not easy to determine an accurate oxidation state for arsenic that reflects its potential reactions. This is particularly a problem for intermetallic and methylated compounds. Despite these problems, this review has approached these arsenic toxicity comparisons in an oxidation state-specific manner. It is concluded that only arsenic compounds or solution species in the same oxidation state should be compared. TriQuint has been in contact with one of the principal authors of the Carter, et al (2003) paper – Dr. H. Vasken Aposhian of the Department of Molecular and Cellular Biology of the University of Arizona, USA. Dr. Aposhian was kind enough to prepare a document (Aposhian, 2011) that will be submitted to ECHA regarding this proposed classification. Dr. Aposhian is one of the world's most respected experts on gallium arsenide and arsenic toxicology. To sum up Dr. Aposhian's comments on the BD (emphasis in original): 1. The purpose of this report is to request the Committee to reconsider its May 25, 2010 report on gallium arsenide. Suggestions and recommendations are respectfully offered. 2. **The present author believes that published statements in peer-reviewed articles from various highly-regarded arsenic experts that are quoted in this present report indicate that the read across method should not be used for gallium arsenide. There is insufficient evidence to equate the different arsenic compounds.** 3. There is published information which provides evidence that GaAs acts differently than As relative to carcinogenicity. We doubt that total arsenic in all environmental arsenic exposures is representative of risk when there	

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		appear to be several different "most toxic arsenic compounds." 4. Gallium arsenide is not found in nature and should not be judged by the same drinking water exposure scenarios that are used for the inorganic arsenic oxides. 5. The rat is an atypical and very poor mammalian model for inorganic As or GaAs toxicity in humans. The published evidence is presented and cited**. Yet, the RAC Background document appears to inappropriately use the rat data especially in the example of the carcinogenicity in female rats.** 6. There are other factors, not considered in the ECHA background document, which need to be considered for proper classification of GaAs with respect to carcinogenicity. 7. **Summary of Reactions and Recommendations. It appears that the RAC is completely disregarding major points cited in the Carter et al (2003) paper which is a widely quoted classic in the field of arsenic and GaAs metabolism and toxicity. Since GaAs behaves differently from other arsenic compounds, and since rats are a poor model for how the human processes arsenic, the change to a 1A recommendation is not scientifically warranted and needs to be reconsidered.** **In summary, the French rapporteurs did not perform a proper "read across" process. They did not analyze the physicochemical characteristics of the analogues they chose to compare to gallium arsenide. They did not perform any of the subsequent steps to properly use the read-across method that are recommended in the OECD (2007) guidance document on the grouping of chemical substances. In addition, the papers that are being cited by the rapporteurs as evidence that gallium arsenide is carcinogenic in their use of a flawed read-across method do not support such a classification. The authors of these papers uniformly think that gallium arsenide is much less toxic than the inorganic arsenic oxide compounds that the rapporteurs have chosen to read-across from.** **Part IV: General Comments on inaccuracies within the Background Document** On page 7 of the BD, the comment is made that in 1981, the electronics industry employed approximately 180000 workers in the USA, with over 500 plants manufacturing semiconductors. It is unknown what the relevance of this statement is. This is a statement about the general semiconductor industry in the United States from 30 years ago. It does not apply to the portion of the semiconductor industry that uses or manufactures gallium arsenide as its main substrate material, which is a very small segment of the entire semiconductor industry. Nor does it have any application to the European Union, which is where these proposed classifications would be necessary. It seems that the statement in the BD has been added to purposely inflate the scope of the imagined "problem" of the gallium arsenide industry. This statement has no relevance to the manufacture of gallium arsenide, and is highly misleading in this context. If the rapporteurs desire to use more recent data (although still not applicable to the gallium arsenide industry, but with some EU data), TriQuint would recommend the following: • Boice et al (2010) – In summary, our study provides no strong or consistent evidence of increased cancer mortality overall or by cancer site in a large cohort of US workers employed in semiconductor wafer fabrication.	

Date	Country/ Person/ Organisation/ MSCA	Comment	RAC response
		• Beall et al (2005) – **Problem:** We evaluated mortality during 1965 to 1999 among 126,836 workers at two semiconductor facilities and one storage device facility. **Method:** We compared employees' cause-specific mortality rates with general population rates and examined mortality patterns by facility, duration of employment, time since first employment, and work activity. **Results:** Employees had lower-than-expected mortality overall (6579 observed deaths, standardized mortality ratio [SMR] = 65; 95% confidence interval [CI] = 64-67), for all cancers combined (2159 observed, SMR = 78, 95% CI = 75-81) and for other major diseases. Central nervous system cancer was associated with process equipment maintenance at one of the semiconductor facilities (10 observed, SMR = 247, 95% CI = 118-454). Prostate cancer was associated with facilities/laboratories at the storage device facility (18 observed, SMR = 198, (5% CI = 117-313). **Conclusions:** Further evaluation of workplace exposures or independent investigations of similar occupational groups may clarify the interpretation of associations observed in this study • Bender et al (2007) **Aims:** To evaluate cancer incidence among workers at two facilities in the USA that made semiconductors and electronic storage devices. **Methods:** 89 054 men and women employed by International Business Machines (IBM) were included in the study. We compared employees' incidence rates with general population rates and examined incidence patterns by facility, duration of employment, time since first employment, manufacturing era, potential for exposure to workplace environments other than offices and work activity. **Results:** For employees at the semiconductor manufacturing facility, the standardised incidence ratio (SIR) for all cancers combined was 81 (1541 observed cases, 95% confidence interval (CI) 77 to 85) and for those at the storage device manufacturing facility the SIR was 87 (1319 observed cases, 95% CI 82 to 92). The subgroups of employees with _15 years since hiring and _5 years worked had 6–16% fewer total incidents than expected. SIRs were increased for several cancers in certain employee subgroups, but analyses of incidence patterns by potential exposure and by years spent and time since starting in specific work activities did not clearly indicate that the excesses were due to occupational exposure. **Conclusions:** This study did not provide strong or consistent evidence of causal associations with employment factors. Data on employees with long potential induction time and many years worked were limited. Further follow-up will allow a more informative analysis of cancer incidence that might be plausibly related to workplace exposures in the cohort. • Darnton et al (2010) – This is a follow-up study to the McElvenney et al (2003) study that is listed in the Introduction to The Monographs on Gallium Arsenide and Indium Phosphide in Monagraph 86 (IARC 2006). In contrast to the information in the IARC (2006) monograph, new research shows that there are no concerns regarding a	

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		link between working at a semiconductor facility and the incidence of cancer: Our new research does not support the earlier concerns about a link between working at NSUK and developing cancer, especially when taking account of new information about cancer at two IBM semiconductor factories in America. The evidence from this most recent study does not prompt HSE to recommend any further epidemiological research in the way the evidence from previous study did. In any case there is no such research that could be done within the NSUK setting at this stage. Aposhian, H. Vasken, PhD, (2011) *Reactions to and recommendations for modifying the Background document to the Opinion proposing harmonized classification and labeling at Community level of gallium arsenide ECHA/RAC/CLH-0000000792-73-03-A1 Which was adopted 25 May 2010*, manuscript prepared by Dr. Aposhian for submission to ECHA/RAC on April 18, 2011. Arnold, L.L., van Gemert, M., Eldan, M., Nyska, A., and Cohen, S.M. Submitted. *Dimethylarsinic acid: Results of chronic toxicity/oncogenicity studies in Fischer F344 rats and B6C3F1 mice.* Beall C, Bender TJ, Cheng H, Herrick R, Kahn A, Matthews R, Sathiakumar N, Schymura M,Stewart J, Delzell E. (2005) *Mortality among semiconductor and storage device-manufacturing workers.* J Occup Environ Med. 47(10):996-1014. Bender TJ, Beall C, Cheng H, Herrick RF, Kahn AR, Matthews R, Sathiakumar N, Schymura MJ, Stewart JH, Delzell E. (2007) *Cancer incidence among semiconductor and electronic storage device workers.* Occup Environ Med. 64(1):30-6. Boice, John D., Jr, ScD, Marano, Donald E., P.E., CIH,; Munro, Heather M., MS,; Chadda, Bandana K., MPH; Signorello, Lisa B., ScD; Tarone, Robert E., PhD; and McLaughlin, Joseph K., PhD, *Cancer Mortality Among US Workers Employed in Semiconductor Wafer Fabrication*, Journal of Occupational and Environmental Medicine, Vol 52 (11), November 2010, pp 1082- 1097. Carter, D. E.; Aposhian, H. V.; and Gandolfi, A. J.; (2003), *The metabolism of inorganic arsenic oxides, gallium arsenide and arsine: a toxicological review*, Toxicol and Applied Pharmacol, 193, pp 309-334. Cohen, Samuel M.; Arnold, Lora L.; Eldan, Michal; Lewis, Ari S.; and Beck, Barbara D. (2006), "*Methylated Arsenicals: The Implications of Metabolism and Carcinogenicity Studies in Rodents to Human Risk Assessment*," Critical Reviews in Toxicology, Vol 36, pp 99-133. Darnton, Andrew; Wilkinson, Sam; Miller, Brian; MacCalman, Laura; Galea, Karen; Shafrir, Amy; Cherrie, John; McElvenny, Damien; Osman, John, (2010), *A further study of cancer among the current and former employees of National Semiconductor (UK) Ltd., Greenock*, HSE Books, Sudbury, Suffolk.	

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		IARC. (2004) *Some drinking-water disinfectants and contaminants, including arsenic.* IARC Monogr Eval Carcinog Risks Hum*:* **84:** 1–477. IARC (2006) Monograph *Cobalt in Hard Metals and Cobalt Sulfate, Gallium Arsenide, Indium Phosphide and Vanadium Pentoxide",* World Health Organization, International Agency for Research on Cancer, Vol. 86. IARC (2009), *Special Report: Policy – A review of human carcinogens – Part C: metals, arsenic, dusts, and fibres,* Lancet, Vol. 10, pp 453-454. McElvenny, D.M., Darnton, A.J., Hodgson, J.T., Clarfke, S.D., Elliott, R.C. & Osman, J. (2003) *Investigation of cancer incidence and mortality at a Scottish semiconductor manufacturing facility.* Occup. Med., **53**, 419–430 National Toxicology Program (2000) *Toxicology and Carcinogenesis Studies of Gallium Arsenide (CAS No. 1303-00-0) in F344/N Rats and B6C3F1 Mice (Inhalation Studies)* (NTP Technical Report 492), Research Triangle Park, NC. Thomas, Johnson; Haseman, Joseph K.; Goodman, Jay I.; Ward, Jerrold M.; Loughran, Jr., Thomas P.; and Spencer, Pamela J., (2007) *A Review of Large Granular Lymphocytic Leukemia in Fischer 344 Rats as an Initial Step Toward Evaluating the Implication of the Endpoint to Human Cancer Risk Assessment*, Toxicological Sciences, 99 (1), pp 3-19. U.S. EPA (1997). *Health Effects Assessment Summary. Tables: FY-1997* update [HEAST]. EPA/540/R- 97/036. U.S. EPA (2004). Integrated Risk Information System (IRIS). http://www.epa.gov/iris U.S. EPA (2005), *Guidelines for carcinogen risk assessment.* U.S. Environmental Protection Agency, Washington, C. http://www.epa.gov/cancerguidelines. van Gemert, M., and Eldan, M. (1999). *Cacodylic acid—A reviewof the scientific data of carcinogenicity studies in response to the USEPA memorandum July 27, 1994*. Luxembourg- Pamol, Inc., Memphis, TN.	
21/04/2011	United States / Bogdan Golja / WIN Semiconductors / Company-Downstream user	*ECHA comment: The attached document (WIN Comments on GaAs Classification.pdf) is copied below.* **Position of WIN Semiconductors 20th April 2011** **On "Opinion of the Committee for Risk Assessment (RAC) proposing harmonized classification and labeling at EU level of Gallium Arsenide adopted 25th May 2010"** As a pure play GaAs foundry services company the Harmonized Classification and Labeling case of Gallium Arsenide is of particular concern to WIN Semiconductors. WIN provides a technology portfolio centered on GaAs based products. Our global customers provide solutions for mobile communications, satellite communications, cellular base stations, WLAN , high frequency measurement systems and GPS. Any classification, particularly one that impacts a global industry, needs to be made based on all available data. It is critical that the most up to date evidence and data	Your comments on use of gallium arsenide are noted. However use of a substance is not relevant for the classification which is a result of assessment of intrinsic properties of the substance. Assessment of the hazard properties of GaAs as a substance and

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		are used to reach a comprehensive, scientifically based decision. GaAs is a compound which behaves differently from other As compounds; and, in addition, it acts differently from As, as far as carcinogenicity is concerned (Carter et al, 2003). WIN has been manufacturing GaAs electronics for over ten years and is well aware of the epidemiological studies that have been performed in the GaAs semiconductor industry (Beall et al [2005], Bender et al [2007]). These studies did not indicate increased cancer risks attributable to As exposure. The accumulation of As in workers, involved in this industry, is not supported by the published data. It appears that this data indicating the absence of a correlation between cancer and the work environment was not considered when the read across approach was taken to link the carcinogenicity of As2O3 with GaAs. These two compounds behave very differently with different oxidation states and water solubility (GaAs: <<1 g/L, As2O3: 660 g/L). Carter et al, 2003 stated: "It is clear that highly insoluble arsenide semiconductors were less acutely toxic than equal amounts of arsine or their more soluble arsenious acid products". The oft-quoted Carter review draws an unambiguous conclusion with respect to GaAs stating "there is insufficient evidence to equate the different arsenic compounds." The Carter et al review is cited in a number of instances by the RAC without extensive elaboration giving the impression that the Carter review supports the proposed classification of GaAs. However, a reading of the paper leads to quite different conclusions. In addition, to the Carter et al review the Yamauchi (1986) paper commented that "The low solubility and poor oral absorption may make this compound [gallium arsenide] less toxic that other inorganic arsenic compounds." Neither of these papers supports the RAC opinion on the proposed classification of GaAs; and, in fact, should have been instrumental at arriving at a much different opinion. Studies have shown that the rat is an inappropriate animal from which to draw conclusions about As carcinogenicity in humans (Carter et al, Vahter et al). To quote from Carter et al [2003], "It is not possible to use animal data as a model for humans or for the rat to serve as a model for other laboratory animals. It was a surprise when the results from long-term animal studies did not model humans". It is of concern when the opinions and conclusions of subject matter experts are not openly considered when determining the carcinogenicity of GaAs in humans. In fact recent evidence has emerged that the F344/N rat has been discontinued from use in Toxicity Studies, King-Herbert and Thayer [2006]. It appears that the chronic inflammatory effects of particles are probably more responsible for the neoplastic transformations observed in animal species, than the carcinogenic effects of GaAs. In conclusion, it does not appear that the totality of the available data provides compelling evidence for the classification of GaAs as carcinogenic. WIN requests that the proposed classification of GaAs be reviewed taking into account all the available evidence in order to arrive at an appropriate classification. WIN, in its daily operations, has done the due diligence and put measures in place to keep employees safe. This was done by a thorough understanding of GaAs, together with the studies that provide guidance in its use and handling. WIN merely requests that the RAC employ the same due diligence in order to reach a conclusion supported by current scientific evidence. Bogdan Golja Senior Director, Marketing and Sales WIN Semiconductors	risk assessment from exposure related to usage of GaAs in the microelectronic industry are different things. For RAC evaluation of Carter et al. (2003) please see point 6) of the Annex to RCOM (Additional response to comments). Regarding your comment on occupational epidemiological studies please see response to Germany / Christian Eckert / ZVEI / Industry or trade association in the beginning of this document. The F344/N rat is known to have high background incidences of certain types of tumors including testicular interstitial cell tumors and mononuclear cell leukemia, and was discontinued from use by NTP because of this. Regarding your comment on effects from particles, please see point 3) of the Annex to RCOM (Additional response to comments). We are happy to hear that

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		No. 358, Hwaya 2nd Road, Hwaya Technology Park Kuei Shan Hsiang, Tao Yuan Shien 333, Taiwan **References** Beall C, Bender TJ, Cheng H, Herrick R, Kahn A, Matthews R, Sathiakumar N, Schymura M, Stewart J and Delzell E, "Mortality among Semiconductor and Storage Device-Manufacturing Workers", J. Occup. Environ. Med., **47**, 996-1014 (2005) Bender TJ, Beall C, Cheng H, Herrick R, Kahn A, Matthews R, Sathiakumar N, Schymura M, Stewart J and Delzell E. Cancer incidence among semiconductor and storage device workers. Occup Environ Med 64, 2007 30-36. Carter, D. E., Aposhian, H. V., and Gandolfi, A. J. (2003). The metabolism of inorganic arsenic oxides, gallium arsenide and arsine: a toxicochemical review. *Toxicol and Applied Pharmacol*, *193*, 309-334. King-Herbert A and Thayer K, "NTP Workshop: Animal Models for the NTP Rodent Cancer Bioassay: Stocks and Strains – Should we Switch?", Toxicol. Path., **34**, 802-805 (2006) Vahter, M., E. Marafante, and L. Dencker. 1984. Tissue distribution and retention of 74As-dimethylarsinic acid in mice and rats. Arch. Environ. Contam. Toxicol. 13:259-264 Vahter, M. 1994. Species differences in the metabolism of arsenic compounds. Appl. Organomet. Chem. 8: 175-182. Yamauchi H, Takahashi K and Yamamura Y, "Metabolism and excretion of orally and intraperitoneally administered Gallium Arsenide in the Hamster", Toxicology, **40**, 237-246 (1986)	you provide a safe working environment. However classification is based on assessment of the intrinsic properties of the substance and not on the risk at use.
21/04/2011	Germany / Frauke Schröder / Member State	Following reference dealing with carcinogenicity of arsenic compounds might be helpful for the RAC discussion on GaAs: Tokar, E.J et al, Critical Rewiews in Toxicology, 210; 40 (10):912-927 (see attached cover note) *ECHA comment: The attached document (CritRevTox2010.pdf) is copied below.*	Thank you for your comment. This paper is mentioned in the opinion.

Date	Country/ Person/ Organisation/ MSCA	Comment	RAC response
		Critical Reviews in Toxicology, 2010; 40(10): 912–927 informa healthcare REVIEW ARTICLE # Cancer in experimental animals exposed to arsenic and arsenic compounds Erik J. Tokar[1], Lamia Benbrahim-Tallaa[2], Jerrold M. Ward[3], Ruth Lunn[4], Reeder L. Sams II[5], and Michael P. Waalkes[1] [1]*National Toxicology Program, National Institute of Environmental Health Sciences, and Laboratory of Comparative Carcinogenesis, National Cancer Institute at the National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina, USA,* [2]*IARC Monographs Section, International Agency for Research on Cancer, Lyon, France,* [3]*Global VetPathology, Montgomery Village, Maryland, USA,* [4]*Report on Carcinogens Office, National Toxicology Program, National Institute of Environmental Health Science, Research Triangle Park, North Carolina, USA, and* [5]*National Center for Environmental Assessment, Office of Research and Development, US Environmental Protection Agency, Research Triangle Park, North Carolina, USA* **Abstract** Inorganic arsenic is a ubiquitous environmental contaminant that has long been considered a human carcinogen. Recent studies raise further concern about the metalloid as a major, naturally occurring carcinogen in the environment. However, during this same period it has proven difficult to provide experimental evidence of the carcinogenicity of inorganic arsenic in laboratory animals and, until recently, there was considered to be a lack of clear evidence for carcinogenicity of any arsenical in animals. More recent work with arsenical methylation metabolites and early life exposures to inorganic arsenic has now provided evidence of carcinogenicity in rodents. Given that tens of millions of people worldwide are exposed to potentially unhealthy levels of environmental arsenic, in vivo rodent models of arsenic carcinogenesis are a clear necessity for resolving critical issues, such as mechanisms of action, target tissue specificity, and sensitive subpopulations, and in developing strategies to reduce cancers in exposed human populations. This work reviews the available rodent studies considered relevant to carcinogenic assessment of arsenicals, taking advantage of the most recent review by the International Agency for Research on Cancer (IARC) that has not yet appeared as a full monograph but has been summarized (IARC, 2009, IARC Special Report: Policy, Vol. 10. Lyon: IARC Press, 453–454). Many valid studies show that arsenic can interact with other carcinogens/agents to enhance oncogenesis, and help elucidate mechanisms, and these too are summarized in this review. Finally, this body of rodent work is discussed in light of its impact on mechanisms and in the context of the persistent argument that arsenic is not carcinogenic in animals. **Keywords:** *Arsenicals; carcinogenesis; inhalation; mouse; oral exposure; rat; rodents; transplacental exposure* **Abbreviations:** DMBA, 7,12-dimethylbenz[α]anthracene; TPA, 12-O-tetradecanoyl phorbol-13-acetate; CSC, cancer stem cell; DES, diethylstilbestrol; DMA^{V}, dimethylarsinic acid; DMA^{III}, dimethylarsinous acid; GD, gestation day; IARC, International Agency for Research on Cancer; IT, intratracheal installations; i.v., intravenous; MMA^{III}, methylarsonous acid; MMA^{V}, monomethylarsonic acid; NSF, National Science Foundation; NTP, National Toxicology Program; $NaAsO_2$, sodium arsenite; SCC, squamous cell carcinoma; SC, stem cell; s.c., subcutaneous; TCC, transitional cell carcinoma; TAM, tamoxifen; UV, ultraviolet irradiation; UB, urinary bladder; UGS, urogenital system.	
21/04/2011	Germany / Dietmar Schmitz / AIXTRON SE / Company-Manufacturer	*ECHA comment: The same comment was also submitted as an attachment (AIXTRON GaAs.pdf).* 20 April 2011 To: European Commission ECHA From : AIXTRON SE	Thank you for your comments. Your comments on use of gallium arsenide are noted. However use of a substance is not relevant

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		Subject: Risk Assessment Committee concerning Gallium Arsenide: Opinion proposing harmonised classification and labelling at Community level of gallium arsenide ECHA/RAC/CLH-0000000792-73-03/F On behalf of AIXTRON SE, I am writing to request a reopening of the recommendation procedure for classification of gallium arsenide. We are considered world leading manufacturer of special equipment for growth of crystalline layers of compound semiconductors with our principal office in Europe. Our products are used for production of advanced electronic devices. We are performing development work in deposition processes and process hardware. In the sequence of doing so Gallium arsenide is present in our daily environment as a solid and inert material. Aware of the potential hazards arising from the single constituents our handling of substances is subject to very serious risk assessment procedures. We follow a clear zero-emission policy for hazardous substances from our work environment. Our expertise is also used to effect safe work conditions and awareness in the industrial application of our products. Being a major participant in European compound semiconductor industry we were not made aware of the original opinion which was adopted on 25 May 2010. We feel strongly that the procedure used by the Risk Assessment Committee (RAC) of ECHA to determine the CLP classification for gallium arsenide is not fully appropriate to determine whether or not gallium arsenide represents a biological risk. Carefully assessing the “read-across” approach that assigns to gallium arsenide the toxicity of related compounds like arsenic or arsenic oxides appears not relevant. As the same procedure applied to commonplace substances like table salt would imply the same toxicity to it as chlorine, one of its constituent chemicals. We support the REACh initiative of the European Commission and its classification of biologically hazardous materials, provided of course that each classification be determined by a rigorous and scientifically supported testing procedure. It is critical that these tests measure the innate toxicity of the material being cited, not its form or its apparent relationship to some other material that may be toxic. GaAs is used in a wide field of electronic devices such as high frequency transistors applied in fields of telecommunications and signal processing. Moreover optoelectronic devices such as LEDs and semiconductor lasers applied in display, data storage and handling base on GaAs for a significant part. Finally in renewable energy technology for harvesting Solar energy through Photovoltaic devices GaAs plays a substantial role. In the perception of AIXTRON SE there is no immediate replacement that could take the place of this material in a technology field of such great importance for the European Market. Recommendations about its continued use should be made carefully, using contemporary scientific standards that are relevant both to gallium arsenide and to the way it is used in various applications. Such a procedure may be more	for the classification which is a result of assessment of intrinsic properties of the substance. Regarding your comments on read-across, please see point1) of the Annex to RCOM (Additional response to comments). Regarding your comment on toxicity to reproduction, please see response to France / Thomas Pearsall / European Photonics Industry Consortium / Industry or trade association in the beginning of this document.

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		costly and time-consuming, but would be easily justified by the economic and technological importance of this material. A restriction in applicability of the material can imply a risk in fading of technological advantages of European Hi Tech industry that may have been gained over a long application of solid scientific development applying and disseminating example safety assessment and standards. Additional risk is to lose the control and influence to regions outside Europe potentially less aware of environmental health and safety standards. We are pleased by the decision of the Commission to review the RAC opinion on the CLP classification of gallium arsenide with respect to the endpoint carcinogenicity. We regard it necessary however, that the RAC opinion on the CLP classification of gallium arsenide be also reviewed with respect to all endpoints and in particular with respect to the endpoint fertility. Sincerely, Dietmar A. Schmitz AIXTRON SE Vice President Corporate Technology Transfer	
21/04/2011	Germany / European Technology Platform Photonics21 / Industry or trade association	*ECHA comment: The attached document (REACh_Photonics21.docx) is copied below.* To: European Chemicals Agency From : European Technology Platform Photonics21 Subject: **Risk Assessment Committee concerning Gallium Arsenide:** **Opinion proposing harmonised classification and labelling at Community level of** **gallium arsenide ECHA/RAC/CLH-0000000792-73-03/F** Submission on-line at: http://echa.europa.eu/consultations/harmonised_cl_en.asp On behalf of the European Technology Platform Photonics21 I am writing to request a reopening of the recommendation procedure for classification of gallium arsenide. We feel strongly that the procedure used by the Risk Assessment Committee (RAC) of ECHA to determine the CLP classification for gallium arsenide is not appropriate to determine whether or not gallium arsenide represents a biological risk.	Thank you for your comments. Regarding your comments on read-across, please see point 1) of the Annex to RCOM (Additional response to comments). Regarding your comment on occupational epidemiological studies please see response to Germany / Christian Eckert / ZVEI / Industry or trade association in the beginning of this

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		In particular, the Read-Across approach was applied without sufficient proof of the appropriateness. The approach was used to overrule the toxicological test findings despite strong evidence that the carcinogenicity of arsenicals is likely to have a threshold below which there is no carcinogenic activity[2]. The supportive value of the epidemiological studies in the semiconductor industry was not recognized, thereby ignoring the existence of exposure data in this industry[3,4] We support the REACh initiative of the European Commission and its classification of biologically hazardous materials, provided of course that each classification be determined by a rigorous and scientifically supported testing procedure. It is critical that these tests measure the innate toxicity of the material being cited, not its form or its apparent relationship to some other material that may be toxic. Gallium arsenide is present in our daily environment as a solid and inert material. It is used to make transistors and lasers. The transistors are required for every mobile telephone. There is a gallium arsenide laser in every CD player, and also in every industrial solid-state laser. These are used to cut and weld steel on automobile assembly lines and in critical surgical operations on the eye. Gallium arsenide lasers are widely used for amplification in modern optical fiber telecommunications. In the opinion of Photonics21 it would be very hard to imagine a world without mobile telephones, fiber-optic telecommunications, CDs, and key surgical procedures. We do not know of any other material that could serve as a substitute. It is a material of such importance, that recommendations about its continued use should be made carefully, using contemporary scientific standards that are relevant both to gallium arsenide and to the way it is used in various applications. Such a procedure may be more costly and time-consuming, but would be easily justified by the economic and technological importance of this material. We are pleased by the decision of the Commission to review the RAC opinion on the CLP classification of gallium arsenide with respect to the endpoint carcinogenicity. <u>We regard it necessary, however, that the RAC opinion on the CLP classification of gallium arsenide be also reviewed</u> with respect to all endpoints and in particular with respect to the endpoint fertility. Sincerely,	document. Your comments on use of gallium arsenide are noted. However use of a substance is not relevant for the classification which is a result of assessment of intrinsic properties of the substance. Assessment of the hazard properties of GaAs as a substance and risk assessment from exposure related to usage of GaAs in the microelectronic industry are different things. Regarding your comment on toxicity to reproduction, please see response to France / Thomas Pearsall / European Photonics Industry Consortium / Industry or trade association in the beginning of this document.

[2] Dr. Ernst M. Bomhard, Comments on the RAC Opinion on Gallium Arsenide, Jan. 2011
[3] Dr. Ernst M. Bomhard, *Derivation of a DNEL (Inhalation local and systemic) for Gallium Arsenide,* 15 November 2010
[4] Gallium Arsenide -Position of ZVEI – German Electrical and Electronic Manufacturers' Association
On "Opinion of the Committee for Risk Assessment (RAC) proposing harmonized classification and labelling at Community level of Gallium Arsenide, adopted 25th May 2010" Frankfurt am Main, 28. January 2011

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		Bernd Schulte Vice President, Photonics21 European Technology Platform Executive Vice President and Chief Operating Officer, AIXTRON	
21/04/2011	Germany / AZURSPACE SOLAR POWER GmbH / Company-Downstream user	European Chemicals Agency Annankatu 18, P.O. Box 400 Fl-00121 Helsinki, Finland Heilbronn, April 20, 2011 Gallium Arsenide harmonized classification challenging the credibility of REACH and affecting European Semiconductor industry, photovoltaic, aerospace industry, military and photonic industry Greetings: European REACH process has been shared and supported by AZUR SPACE Solar Power GmbH in cooperation with our suppliers and customers since 2008. The harmonized classification and labelling process of Gallium Arsenide has raised our attention and serious concern. Our major concerns are : - the nontransparent way this substance has been assessed under the new REACH rules - the challenge this precedent causes for REACH and its stakeholders within ECHA - a long term threat for whole European compound semiconductor industry and market – especially the aerospace industry, concentrated solar power, wireless communication, laser and photonics, LED lightening that means threat to the most important future technologies. 1. Gallium Arsenide (GaAs) is the key semiconductor material for a wide family of applications, for industry, national safety and infrastructure. Mobile phones, LEDs for cars and lightening, remote control, CD/DVD, displays, as well as mobile communication networks, microwave radar, laser technique and solar power for European space application and recently introduced highly efficient concentrator photovoltaics (CPV) might be listed as well known examples. GaAs is used as a basic substrate (supplied as thin wafer) for the mentioned device structures grown on top of them as single crystalline layers as well as a basic constitutional material within these layer structures. It cannot be replaced from physical reasons - its structural and semiconductor properties - without loosing most of these applications. It is well known that GaAs is very stable under normal conditions and behaves completely different compared to its components from the hazardous point of view. It has to be mentioned that within industrial production this material is handled in closed cycles and processes to meet the demands of specification, technology, purity, quality and human and environmental safety as well. Finally all mentioned devices are encapsulated like every electronic device not allowing any human contact to any of the device materials. Waste management and recycling is well defined and established. 2. AZUR SPACE Solar Power GmbH is a world leading developer and manufacturer of high efficient GaAs solar cells for space and terrestrial applications. Compared to silicon or thin film photovoltaics the GaAs stackable solar cell technology will allow in future very high efficiency beyond 50 %. More than 40 % have been achieved currently.	Thank you for your comments. Your comments on use of gallium arsenide are noted. However use of a substance is not relevant for the classification which is a result of assessment of intrinsic properties of the substance. Regarding your comment on the Annex XIV, eliciting the authorisation regime please see the response to Germany / Christian Eckert / ZVEI / Industry or trade association earlier in this document. Quantitative risk estimation is not a part of the assessment for the classification of a substance. In the preamble to the IARC Monographs (amended January 2006) that you refer to it is also stated that “A cancer ‘hazard’ is an agent that is capable of causing cancer under some circumstances, while a cancer ‘risk’ is an estimate of the

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		In case the irreplaceable key material GaAs would nevertheless be included into Annex XIV of REACH for substances of very high concern (SVHC) followed by a time limited authorization, AZUR SPACE Solar Power GmbH and its customers would be essentially affected regarding - the reliable delivery of GaAs wafers from European wafer manufacturers for testing, development and device production as explained above due to a direct or indirect impact, - risk of restriction under Annex XVII which would affect even the GaAs material internally synthesized and included in the device structures of our products - risk on long term trust and supply reliability for our customers manufacturing solar cells for i.g. Galileo GPS system, Meteosat, diverse communication satellites, space based environmental monitoring systems as well as European concentrator photovoltaic (CPV and CHP) power stations in the Mediterranean area. - risk of interrupting the European adding value chain (starting with the GaAs wafer manufacturing) and the physical supply chain as well as for this strategic basic material for the compound semiconductor applications under strategic interest of EC comm. - risk of preferring other global suppliers against the European ones due to the regulation rules on the basis of a substance inclusion into Annex XIV . 3. In 2006 IARC classified gallium arsenide as carcinogenic for humans (group 1) /1, p.163-190/. In 2009 gallium arsenide was submitted by the French Competent Authorities to the risk assessment committee of ECHA as a transitional classification dossier, although it remains unclear for what reason, given the lack of priority due to the absence of exposure /2/. RAC drafted an opinion and background document on the French proposal that was adopted on May 25, 2010. The substance was recognized by RAC as a Carcinogen Class 1a and Reprotoxic substance Class 1b /3/. At RAC meeting March 8th-10th 2011 a reopening of public consultation has been decided starting it already at the next day, March 11th, without premature public announcement to prepare for this consultation. During our application of the REACH process in general and study of the GaAs classification related documents in detail we noticed some serious oddities in their content and the classification process itself: a) IARC formulated in 2006 its basic approach that “the Monographs represent the first step in carcinogenic risk assessment, which involves examination of all relevant information in order to assess the strength of the available evidence that certain exposures could alter the incidence of cancer in humans. The second step is quantitative risk estimation. Detailed, quantitative evaluations of epidemiological data may be made in the Monographs, but without extrapolation beyond the range of the data available. Quantitative extrapolation from experimental data to the human situation is not undertaken“ /1, p.9/. Thus any quantitative extend and extrapolation beyond the summarized data has been excluded by this limited approach of this monograph. In contradiction to this, for GaAs a detailed carcinogenic classification has been proposed. The required assessment of the human related relevance of the cited data as well as the biological “mode of action” have not been given therein. b) This monograph and its original data source was revised in detail later in 2009 and recently /2,p.37/,/4,p.3/. The limited evidence of this IARC monograph for humans has been acknowledged therein. c) A recent review of all available GaAs related scientific toxicological data /4/ has revealed that IARC monograph and the RAC opinion background document obviously have nearly completely ignored last ten years literature about	carcinogenic effects expected from exposure to a cancer hazard. The Monographs are an exercise in evaluating cancer hazards, despite the historical presence of the word ‘risks’ in the title. The distinction between hazard and risk is important, and the Monographs identify cancer hazards even when risks are very low at current exposure levels, because new uses or unforeseen exposures could engender risks that are significantly higher.” For discussion of your comments on exposure and the IPC Comments on Fine Particulate Matter (your ref /5/), please see response to United States / John Sharp / TriQuint Semiconductor, Inc. / Company-Manufacturer later in this document as well as under point 3) and comments on bioavailability under point 4) of the Annex to RCOM (Additional response to comments). We note that you have provided us with exposure measurements from AZUR, and that these

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		this item and arsenide mode of action evaluation. d) A lot of industrial reports including practical human exposition studies have been skipped as well /4, ch.5/, also those informed about already in 2009 during public consultation /5/. These results show that practical As exposition concentrations in GaAs related working areas are in the range of <50µg/m3 . This concentration is that low that practically no proven relation to production versus environmental background concentration or often much higher food related influence (fish!) could be concluded. e) Upper results in d) have been approved by measurements of As-containing dust at our semiconductor fab work places by the certified institution TÜV Süd in 2006 and 2008 /6, 7/. All measurements have been found to be within a 25 to 35µg/m3 range independent of the distance to GaAs handling work places. f) Nevertheless the French Competent Authorities (2009) and RAC (in 2010) respectively adopted the former IARC classification apparently without further appraisal of more recent empirical data. Especially RAC did not evaluate the quality and validity of the quoted original data and publications cited and performed by the RAC itself ! Therefore, the RAC approach and its conclusion unfortunately do not reflect today's understanding the toxicology of arsenicals !! g) We have realized that selected carcinogenic and fertility affecting findings at test animals have been considered under extreme GaAs and As exposition scenario /1,4,5 and citation therein/ – many orders above the realistic concentration found in the air at GaAs related work places (see d+e above). They were limited to very high concentration, to specific toxic effect not considering others or to specific animal species or sex. Also some results of comparable studies contradict each other. Their general toxicological validity, the approval of such test conditions for human related conclusions, the transfer of these results by an approved "mode of action" to human metabolism and its quantification by proven thresholds kept open. h) The read across principle has been widely used within the RAC opinion and its background document. We identified from literature in example that a major biological resorption of As from GaAs as well as the assumed basic bioavailability of DMAv have not yet been well proven. Concentration and particle effects have not been separated in the exposition tests of the lung tissue. A proven relation between the DMAv concentration and the carcinogenicity have not been demonstrated either. Finally the application of the read across principle for GaAs vs. other As containing compound is rejected in general by many experts due to the lack of chemical and physical comparability and quite different metabolism /4, 5, 8,9,10,13, 16/. i) It would have been more accurate if the authors of the BD and rapporteurs would have cited papers completely. To give only two examples: - The Carter et al (2003) paper's conclusions. On page 326 in /15/ the authors stated, that "..it is clear that highly insoluble arsenide semiconductors were less acutely toxic than equal amounts of arsine or their more soluble arsenious acid products" (see more in detail also /4, 14/). This is in contradiction to the citation of BD on page 11 and suggestion drawn from there. - BD cites industrial exposure and employee data /2, p.ch.2.1/ that are very old and obviously confused the compound semiconductors issue with much bigger silicon semiconductor industry. - All that causes doubt of a serious, scientific and unbiased way of evaluation of data and information within this evaluation process. 4. AZUR SPACE Solar Power GmbH principal concerns : As non-toxicologists , but technicians, physicists and material scientists we are very familiar with best practice	indicate low exposure. However assessment of intrinsic properties for classification does not include assessment of exposure. Regarding your comment on the concentrations in animal studies, we would like to state that the test protocol in the NTP study in rats (NTP, 2000) followed OECD test guideline 451, concentration wise. We acknowledge that similar air concentations does not take place in the semiconductor industry. Regarding your comments on read-across, please see point 1) of the Annex to RCOM (Additional response to comments). Regarding comments on bioavailability, please see point 4) of the Annex to RCOM (Additional response to comments). Regarding your comment on particle effect, please see point 3) of the Annex to RCOM (Additional response to comments). The ultimate carcinogenic form of arsenic has not

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		scientific approaches and methods to analyse problems, formulate theories and draw conclusions. In comparison to ch.3. (above) it seems to be, that RAC has not met these self-evident rules in the case of GaAs evaluation, summarized in the OECD and CLP guidelines for classification and read across /11,12/. Our concerns are with respect to this case: a) The validity of GaAs recognition by RAC as a Carcinogen Class 1a and Reprotoxic substance Class 1b, b) The way the assessment process is proceeded, i.e. - the application of the read across principle to quite different materials, like the stable GaAs and the soluble Arsinic oxides - Obviously many scientific papers have been excluded from the RAC assessment or cited in a very selecting manner. - within RAC assessment occurrence, distribution, concentration and exposure opportunities of an agent are out of consideration. That results in serious conflicts to practical reality. c) Exclusion of the reprotoxic properties from the current public consultation as well as its limitation to "new" results without a definition of what that might be in the light of our claim above. d) RAC opinions and decision play a very substantial role for decisions of EU commission for strong regulation and authorization followed the Appendix XIV list. Also other administration and regulation processes rely on these decisions like CLP and RoHS. Therefore the reliability, transparency and scientific accuracy of ECHA and RAC is of very high importance. e) Indicated GaAs key material uncertainty will unsettle all customers and will exclude any long term contract or program. Customers then will buy outside Europe. 5. The AZUR SPACE Solar Power GmbH expectations are : a) Please reopen the GaAs evaluation process for a full assessment of all CMR criteria on the basis of all available scientific results due to the obviously insufficient scientific evaluation procedure until now within RAC. b) Please review crucially the validity of RAC´s application of the read across principle even on substances with totally different properties – like the stable GaAs vs. other soluble As compounds. c) Please be aware of the importance of RAC and ECHA decisions regarding the substance evaluation not only for REACH but to all other European and national regulation processes touching substances, their manufacturing, use and handling. Therefore the scientific accuracy and transparency of ECHA and RAC should be improved and ensured. d) Please include also an appropriate assessment of the occurrence, distribution, concentration and exposure opportunities within the RAC evaluation of substances as it has been announced within the basic approach of ECHA. Be aware of the drawback of an isolated substance characterization within REACH evaluation process totally separated from the evaluation of occurrence, application, handling and socioeconomical aspects for risk and unsteadiness of industrial application and perspective. An authorization phase years later could not absorb this threat. Appendix: AZUR SPACE Solar Power GmbH as an ISO 14001 qualified company is open for information and demonstration of GaAs processes including the products content analyses. References: /1/ IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Vol.86(2006)	yet been identified, as elucidated in 2010 in a paper by Tokar et al. (2010) . However, RAC believes that there is sufficient information showing the systemic release of the same arsenic ions and metabolites following GaAs exposure as following exposure to classified carcinogenic inorganic arsenicals, and that this must be given weight in the weight of evidence analysis. For RAC evaluation of Carter et al. (2003) please see point 6) of the Annex to RCOM (Additional response to comments). Regarding your comments to the BD and the semiconductor industry in 1981, we agree that the numbers were out of date and covered a larger sector than the gallium arsenide-using industry. The more suitable recent occupational epidemiological studies that you mention have been included in the opinion and BD. Regarding your comment

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		/2/ Annex 1,BD to the opinion proposing harmonized classification and labeling at community level of gallium arsenide, ECHA/RAC/CLH-0000000792-73-03/A1, 25.05.2010 /3/ Opinion proposing harmonized classification and labeling at community level of gallium arsenide, ECHA/RAC/CLH-0000000792-73-03/F, 25.05.2010 /4/ E.M.Bomhard, REACH ChemConsult GmbH, Gallium Arsenide, On the Subject of Carcinogenicity and Fertility effects, March 11, 2011 /5/ IPC contribution to public consultation of GaAs harmonized classification, 24.7.2009, i.e. table 1-3 and text explanation /6/ TÜV Süd, Expositionsmessung nach TRGS 402, 8.3.2006, measured at AZUR at 15.2.2006 /7/ TÜV Süd, Expositionsmessung nach TRGS 402, 31.3.2006, measured at AZUR at 13.3.2008 /8/ Jl Davies, IQE plc Gallium Arsenide Classification; Read across, April 15 2011 /9/ H.V.Aposhian, Reaction to and recommendation for modifying the Background document to the Opinion opinion proposing harmonized classification and labeling at community level of gallium arsenide, ECHA/RAC/CLH-0000000792-73-03/A1, submitted April 18, 2011 /10/ Letter of Eurometaux to DG Enviornment and Enterprise, 2011-02-17, /11/ Guidance on information requirements and chemical safety assessment Chapter R.6: QSARs and grouping of chemicals (May 2008) /12/ OECD Environment Health and Safety Publications, Series on Testing and Assessment No. 80 , Paris 2007, Doc. ENV/JM/MONO(2007)28 /13/ E.M.Bomhard, REACH ChemConsult GmbH, Gallium Arsenide, On the Subject of Carcinogenicity and Fertility effects, April 21, 2011 /14/ Position of TriQuint Semiconductor, Inc. on the Opinion of the Committee for Risk Assessment proposing harmonized classification and labeling at the EU level for GaAs adopted 25 May 2010, April 20, 2011 /15/ Carter et al. The metabolism of inorganic arsine oxides, gallium arsenide, and arsine: a toxicochemical review. Toxicol Appl Pharmacol 193, 2003, 309-334. /16/ H. Vasken Aposhian, PhD, Reactions to and recommendations for modifying the Background document to the Opinion proposing harmonised classification and labelling at Community level of gallium arsenide , ECHA/RAC/CLH-0000000792-73-03/A1 , April 18, 2011	on toxicity to reproduction, please see response to France / Thomas Pearsall / European Photonics Industry Consortium / Industry or trade association in the beginning of this document. RAC agrees with IND who claims that the spontaneous incidence of mononuclear-cell leukemia (MCL)5 in Fischer F344 rats is so high that this effect should be disregarded. Please see the opinion (of 1 December 2011).. We also agree with IND that due to irrelevance to humans the findings of benign pheochromocytoma of the adrenal medulla should be disregarded when assessing carcinogenicity, with reference to Greim et al. (2009). Please see the opinion (of 1 December 2011). Regarding your comments on genotoxicity, please see point 2 of the Annex to RCOM (Additional

[5] synonyme LGLL (Large Granular Lymphocyte Leukemia)

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			response to comments).
21/04/2011	Belgium / European Trade Union Institute	*ECHA comment: The attached document (GALLIUM ARSENIDE CARCINOGENICITY.doc) is copied below.* **GALLIUM ARSENIDE CARCINOGENICITY** - **IARC** (International Agency for Research on Cancer). (2006) IARC monographs on the evaluation of carcinogenic risks to humans - Cobalt in hard metals and cobalt sulfate, gallium arsenide, indium phosphide and vanadium pentoxide. Vol 86: 1-294. World Health Organization, Geneva, Switzerland. - [**American Conference of Governmental Industrial Hygienists** (**ACGIH**) TLVs and BEIs. Threshold Limit Values for Chemical Substances and Physical Agents and Biological Exposure Indices. Cincinnati, OH, 2008, p. 12] A1: Confirmed human carcinogen. /Arsenic and inorganic compounds, as As/ **QC REVIEWED** - **[U.S. Environmental Protection Agency's Integrated Risk Information System (IRIS)**. Summary on Arsenic, inorganic (7440-38-2). Available from, as of March 15, 2000: http://www.epa.gov/iris/ CLASSIFICATION: A; human carcinogen. Basis for classification: Based on sufficient evidence from human data. *An increased lung cancer mortality was observed in multiple human populations exposed primarily through inhalation. Also, increased mortality from multiple internal organ cancers (liver, kidney, lung, and bladder) and an increased incidence of skin cancer were observed in populations consuming drinking water high in inorganic arsenic.* Human carcinogenicity data: Sufficient. animal carcinogenicity data: Inadequate. /Inorganic Arsenic/ **PEER REVIEWED** - **ILO**: Cancer caused by the following agents: Arsenic and its compounds. http://www.ilo.org/wcmsp5/groups/public/---ed_protect/---protrav/---safework/documents/publication/wcms_125137.pdf - **The Office of Environmental Health Hazard Assessment (OEHHA) within the California Environmental Protection Agency. California Proposition 65**: http://www.oehha.org/prop65/prop65_list/files/P65list041511.xlsx - **NIOSH carcinogen list**: http://utweb.ut.edu/chemicalsafety/files/Download/NIOSH%20CARCINOGEN%20LIST%20v1.pdf - **OSHA** PEL: OSHA: Cancer Hazard Supporting Studies: - J Pharmacol Exp Ther. 2003 Dec;307(3):1045-53. Epub 2003 Oct 14. Gallium arsenide selectively up-regulates inflammatory cytokine expression at exposure site. Becker SM, McCoy KL.	Thank you for the provided references.

Date	Country/ Person/ Organisation/ MSCA	Comment	RAC response
		Department of Microbiology and Immunology, Box 980678, Virginia Commonwealth University, Richmond, VA 23298-0678, USA. Abstract Gallium arsenide (GaAs), a technologically and economically important semiconductor, is widely utilized in both military and commercial applications. This chemical is a potential health hazard as a carcinogen and immunotoxicant. We previously reported that macrophages at the exposure site exhibit characteristics of activation. In vitro culture of macrophages with GaAs fails to recapitulate the in vivo phenotype, suggesting that complete GaAs-mediated activation in vivo may require other cells or components found in the body's microenvironment. Our present study examined the role of cytokines upon GaAs-mediated macrophage activation. Intraperitoneal administration of GaAs elicited rapid specific recruitment of blood monocytes to the exposure site. This recruitment occurred concomitant with up-regulation of 17 chemokine and inflammatory cytokine mRNAs, while transcripts of three inhibitory cytokines diminished. Administration of latex beads caused less cytokine induction than GaAs, indicating that changes in mRNA levels could not be attributed to phagocytosis. Four representative chemokines and cytokines were selected for further analysis. Increased cytokine mRNA expression was paralleled by similar increases in cytokine protein levels, and secreted protein products were detected in peritoneal fluid. Cytokine protein expression was constrained to myeloid cells, and to a lesser extent to B cells. Alterations in patterns of cytokine gene expression elucidate mechanisms for increased cellular activation and antigen processing, and modulation of the inflammatory response. Our findings indicate that in vivo GaAs exposure alters cytokine gene expression, which may lead to an inflammatory reaction and contribute to pathological tissue damage. - Toxicol Appl Pharmacol. 2003 Jan 1;186(1):18-27. Impact of in vitro gallium arsenide exposure on macrophages. Harrison MT, Hartmann CB, McCoy KL. Department of Microbiology and Immunology, Virginia Commonwealth University, Ricchmond, VA 23298-0678, USA. Abstract The semiconductor gallium arsenide (GaAs) is classified as an immunotoxicant and a carcinogen. We previously showed that GaAs in vivo induces several phenotypic changes in macrophages located at the exposure site, indicative of an activated state. These physiological alterations may be a primary or secondary consequence of chemical exposure. To discern primary influences, our current study examined the in vitro effects of the chemical on macrophage cell lines and murine peritoneal macrophages. GaAs augmented cathepsins L and B proteolytic activities in all three sources of macrophages. Expression of the two mature isoforms of invariant chain and its cleavage	

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		fragment was also significantly increased, indicating that the chemical directly affects macrophages. However, GaAs did not alter the overall cell surface expression of major histocompatibility complex class II molecules on macrophages nor influence their ability to stimulate antigen-specific helper T cell hybridomas to respond to intact antigens that require processing. These findings raise the possibility that the chemical's complete in vivo impact may involve cytokines. Further, GaAs in vitro enhanced steady-state cathepsin L protein, and cathepsins L and B mRNA expression in macrophages, indicating that GaAs may alter gene expression, which may contribute to the chemical's adverse biological effects. Copyright 2003 Elsevier Science (USA) - PMID: 12583989 [PubMed - indexed for MEDLINE] Use of the Syrian hamster embryo cell transformation assay for determining the carcinogenic potential of heavy metal compounds. Kerckaert GA, LeBoeuf RA, Isfort RJ. Corporate Professional & Regulatory Services, Procter & Gamble Company, Miami Valley Laboratories, Cincinnati, Ohio 45253-8707, USA. Abstract Cobalt sulfate hydrate, gallium arsenide, molybdenum trioxide, vanadium pentoxide, and nickel sulfate heptahydrate were tested in the Syrian hamster embryo (SHE) assay in order to increase the SHE assay database for heavy metals. All five compounds produced significant morphological transformation at one or more doses in a dose-responsive manner. Cobalt sulfate hydrate, gallium arsenide, molybdenum trioxide, and nickel (II) sulfate heptahydrate were all positive with a 24-hr exposure, suggesting direct DNA perturbation. Vanadium pentoxide was negative with a 24-hr exposure, but positive with a 7-day exposure. This pattern of response (24-hr SHE negative/7-day SHE positive) has been seen with other chemicals which have tumor promotion-like characteristics. Since the inception of the use of the SHE cell transformation assay for detecting the neoplastic transformation potential of chemicals, over 42 heavy metal compounds have been tested in this assay. Based on the 24 metal compounds which have been tested in the SHE, Salmonella, and some type of rodent bioassay, the SHE assay is 92% concordant with rodent bioassay carcinogenicity results, including a sensitivity of 95% (21/22) and a specificity of 50% (1/2). At this time, the measure of SHE assay specificity for rodent carcinogenicity of metals is limited by the paucity of metal compounds which are rodent noncarcinogens. The Salmonella assay results are only 33% concordant with the rodent bioassay for these same chemicals. This relatively high concordance between the SHE assay and the rodent bioassay carcinogenicity results demonstrates the utility of the SHE assay for determining the carcinogenic potential of heavy metal compounds in rodent cancer bioassays.	

Date	Country/ Person/ Organisation/ MSCA	Comment	RAC response
		PMID: 8937893 [PubMed - indexed for MEDLINE] - Environ Health Perspect. 1996 Oct;104 Suppl 5:1011-6. COMPACT and molecular structure in toxicity assessment: a prospective evaluation of 30 chemicals currently being tested for rodent carcinogenicity by the NCI/NTP. Lewis DF, Ioannides C, Parke DV. School of Biological Sciences, University of Surrey, Guildford, United Kingdom. dlewis@surrey.ac.uk Abstract A new series of 30 miscellaneous National Toxicology Program chemicals has been evaluated prospectively for carcinogenicity and overt toxicity by COMPACT (Computer Optimised Molecular Parametric Analysis for Chemical Toxicity. CYP1A and CYP2E1). Evaluations were also made by Hazardexpert, and for metal ion redox potentials; and these, together with COMPACT, were compared with results from the Ames test for mutagenicity in Salmonella, the micronucleus test, and 90-day subchronic rodent pathology. Seven of the 30 chemicals (nitromethane, chloroprene, xylenesulphonic acid, furfuryl alcohol, anthraquinone, emodin, cinnamaldehyde) were positive for potential carcinogenicity in the COMPACT evaluation; xylenesulphonic acid and furfuryl alcohol were only equivocally positive. Four of the 30 chemicals-scopolamine, D&C Yellow No. 11, citral, cinnamaldehyde-were positive by Hazardexpert; 6 of 30-D&C Yellow No. 11, 1-chloro-2-propanol, anthraquinone, emodin, sodium nitrite, cinnamaldehyde-were positive in the Ames test; 2 of 30-phenolphthalein and emodin-were positive in the in vivo cytogenetics test; and 3 of 30-molybdenum trioxide, gallium arsenide, vanadium pentoxide-were metal compounds with redox potentials of the metal/metal ion indicative of possible carcinogenicity. The overall prediction for carcinogenicity was positive for 12 of 30 chemicals: nitromethane, chloroprene, D&C Yellow No. 11, molybdenum trioxide, 1-chloro-2-propanol, furfuryl alcohol, gallium arsenide, anthraquinone, emodin, sodium nitrite, cinnamaldehyde, vanadium pentoxide). This overall prediction has been made on the basis of the results of the computer tests and from consideration of the information from bacterial mutagenicity, together with likely lipid solubility and pathways of metabolism and elimination. PMID: 8933049 [PubMed - indexed for MEDLINE]PMCID: PMC1469712Free PMC Article - [NCI/**NTP** carcinogenesis technical report series; National Cancer Institute/National Toxicology Program; U.S. department of health and human services, TR-492 Y00] Species: RAT Strain/Sex: F344/N/FEMALE	

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		Route: INHALATION Dose: 0; 0.01; 0.1; 1 MG/M3 6 HR/D 5D/WK FOR 105 WK (STUDY DURATION: 105 WK) Tumor Site/ Type of Lesion: LUNG: ALVEOLAR/BRONCHIOLAR ADENOMA Results: POSITIVE Reference: - **NTP 2000** reported GaAs not mutagenic in Salmonella typhimurium, with or without S9 metabolic activation enzymes, and no increase in the frequency of micronucleated erythrocytes was observed in peripheral blood of male or female mice exposed to GaAs by inhalation for 14 weeks. No evidence of carcinogenic activity in male F344/N rats or male/female B6C3F mice exposed to GaAs; clear evidence in female F344/N rats at the 1 mg/M3 dose. There were increases in alveolar/bronchiolar neoplasms and mononuclear cell leukemia. Doses were 0, 0.01, 0.1 and 1 mg/M3, 6 hours/day, 5 days/week for 105 weeks. http://www.socalbuilders.org/docs/GaAs4_29_2010_Revised.pdf - **CDC**: Reducing the Potential Risk of Developing Cancer from Exposure to Gallium Arsenide in the Microelectronics Industry. http://www.cdc.gov/niosh/88-100.html The National Institute for Occupational Safety and Health (NIOSH) is requesting assistance in reducing the potential risk of developing cancer in workers exposed to gallium arsenide particulates in the microelectronics industry. Three recent experimental animal studies have indicated that gallium arsenide dissociates in the body to release gallium and arsenic. The arsenic is inorganic, biologically available, and distributed throughout the body. Inorganic arsenic has been determined by NIOSH to be a carcinogen, whereas gallium, based on available data, is believed to be of low toxicity. Engineering controls, proper work practices, and appropriate personal protective equipment should be used to prevent or greatly reduce the potential for exposure to gallium arsenide. Safety and health officials, editors of appropriate trade journals, and manufacturers of gallium arsenide semiconductor devices are requested to bring these recommendations to the attention of employers, managers, and workers. - The Effect of Arsenic Exposure on Semiconductor Workers at the AXT Plant **Jill Collins. http://nature.berkeley.edu/classes/es196/projects/2005final/Collins.pdf**	
21/04/2011	Germany / Gerhard Hirschle / United Monolithic Semiconductors / Company-Downstream user	*ECHA comment: The attached document (Bomhard_Scientific coments on RAC Opinion on GaAs) is copied below.* United Monolithic Semiconductors (UMS) welcomes the further public consultation on the carcinogenicity of gallium arsenide by ECHA. But based on the attached dossiers of tox. experts we recommend to review and to evaluate again the harmonised classification and labelling of Gallium Arsenide on Carc. 1A and Repr. 1B. **Comments on the RAC Opinion on Gallium Arsenide by Dr. Ernst M. Bomhard** **REACH ChemConsult GmbH** Gallium arsenide (GaAs) is in widespread use in the microelectronic industry. It is marketed mainly as a wafer, in rare	Thank you for your comments. The response also covers the comments from Dr. E.M. Bomhard below. Assessment of the hazard properties of GaAs as a substance and risk assessment from exposure

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		cases also as an ingot. Exposure can occur at production and processing workplaces. The hazards and risks of those exposures have to be carefully evaluated taking up-to-date knowledge on experimental data and experience in humans into account. The Committee for Risk Assessment (RAC), in accordance with Article 37 (4) of the Regulation (EC) No 1272/2008 (CLP Regulation), has adopted an Opinion (1) on the proposal for harmonised classification and labelling of GaAs. According to the opinion of RAC, GaAs should be classified and labelled as follows: **Carcinogenicity category 1A - H350** **Reprotoxicity 1B - H360F** **STOT RE 1 - H372** Labelling: GHS08, GHS09; Dgr; H350 May cause cancer, H360F May damage fertility, H372 Causes damage to the respiratory and haematopoietic system and testes through prolonged or repeated exposure. The original proposal on carcinogenicity classification submitted by France was **Carcinogenicity category 2 – H351**. The action of the RAC was justified by the suggested CMR properties of GaAs. In the following, we would like to comment on the RAC opinion, focusing on the two following issues: reproduction toxicity/fertility and carcinogenicity. **1. Reproduction toxicity/fertility** As mentioned above, RAC is of the opinion that GaAs should be classified as Reprotoxic 1B – H360F due to reported effects on fertility parameters in rodent species. This opinion was justified by: ***"Clear evidence of effects at low doses in the absence of other toxic effects…also supported by the potential of gallium to accumulate in rat testis following inhalation exposure"*** *1.1 Ad "clear evidence of effects on fertility at low doses in the absence of other toxic effects"* A total of four studies reporting effects on fertility parameters have been taken into account by RAC: two studies using intratracheal administration to rats and hamsters (2,3), and two studies from the US National Toxicology Programme, examining effects after a 14-week inhalation exposure in rats and mice (4). In the two publications where GaAs was administered via intratracheal instillation (2, 3), effects other than fertility were not looked at specifically. However, other papers investigating the effects of GaAs after single or repeated intratracheal instillation in comparable conditions reported that the lungs of the animals were severely affected (5-9). These studies contradict the absence of other toxic effects at those exposures. However, these latter studies were not evaluated by RAC. In the NTP inhalation studies on rats and mice, there were rather severe effects on the lungs at and below the concentrations affecting sperms and testes (4). It shall also be noted that the concentration levels at which fertility	related to usage of GaAs in the microelectronic industry are different things. Regarding your comment on toxicity to reproduction, please see response to France / Thomas Pearsall / European Photonics Industry Consortium / Industry or trade association in the beginning of this document. You claim that animal data on gallium arsenide was discarded by RAC. That is not correct, but RAC considered it proper to take into consideration the available knowledge on carcinogenicity from arsenic compounds. We appreciate that gallium arsenide so far is the only arsenic species tested in a long term carcinogenicity study by inhalation. Regarding your comment on occupational epidemiological studies please see response to Germany / Christian Eckert / ZVEI / Industry or trade association in the beginning of this document.

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		effects were observed (10,000 µg/m3 and above!) do not relate with the typical or even worst-case exposure levels to GaAs at production and processing sites (range: 10 – 100 µg/m3). *2.2 Ad "This is also supported by the potential of gallium to accumulate in rat testis following inhalation exposure*". In the rat study (4), it is quoted: "The concentrations in these tissues [blood, serum or testes as mentioned in the sentence before] were small relative to the concentrations of Ga and As in the lung; this also indicates that there was **no accumulation** [emphasis added] of either Ga or As in these tissues" (4). However, RAC ignored this conclusion from the rat study (4). **2. Carcinogenicity** The RAC opinion mentions that the ***"evaluation of carcinogenic effects of gallium arsenide solely based on results from animal studies is insufficient, especially since animals are less sensitive than humans to the carcinogenic effect of arsenic."*** Therefore RAC decided to include information from human studies1 on arsenic compounds listed as carcinogens in category 1A in CLP Annex VI and apply read-across to GaAs. It was further stated that ***"a read-across approach is further supported by toxicokinetic data describing the formation of similar arsenic metabolites following GaAs exposure as those formed following exposure to classified arsenic compounds"*** and it was agreed ***"that the carcinogenicity of arsenic and arsenic compounds is of relevance to gallium arsenide and must be taken into account."*** However, we would like with regard to the above, raise the following arguments: □ Animal data on GaAs exist but this information was discarded by RAC □ Inorganic arsenicals others than GaAs have never been tested adequately for carcinogenesis, and never by the inhalation route (10) 1 Results of epidemiological studies of carcinogenicity from exposure to arsenic compounds in copper smelters and from drinking water □ Several human epidemiological studies on As carcinogenicity *in the semiconductor industry* were not considered □ The genotoxic effects of GaAs do not seem totally comparable with other arsenicals, limiting the validity of the read-across □ Recent evaluations pointing towards a threshold for the carcinogenic effects of As were not considered by RAC *2.1 Animal experiments with GaAs* Two valid **carcinogenicity studies** with inhalation exposure of F344/N rats and B6C3F1 mice performed within the US NTP are available (4). Exposure in these studies was to GaAs aerosols (whole-body 6 hours/day, 5days/week for 105 weeks, at concentrations of 0.01, 0.1, 1.0 mg/m3 in the rat study; 0.1, 0.5, or 1.0 mg/m3 in the mouse study). The results can be summarised as follows: □ significantly increased incidences of benign and malignant neoplasms in the lung in female F344/N rats at the	Regarding your comments on genotoxicity, please see point 2) of the Annex to RCOM (Additional response to comments). Regarding your comments on threshold for carcinogenicity, please see point 2) of the Annex to RCOM (Additional response to comments). Regarding your comment on particle effect, please see point 3) of the Annex to RCOM (Additional response to comments). Response to comment on carcinogenicity in female rats as secondary effect from chronic active inflammation/chronic irritation of the lungs, please see point 3) of the Annex to RCOM (Additional response to comments). Regarding your comment on mode of action for carcinogenicity we refer to point 2) of the Annex to RCOM (Additional response to comments). Regarding your comment on use ("Facts") please see response to France /

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		highest concentration (i.e. 1.0 mg/m3). increased incidences of benign neoplasms of the adrenal medulla and increased incidences of mononuclear cell leukaemia at the highest concentration (1.0 mg/m3). It shall be noted here that the relevance for humans of these increased incidences is questioned (11-13). there was no evidence of carcinogenic activity of GaAs in male F344/N rats exposed to 0.01, 0.1, or 1.0 mg/m3. there was no evidence of carcinogenic activity in male or female B6C3F1 mice exposed to 0.1, 0.5, or 1.0 mg/m3. In the rats, chronic active inflammation of the lungs was observed at all concentrations tested. This inflammation was similar to that caused by other particles like talc or quartz. It is important to note that the occurrence of lung tumours in rats under conditions of chronic inflammation of the lungs is a phenomenon that has been observed with other particulatematters and reported in the literature (14). The rat seems to be the most sensitive species to that kind of phenomenon and female rats are reported as being generally more susceptible (4, 14-18). The lung tumours observed in the female rats shall therefore be considered in the context of the chronic inflammation of the lungs as a secondary mechanism and not as an indication of a primary carcinogenic effect of GaAs. These facts were not considered by RAC who concluded that "GaAs is a carcinogen of high potency ". *2.2 Human data on arsenic carcinogenicity in the semiconductor industry* Several recent well conducted epidemiological studies on large populations in the semiconductor industry have not provided evidence of causal associations with exposure to arsenicals (not further specified). No excess of typical cancers associated with arsenic exposure (lung, skin, urinary bladder) was reported (19-23). RAC did not evaluate such studies but referred to IARC 2006 (24), which found, without further explanation, that "none of the [two described (25,26)] studies of cancer in the semiconductor industry were informative with regard to GaAs". Three of the new studies or updates of epidemiological studies published since 2006 (19-23) could have been included in the RAC evaluation. Further two studies investigating exposure to arsenicals were published after adoption of the RAC opinion (21,22). A careful and comprehensive evaluation of all these studies could have come to the conclusion that exposure to GaAs/arsenicals at workplaces is not associated with an increased risk of cancer, despite the fact that exposure was demonstrated. As (and Ga) exposure has not been quantified in these studies. However, there are several publications available reporting exposure situations at different workplaces in the semiconductor industry and partly also including biomonitoring data (27-36). Altogether, they allow the conclusion that there is exposure to As at these workplaces which despite of the high worker protection level in this industry results in increased As absorption. *2.3 Mode of action of arsenic carcinogenicity* Referring to IARC 2006 (24), which assigned GaAs to a group 1 carcinogen based on the bioavailability of As from GaAs and a suspected role of Ga in the induction of lung tumours in female rats, RAC only briefly mentioned some "established mechanistic events of carcinogenicity" (page 37), all of which relate with indirect action on the DNA. Further, RAC stated that "no threshold has been identified for the carcinogenic effect of arsenic and it is assumed that the risk of cancer increases linearly with the dose".	Thomas Pearsall / European Photonics Industry Consortium / Industry or trade association in the beginning of this document. Regarding your comments on read-across, please see point 1) of the Annex to RCOM (Additional response to comments). Regarding your comment on organoarsenic from seafood, please see the opinion. Regarding comments on bioavailability, please see point 4) of the Annex to RCOM (Additional response to comments).

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		There are no indications in the database on GaAs for those “established mechanistic events”. To the contrary, those genotoxicity tests which are mostly positive with other arsenicals, i.e. the micronucleus tests, were negative with GaAs in vitro and in vivo. In recent years, both a large body of mode of action data as well as results from various epidemiological studies clearly argue for a threshold of the carcinogenic effects of As (37-41). Admittedly there is as yet no generally accepted and quantified threshold value. RAC has not considered these data and referred only to epidemiological studies in highly As exposed copper smelters and people exposed to high As concentrations in drinking water. Epidemiological data showing no increased (or even reduced) risk of cancer at lower exposures were not included. **3. Concluding remarks** The available database does not support the conclusion that GaAs is a human carcinogen. Therefore, classification of GaAs into Carc. 1A - H350 is not justified. The RAC’s rationale for applying read-across to arsenicals carcinogenic in humans ignores recent developments in the assessment of the mode of action of As carcinogenicity (threshold). The claims by RAC for classification of GaAs into Reprotoxicity 1B – H360F are not supported by the available data. The fertility effects secondary to inflammatory effects are not GaAs specific and do not justify classification into Reprotoxic 1B – H360F. The RAC failed to critically and carefully evaluate the comprehensive dataset on GaAs and the issue of the carcinogenicity of As. **4. References** 1. RAC. Committee for Risk Assessment. Opinion proposing harmonised classification and labelling at Community level of gallium arsenide. European Chemicals Agency. Adopted 25 May 2010. 2. Omura et al. Fundam Appl Toxicol 32, 1996, 72-78. 3. Omura et al. Toxicol Lett 16, 1996, 123-129. 4. NTP Technical Report on the Toxicology and Carcinogenesis of Gallium Arsenide in F344/N Rats and B6C3F1 Mice (Inhalation studies), NTP TR 492, Sept. 2000 5. Goering et al.Toxicol Appl Pharmacol. 92, 1988, 179-193. 6. Tanaka et al. Fukuoka Igaku Zasshi 91, 2000, 21-33. 7. Webb et al. Toxicol Appl Pharmacol 76, 1984, 96-104. 8. Webb et al. Toxicol Appl Pharmacol 82, 1986, 405-416. 9. Webb et al.. Am Ind Hyg Assoc J. 48, 1987, 660-667. 10. Huff et al. Toxicol Sci 55, 2000, 17-23. 11. Greim et al. Crit Rev Toxicol 39, 2009, 695-718. 12. Caldwell. Reg Toxicol Pharmacol 30, 1999, 45-53. 13. Lington et al. Fundam Appl Toxicol 36, 1997, 79-89. 14. Nikula. Inhal Toxicol 12, 2000, 97-119.	

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		  1 INTRODUCTION Effective May 25th 2010 the Committee for Risk Assessment (RAC) has proposed the following for the harmonized classification and labeling of gallium arsenide (EC Number: 215-114-8, CAS Number: 1303-00-0) according to the Regulation (EC) No 1272/2008 (CLP Regulation). Carcinogenicity Cat. 1A Reprotoxicity Cat. 1B (RAC, 2010) The original proposal for classification had been submitted by France. France originally proposed a classification in category 2 (H351) for carcinogenicity (CLH-GaAs, 2009). The RAC opinion to propose carcinogenicity Cat. 1A for gallium arsenide is based on the IARC Monograph No. 86 (2006) classifying gallium arsenide as as carcinogenic to humans. This classification has been developed in the working group (October 7-14, 2003) and presumably adopted at that meeting. Except for two papers (Carter et al., 2003; Styblo et al., 2000), all literature on toxicology and epidemiology of gallium arsenide and other arsenicals as well as on the epidemiology in the semiconductor industry quoted in the IARC monograph predominantly originates from the decades 1980 and 1990. However, over the past decade an ample range of new studies on epidemiology and the toxicological mode of action of arsenic have been published. Almost none of these results have been included into the IARC monograph. The preamble of the IARC monograph highlights that considerations on the mode of action normally should not play a decisive role in the evaluation of the hazardous potential of a substance: “These categories refer only to the strength of the evidence that an exposure is carcinogenic and not to the extent of its carcinogenic activity (potency) nor to the mechanisms involved”. In the case of gallium arsenide IARC apparently deviated from this principle. In fact, the category “carcinogenic to	

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		humans" was derived solely from data on the bioavailability of arsenicals after oral and intratracheal (i.t.) administration and on data from hamsters indicating metabolism comparable to other arsenicals known to be carcinogenic to humans (i.e. after to i.t. instillation of 5 mg/kg body weight in 0.05 % Tween 80/phys. NaCl; bioavailability of arsenic from gallium arsenide about 10% compared to sodium arsenate and sodium arsenite; Rosner and Carter, 1987). A mode of action justifying this extrapolation was, however, not presented by IARC. RAC adopted the IARC classification apparently without further appraisal of more recent empirical data. Beyond the IARC monograph the RAC opinion essentially quotes older publications that are listed in the ATSDR (2007) review and in the NTP report (2000), in particular, on the epidemiology of arsenic (a rather selective compilation). The RAC opinion does not reveal any proper assessment of the quality and validity of the quoted data performed by the RAC itself. Therefore, the RAC approach and its conclusion do not reflect today's understanding the toxicology of arsenicals. Hence, the RAC opinion on the carcinogenicity of gallium arsenide hardly represents an independent evaluation performed sufficiently diligent and based on up-to-date scientific knowledge to appropriately reflect the importance of the case. With respect to the data assessing the possible impact on male fertility, RAC has adopted the claim of IARC (2006) that gallium is accumulating in the testicular tissue without explaining the contradiction to the NTP study reporting expressis verbis no accumulation. In addition, RAC claimed that the findings on testes and spermatogenesis are primary effects observed in the absence of other relevant toxic effects. **2 FACTS** Gallium arsenide is a most important semiconductor material and key to numerous technologies in civil and defense applications. It is not conceivable that gallium arsenide can be replaced in the foreseeable future. Gallium arsenide is marketed as article made from bulk material predominantly in the shape of wafers (up to 8'' in diameter). According to the CLP directive there is consequently no requirement for labeling or classification as hazardous material. Exposure to gallium arsenide may occur during the manufacturing process (worldwide, there are about 4 major producers with only a small number of workers exposed to gallium arsenide and processing of the wafers). The subsequent value chain embraces a large number of companies with hundred thousands of employees. There is no exposure to gallium arsenic during use of electronic devices. Concerning the actual exposure at the workplace, there is a number of publications as well as unpublished data available. Except for a few cases, all measurements show values substantially below 50 µg arsenic/m^3. Bioavailability of arsenic at the sites of industrial exposure reported has been demonstrated by some studies. In general it can be concluded that the bioavailability detected is fairly low. It is, however, difficult to attribute the bioavailable arsenic to particular sources since individuals are exposed to a	

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		comparatively significant level of arsenic from natural sources (geogenic sources and nutrition, in particular, seafood). Furthermore, there is some exposure originating from arsenic being used as raw material during synthesis of gallium arsenide. **3 SUMMARY OF DATA ON THE TOXICOLOGY AND CARCINOGENICITY OF GALLIUM ARSENIDE** Till to day, there is to the best of our knowledge no case of an individual reported that has been damaged by an exposure to gallium arsenide. Accordingly, there are no reports on workers exposed to gallium arsenide showing an increased cancer incidence. For gallium arsenide a data set is available covering all important endpoints and containing studies mostly performed to existing guidelines. There exists no other inorganic arsenic compound for which this is the case. Up to now, gallium arsenide is the only inorganic arsenic compound that has been studied by means of long-term exposure (via inhalation) in 2 species (NTP, 2000). The experimental conditions employed by NTP (whole-body exposure, very small particles at concentrations causing irritation to the lung) are beyond doubt representing a “worst case” scenario. Taking into account the secondary effects caused by the toxicity to the lung no primary carcinogenic effect of gallium arsenide can be derived. Contrary to various other arsenicals, the studies conducted so far on the genotoxicity of gallium arsenide (Ames-, HPRT-, micronucleus tests) revealed no clastogenic/aneugenic and also no mutagenic effects. Gallium arsenide particles apparently have a high potential to cause irritation to the lung when used under the experimental conditions of inhalation or i.t. instillation. This effect is known to be most pronounced at the highly sensitive species rat (Warheit 1997). No evidence exists for humans in this regard. It is known that the inhalation of particles by humans may cause chronic toxicity to the lung and subsequently as a long-term sequela may cause cancer (Valavanidis et al. 2008). Incidentally cancer may be caused by any chronic damage to the lung and also other tissues. While this observation could be seen as attributing a certain carcinogenic potential to small particles, it certainly does not justify in any way the general classification of respirable particles of any composition as carcinogenic to humans. Conclusion: Gallium arsenide is a substance well studied with respect to carcinogenic and genotoxic endpoints. No evidence for a primary genotoxic or carcinogenic effect has been substantiated. **4 SUMMARY OF THE EXPERIMENTAL DATA ON THE POSSIBLE EFFECTS OF GALLIUM ARSENIDE ON FERTILITY**	

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		There exist four studies reporting effects on testes and/or spermatozoa: 16 fold i.t. instillation was applied to rats and hamsters in two studies (Omura et al. 1995, 1996a, b), 14-week inhalation was applied in two studies with rats and mice (NTP 2000). The i.t. – studies do not mention any effects to other organs. However crucial supplemental data on the hamster study were published with four years delay (Tanaka et al. 2000) revealing a weightive impact on the lung. The reported effect on the lung is fully in line with studies by other authors using comparable experimental conditions in rats (Goering et al. 1988; Webb et al. 1984, 1986, 1987). The inhalation studies too report weightive effects to the lung at levels affecting fertility parameters and at concentrations far below these levels. These studies report, in addition, significant haematological changes. In the long-term 2-year inhalation study (NTP 2000) on rats and mice no damage to spermatozoa/-testes were found at concentrations up to 1.0 mg/m3. According to the NTP report (2000) no accumulation of gallium or arsenic in the testicular tissue (nor in blood and serum) has been detected in the 2-year inhalation study. The gallium or arsenic concentrations have not been analyzed in the 14-day and 14-week NTP studies. The aspect of accumulation is further commented in Section 8. In summary it can be concluded that effects on fertility were only observed at dose/concentration ranges causing substantial damage to the lung as well as haematological changes. The concentrations affecting fertility parameters exceeded the concentrations causing damage to the lung by a factor of 1000! Therefore no evidence for a specific effect of gallium arsenide on the male fertility is provided that would justify the classification of gallium arsenide as a reprotoxic substance. **5 NEW EPIDEMIOLOGICAL DATA ON THE SUBJECT OF A THRESHOLD IN THE CARCINOGENICITY OF ARSENIC** A number of more recent epidemiological studies based on quite accurate exposure assessments (essentially studies on drinking water) indicates the existence of a threshold for the carcinogenic effects of (other) arsenicals well above the known exposure experienced during the production and processing of gallium arsenide (Bates et al. 2004; Brown and Ross, 2002; Lamm et al. 2004, 2006, 2007; Meliker et al. 2010; Mink et al. 2008; Schoen et al. 2004; Snow et al. 2005; Tapio and Grosche 2006). New data on the genotoxicity (predominantly on the formation of micronuclei) of (other) arsenicals in humans are also indicative of a threshold at a level that is by far not reached during gallium arsenide production or processing (Basu et al. 2002; Ghosh et al 2007; Paiva et al. 2008; Vig et al. 1984). Overall, above data provide strong evidence for the existence of a threshold for the toxic, carcinogenic and genotoxic effects of arsenic (though the exact value still needs to be quantified). There remains hardly any doubt that there is no way to justify the linear extrapolation of effects to the low non-toxic levels of exposure relevant to gallium arsenide production or processing on scientific grounds.	

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		Various (some of them are very extensive) epidemiological studies carried out in the semiconductor industry consistently show no increase of incidences/prevalences of cancer attributable to arsenic or arsenicals (Beall et al. 2005; Bender et al. 2007; Boice et al. 2010; Darnton et al. 2010; Nichols and Sorahan 2005). **6 EVALUATION OF THE CARCINOGENICITY STUDIES WITH GALLIUM ARSENIDE IN RATS AND MICE** In the 2-year inhalation study perforeds in the framework of the NTP report Fischer F344 rats were exposed to gallium arsenide concentrations of 0, 0.01, 0.1 and 1.0 mg/m3. In the 2-year inhalation study on B6C3F1 mice the concentration levels were 0, 0.1, 0.5 and 1.0 mg/m3. All animals were whole-body exposed 6h/d, 5d/w for 105 weeks . The aerosols used had a MMAD ranging from 0.8 to 1.0 µm (at a geometric standard deviation of 1.9 each). No further data characterizing the aerosols (e.g. their surface morphology) were provided. The non-neoplastic effects reported were: chronic active inflammation, atypical hyperplasia, alveolar epithelial hyperplasia, proteinosis, alveolar epithelial metaplasia in the lung. All of these changes result from a chronic irritation of the lung tissue. They are qualitatively similar to those effects reported as the typical outcome of the exposure to other particles e.g. talc (H2Mg3(SiO3)4) or quartz (SiO2) by inhalation (NTP 2000, Wolff et al. 1988). The increased occurrence of alveolar-bronchiolar neoplasms (mostly adenomas) in female rats is most obviously to be seen as the consequence of the toxicity to the lung. It is not to be interpreted as an indication of a primary carcinogenic effect of gallium arsenide: It is well known that a broad range of chronic inflammatory processes in the lung predispose particular sensitive cells for neoplastic transformations. The longer the inflammation lasts the higher is the resulting risk of cancer formation (Federico et al. 2007). Rats turned out to be the most susceptible species with respect to this mechanism of tumorigenesis (Watson and Valberg 1996). The increased occurrence of mononuclear cell leukemia in female rats at the highest concentration is not relevant to humans. This type of tumor is highly specific to the F344 rat strain. There it is characterized by a high spontaneous incidence and a high variability. Several authors have concluded that this type of tumor is not predictive for humans (Caldwell, 1999; Elwell et al. 1996; Lington et al. 1997). In 2005 NTP stopped using the F344 rat for any experimental work on toxicity for this (and another) reason. Also the increased occurrence of benign pheochromocytomas in female rats most likely has no relevance to humans (Greim et al. 2009). Interestingly, a correlation between non-neoplastic chronic lung lesions and pheochromocytomas has been found in 9 NTP 2-year – inhalation studies with exposure of male F344 rats to particulate matters (female rats have not been includeded in this evaluation). A significant correlation between the occurrence of pheochromocytomas and the severity of inflammations and fibrosis was found. The authors point out that a reduction of the surface area available for gas exchange is resulting from the systemic hypoxaemia that should be expected under the given circumstances. The decrease in gas exchange areas then stimulates the secretion of catecholamines in the adrenal medulla. The	

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		chronic endocrine hyperactivity of the adrenal medulla finally promotes the formation of hyperplasia and neoplasms (Osaki et al. 2002). In summary, it can be concluded that there is no evidence for primary carcinogenic effects of gallium arsenide. **7 EVALUATION OF DATA ON THE GENOTOXICITY OF GALLIUM ARSENIDE** Results from altogether 4 different tests are available (Ames, HPRT, MNT in vitro; MNT in vivo). In the Ames test (preincubation method) gallium arsenide was applied to the *S. typhimurium* stems TA97, TA98, TA100, TA102 and TA1535 at concentrations up to 10000µg/ml. No gene mutation was observed (Zeiger et al. 1992) with and without metabolic activation by means of rat or hamster S9-mix (at concentrations up to 30%). Note: Hamsters are reported to be more similar to humans than rats with respect to the metabolism of arsenic. A gallium arsenide extract (at a loading of 200 mg/ml in DMSO for 72 h at 37 °C, with shaking) was applied to L5178Y lymphoma cells of mice at concentrations ranging from 250 to 2000 µg/ml. The experiment was performed with and without metabolic activation by a rat-S9 mix. In no case a mutation at the HPRT-locus of the L5178Y cells was observed by the microtiter fluctuation technique (Stone 2010). Gallium arsenide was also tested as part of a series of experiments studying the induction of micronuclei in SHE – cells. In this series of experiments within the NTP program, NTP analyzed a totality of 16 chemicals were tested, which were under investigation for carcinogenicity at that time. The concentrations ranged from 2.5 to 10 µg/ml; treatment period was 24 h. Concentrations of 10µg/ml were clearly cytotoxic. In contrast to the (positive) reference substance colchicine no micronuclei were induced by gallium arsenide (Gibson et al. 1992). The frequency of micronuclei in erythrocytes was analyzed in samples of peripheral blood taken from 10 mice (in 2 concentrations only 9 animals) of each of the tested concentrations (0.1 – 75 mg/m3) used in NTP's 14–week study. A total of almost 200,000 normochromatic erythrocytes was evaluated. No indication of any exposure related effect was found (NTP 2000). In conclusion, none of the studies addressing the different endpoints yielded evidence for a genotoxic effect of gallium arsenide. While numerous studies on gene mutation with other arsenicals also do not show positive effects, most studies on chromosomal damage or aneugenic effects do show positive effects in vitro as well as in vivo. Diarsenic trisulfide is an exception though. The oral administration of this substance in 4 different experiments (at doses of 100, 160, 500 and 500 mg/kg body weight) to CBA mice did not increase the incidence of micronuclei in polychromatic erythrocytes in any of the experiments.	

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		It is remarkable, however, that only in the case of diarsenic trisulfide noticeable amounts of arsenic could be detected in the blood (390 – 900 ng/ml, at a detection limit of approx. 100 ng/ml). For all the other tested substances (sodium and potassium arsenite and diarsenic trioxide; all administered intraperitoneally at a doses up to 10 mg/kg body weight) the concentration of arsenic in the blood was below the detection limit. Despite this a significant and partly marked increase of micronuclei was detected with those other substances (Tinwell et al.1991). These findings highlight that obviously the proof of the bioavailability of arsenic originating from inorganic arsenicals does not allow deriving any conclusion about the occurrence or non-occurrence of any effect typical for arsenic. Several life-span studies with Syrian hamsters should be mentioned in this context. The animals were intermittently intratracheally treated over a period of 15 weeks. In the case of potassium arsenate and diarsenic trioxide an increased number of lung tumors was observed. This was not the case for diarsenic trisulfide. Gallium arsenide was also negative but the number of surviving animals was too small to allow for clear-cut conclusions (Ishinishi et al. 1983; Ohyama et al. 1988; Pershagen et al. 1984; Pershagen and Björklund 1985; Yamamoto et al. 1987). Thus, there is some evidence also for qualitative differences between the various inorganic arsenicals with respect to their potential to cause tumors. **8 EVALUATION OF FERTILITY STUDIES WITH GALLIUM ARSENIDE** A total of 4 studies is available which show effects on spermatozoa and testes: two studies in rats and hamsters with 16 x i.t. instillation each, two 14-week inhalation studies on rats and mice (Omura et al. 1985, 1986a,b; NTP 2000). The weekly administered dose in the i.t. studies was 7.7 mg/kg/d in both cases. The concentrations in the inhalation studies were in both studies 0, 0.1, 1.0, 10, 37 and. 75 mg/m3, (6 h/d, 5 d/w). Effects reported in the i.t. studies were essentially related to the stages of spermatogenesis, the morphology of spermatozoa and their motility. In the inhalation study in rats slight effects on the motility of spermatozoa were observed at 10 mg/m3. Minimal testicular atrophy was recorded at 37 mg/m3, whereas this effect was moderate to severe at 75 mg/m3. In the inhalation study in mice hypospermia and testicular atrophy were found at concentrations at or above 10 mg/m3. The i.t. studies do not mention any findings related to other organs. However, other data from the hamster study published elsewhere as well as from studies on rats by other authors using comparable experimental conditions reveal among others quite massive effects on the lung! Tanaka et al. (2000) reported further details on the hamster study performed by Omura et al. (1996b), i.e. decreased body weights, a massive effects on the lung and kidney damage. A number of other studies in rats with single or repeated i.t. instillation at comparable dose levels also demonstrate marked lung toxicity (Goering et al. 1988; Webb et al. 1984, 1986, 1987).	

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		The 14-week inhalation study in rats revealed effects on the lung at 0.1 mg/m3 and above as well as haematological effects at 10 mg/m3 and above. The 14-week inhalation study in mice revealed effects on the lung at 1.0 mg/m3 and above as well as haematological effects at 10 mg/m3 and above. No adverse effects on spermatozoa or testes were reported in the 2-year inhalation studies in mice and rats at concentrations up to 1.0 mg/m3 . One of the two reasons for RAC's decision to classify gallium arsenide into reprotoxicity Cat. 1B was „..clear effects on fertility at low doses in the absence of other toxic effects…" is thus not substantiated by the available data. In fact the dose levels causing effects can not be called low since due to the accumulation in the lung the cumulative doses have to be taken into account for a proper assessment. A plausible explanation for the observed effects on spermatozoa and testes is provided by the fact that all studies without exception report severe damage to the lung. This damage of the lung certainly a persistent hypoxaemia (see also Ozaki et al. 2002). It has been known for quite some time that hypoxaemia of various causes (high altitude exposure, diseases of the lung) has adverse effects on spermatozoa and the function and morphology of testes. This applies to humans as well as to laboratory animals. (Aasebo et al. 1993; Donayre et al. 1968; Farias et al. 2005, 2010; Gasco et al. 2003; Gosney 1984,1987; Liao et al. 2010; Semple et al. 1984; Shevantaeva and Kosyuga, 2006; Verrati et al. 2008). Under the described experimental conditions of gallium arsenide studies it therefore appears completely academic to discuss in this context the potential role of at most minute traces of metalloids possibly involved (here arsenic and/or gallium). The rationale given by RAC „This is also supported by the potential of gallium to accumulate in rat testis following inhalation exposure" is in contradiction to the authors of the NTP study. Obviously RAC took this argument from the IARC monograph (2006) without commenting on the discrepancy with the NTP report. The judgment of the authors of the NTP study was not objected by the 11 independent experts of NTP's Technical Reports Review Subcommittee. Presumably the NTP judgment is based on the observation that compared to the accumulation in the lung the increase of the gallium and arsenic concentration in the testicular tissue is insignificant. Gallium and arsenic concentrations in the lung tissue reached their peak value of more than 100 µg/g after an 6-month exposure to gallium arsenide at a concentration of 1.0 mg/m3 . For comparison, at this time point a concentration of 0.50 µg gallium/g and 1 µg arsenic/g respectively was detected in the testicular tissue. A marked decrease of the gallium and arsenic concentrations in the lung tissue occurred after 6 months. According to the authors this was due to an increased activity of the macrophages. At a concentration of 0.01	

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		mg/m3 (still causing irritation to the lung) there were no traces of gallium detectable in the testes at any time and the concentration of arsenic was at the level of the controls. The relevance of the minimal accumulation of gallium and arsenic in the testes to the task of safeguarding occupational health seems more than questionable. This has to be seen in the light of the substantial mobilization of the gallium arsenide particles accumulated in the lung instigated by the activity of the macrophages at a state of massive lung damage. The absence of any detectable gallium concentration in the testicular tissue at the exposure level closest to the actual situation at the work station i.e. 0.01 mg/m3 does not support the assumption of an accumulation relevant for classification. In summary there is no effect of gallium arsenide on fertility relevant to classification and labeling. **Note:** gallium compounds, e.g. gallium nitrate, are intravenously applied at fairly high dose levels (10 to 25 mg/kg body weight) to treat cancer, hypercalcaemia and metabolic bone diseases. No adverse effects on testes or on fertility have been reported (Chitambar 2010). **9 COMMENTS ON THE „READ-ACROSS“ APPLIED BY RAC IN THE CASE OF GALLIUM ARSENIDE** RAC justifies its opinion on the classification of gallium arsenide by the argument that arsenic becomes bioavailable after oral or I. t. instillation to hamsters. According to RAC the arsenic bioavailable from gallium arsenide is metabolized to form predominantly dimethylarsinic acid (DMAV) through methylation like in the case of other inorganic arsenicals known to be carcinogenic to humans (Rosner and Carter 1986; Yamauchi et al. 1986). With this reasoning RAC adopts the previous arguments of IARC (IARC 2006). In the respective experiments the solubility of gallium arsenide was enhanced by using Tween 80 or a phosphate buffer. Despite this the absorption rate for intracheal instillation amounted to just 5-10%. The absorption rate for oral administration stayed below 1%. No reference was made to a published Japanese study on bioavailability of arsenic and its metabolites in gallium arsenide production. The study analysed the situation in the production and the processing of gallium arsenide ingots at the end of a shift. It monitored inorganic arsenicals, methylarsonic acid (MMAV), DMAV and trimethylarsinic compounds in urine. A significant increase (by 24 and 22% respectively) of arsenic concentratons in the urine of exposed workers was recorded at the end of a shift. However, at the same time no increase of the concentrations of methylated arsenic species was found (Yamauchi et al. 1989). The above results are in line with corresponding studies for the processing of gallium arsenide wafers. The respective studies find in general very low excretion of arsenic mostly on a level barely distinguishable from the reference group. No increased excretion of MMA or DMA in the urine was found in this case either (Farmer et al. 1990; Morton and Leese 2010; Morton and Mason 2006). The claim that arsenic originating from an exposure to gallium arsenide is metabolized by the human organism to form MMA or DMA through the process of methylation is thus not supported by existing data.	

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		But even if it is assumed that the arsenic originating from an exposure to gallium arsenide is metabolized by methylation as assumed by RAC, this still leaves the question whether it can be concluded that this hypothesis necessarily implies a carcinogenic potential of gallium arsenide for humans. This conclusion would require that the mode of action behind the carcinogenicity of inorganic arsenicals is known and it would in addition require the assumption that there is no threshold for this mode of action. Both conditions are not supported by the available data. Several modes of actions to explain the carcinogenicity of arsenic are currently discussed. The most frequently quoted and thus the most likely mechanisms are i) indirect genotoxicity (chromosome aberration), ii) reactive oxygen species, iii) cell proliferation and transformation and iv) hypo-/hypermethylation of the DNA (ATSDR 2007; Cohen et al. 2006; Schuhmacher-Wolz et al. 2009). For the last three modes of action (ii- iv) a threshold definitely has to be assumed. In the case of chromosome aberrations the majority of publications focus on the induction of micro nuclei. New results on human cells now demonstrate the existence of concentration ranges without any effect (Basu et al. 2002; Ghosh et al 2007; Paiva et al. 2008; Vig et al. 1984). The levels of exposure to arsenic discussed in these studies are well above those relevant to the manufacturing and processing of gallium arsenide. (Farmer et al. 1990; FCM 2010; Morton and Leese 2010; Morton and Mason 2006; Mindt-Prüfert and Szadkowski 1999). Furthermore there is no evidence for an adverse effect of gallium arsenide on chromosomes provided in the published experimental data (Gibson et al. 1997; NTP 2000). Further evidence for the argument that the bioavailability of arsenic originating from inorganic arsenicals not necessarily causes the effects typical for arsenic is provided by the study of Tinwell et al. (1991) on diarsenic trisulfide. For this substance Tinwell did not observe the induction of micro nuclei typical for other inorganic arsenicals. It is well known that seafood contains larger amounts of trimethylated arsenic species and arsenosugar. These arsenic compounds are generally deemed toxicological inert. It is however important to note that up to 4% of the arsenic contained in seafood is present in the form inorganic arsenical compounds (Borak and Hosgood, 2007). In some cases this value is actually exceeded (Norin et al. 1985). Therefore populations with a high consumption of seafood have a relatively *[H. Schenk: "significant" missing ?]* intake of inorganic arsenic. As a result not only small amounts of inorganic arsenic and MMA are excreted but especially an increased excretion of DMA at concentrations of up to 100 µg arsenic/l in urine was reported for these populations (Borak and Hosgood 2007; Heinrich-Ramm et. al. 2002; Heitland and Köster 2008; Wei et al. 2003). No evidence is known to the author pointing at an increased risk of cancer or any other disease caused by arsenic for population with high consumption of seafood. All data published on DMA excretion of workers in the gallium arsenide industry show levels substantially below 100 µg arsenic/l urine (Farmer and Johnson, 1990; Morton and Leese 2010; Morton and Mason 2006).	

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		In summary there is no sufficient evidence - that exposure to gallium arsenide results in an increased level of methylated arsenic species in the human body - that the metabolism of arsenic to methylated arsenic species provides a plausible mode of action to derive a carcinogenic potential for the respective arsenical and - that the data on gallium arsenide gave clues for any of the postulated modes of action. Based on this it appears totally inappropriate to derive form the bioavailability of insignificant amounts of arsenic (comparable to those or actually exceeded by those arising from geogenic sources and from nutrition) and the metabolism to methylated species thereof, as demonstrated in the case of hamsters, classifying gallium arsenide as "carcinogenic to humans". (Dr. Ernst M. Bomhard) **10 REFERENCES** Aasebo et al. Reversal of sexual impotence in male patients with chronic obstructive pulmonary disease and hypoxemia with long-term oxygen therapy. J Steroid Biochem Mol Biol. 46, 1993, 799-803. ATSDR. Agency for Toxic Substances and Disease Registry. Toxicological profile for arsenic. August 2007. Basu et al. Enhanced frequency of micronuclei in individuals exposed to arsenic through drinking water in West Bengal, India. Mutat Res 416, 2002, 29-40 Bates et al. Case-control study of bladder cancer and exposure to arsenic in Argentina. Am J Epidemiol 159, 2004, 381-389. Beall et al. Mortality among semiconductor and storage device-manufacturing workers. J Occup Environ Med 47, 2005, 996-1014. Bender et al. Cancer incidence among semiconductor and storage device workers. Occup Environ Med 64, 2007, 30-36. Boice et al. Cancer mortality among US worker employed in semiconductor wafer fabrication. J Occup Environ Med 52, 2010, 1082-1097. Borak and Hosgood. Seafood arsenic: implications for human risk assessment. Regul Toxicol Pharmacol 47, 2007, 204-212. Brown and Ross. Arsenic, drinking water, and health: a position paper of the American Council on Science and Health. Regul Toxicol Pharmacol 36, 2002, 162-174. Caldwell. Review of mononuclear cell leukemia in F-344 rat bioassays and its significance to human risk: a case study using alkyl phthalates. Reg Toxicol Pharmacol 30, 1999, 45-53. Carter et al. The metabolism of inorganic arsine oxides, gallium arsenide, and arsine: a toxicochemical review. Toxicol Appl Pharmacol 193, 2003, 309-334. Chitambar. Medical applications and toxicities of gallium compounds. Int J Environ Res Public Health 7, 2010, 2337-2361. CLH-GaAs, 2009. Annex XV report, Proposal for harmonised classification and labelling. Substance Name: GALLIUM ARSENIDE, EC Number: 215-114-8, CAS Number: 1303-00-0, Submitted by: France, Date: May 2009, Version: 2 Cohen et al. Methylated arsenicals: the implications of metabolism and carcinogenicity studies in rodents to human	

Date	Country/ Person/ Organisation/ MSCA	Comment	RAC response
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		RAC did not extend its review sufficiently to come to an independent opinion. The Read-Across was applied without sufficient proof of the appropriateness of the Read-Across approach. The Read-Across was used to overrule the toxicological test findings despite strong evidence that the carcinogenicity of arsenicals is likely to have a threshold below which there is no carcinogenic activity.1 **2) Content of RAC opinion:** The outcome of the NTP study was only superficially reviewed and not put into a perspective. The negative genotoxicity data were not adequately considered and also not put into a perspective on the likelihood of a threshold/NOEL of the arsenic carcinogenicity. The supportive value of the epidemiological studies in the semiconductor industry was not recognized, thereby ignoring the existence of exposure data in this industry.2 The two claims that supported the rationale for the repro/fertility classification (absence of other toxic effects and accumulation in rat testis) were not checked and a wrong conclusion was taken. A plausible toxicological mode of action of the fertility effects in experimental animals at high dose levels was not recognized. **Arsenic is rigorously managed in the semiconductor manufacturing environment and there is no consumer exposure** The use of arsenic as a component of GaAs in semiconductor manufacturing does not pose a threat to the human health or the environment due to the closed system manufacturing and the stringent manufacturing controls in place in semiconductor factories using GaAs. The use of GaAs as a semiconductor wafer material is stringently monitored and highly regulated. There is no arsenic exposure potential for the consumer during the use phase of the electronic product, e.g. the mobile phone. The end of life phase of the mobile phones and other electronic products are covered by the EU WEEE directive and therefore potential environmental exposure is minimized. The amount of arsenic in a semiconductor device is typically very low, in the atomic range. Furthermore, the tiny amounts of arsenic present in the semiconductor pose no exposure risk to the consumer of the final electronic product. These trace amounts of arsenic are chemically bound in the silicon crystal and then encapsulated in SiO2. The semiconductor device is further encapsulated in a final package to both physically protect the device and to create a practical means of attaching the device to a printed circuit board. **Conclusion:** UMS strongly recommends to review and to evaluate the scientific data of the recent years and take it into a account for the classification of GaAs regarding - Carc. 1A - H350 and ignoring a threshold and - Repr. 1B – H360F. References: - Dr. Ernst M. Bomhard: *Comments on the RAC Opinion on Gallium Arsenide*, Jan. 2011 - Dr. Ernst M. Bomhard, G*allium Arsenide*: On the Subject of Carcinogenicity and Fertility Effects, 08. April 2011 1 Dr. Ernst M. Bomhard, *Comments on the RAC Opinion on Gallium Arsenide*, Jan. 2011 2 Dr. Ernst M. Bomhard, G*allium Arsenide*: On the Subject of Carcinogenicity and Fertility Effects 08. April 2011	
21/04/2011	Germany / Sylvi	Dear Madame or Sir,	Thank you for your

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	Claussnitzer / WirtschaftsVereinigung Metalle / Industry or trade association	we welcome the opportunity to give comments in the relaunched public consultation and to submit new information on the carcinogenicity of Gallium arsenide. Plese find the comments attached as a PDF File. Yours sincerely Sylvi Claussnitzer (representing the Arsenic Consortium and WirtschaftsVereinigung Metalle Germany) *ECHA comment: The attached document (2011-04-21_WVM_Comment_Consultation_GaAs.pdf) is copied below.* **Comments on second public consultation for a harmonised classification & labelling for Gallium arsenide** **Substance name: Gallium arsenide** **CAS Number: 1303-00-0** **EC Number: 215-114-8** 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. Today, WVM has 639 member companies, including producers and processors of rare metals and compounds. Some of our members also produce and handle arsenic and arsenic compounds as this is a natural component of several non ferrous metal ores and concentrates. In addition, we represent one of the leading producers of arsenic metal. We represent the secretariat for the consortium on arsenic and arsenic compound. GaAs is still produced in the EU, and also imported via articles (mobile devices) and IT chips. Gallium arsenide (GaAs) is within the scope of the consortium managed by WVM. Industry already submitted the REACH registration dossier for Gallium arsenide in the first registration phase although the existing harmonized classification for Gallium arsenide (R23/25 and R50/53) in connection with the relevant tonnage would not require such an early action. Consequently, industry takes full responsibility under REACH. We would like to emphasize that the harmonized classification and labelling case of Gallium arsenide has clearly raised the attention and concern of the whole metals sector and their affected downstream users like the companies of the electronics sector. Major concerns are the way in which the substance was assessed under the new REACH rules, which industry felt was both in conflict with the spirit and the letter of REACH and also set unfortunate precedents. We already addressed that and therefore appreciate the involvement of stakeholders in this second consultation round. Our principal concerns in respect of the second public consultation for a harmonised classification & labelling for Gallium arsenide are threefold: 1) Taking into account the registration information While production of the substance is below the trigger limit for REACH registration in 2010, the industry took a pro-active line and submitted an extensive, fact-based and well-documented early registration. Although French CA were informed of this intention the discussion went ahead and resulted in an RAC opinion that does not recognize the information included in the registration file. In our opinion and based on scientific evidence on the substance this would lead to a different conclusion in respect to the hazard classification. Validity and relevance of submitted	comments. Assessment of the hazard properties of GaAs as a substance and risk assessment from exposure related to usage of GaAs in the microelectronic industry are different things. We note that you represent the secretariat for the consortium on arsenic and arsenic compounds and that IND already has submitted the REACH registration dossier on gallium arsenide. However, as is always the case, the starting point for RAC was the classification proposal from the dossier submitter. When processing this RAC became aware that available knowledge on carcinogenicity from other arsenic compounds was not included and felt it properly and according to the CLP Regulation to include this in the assessment. The NTP animal studies were also included in the assessment. Regarding your comment

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		REACH registration data are ignored and the resulted proposals must therefore reflect an incomplete view. 2) Existing substance specific data must not be ignored Data on GaAs include a long-term carcinogenicity evaluation by NTP and others, in general concluding negative evidence. Additional and new epidemiological work also led to negative conclusions and should not only be recognized as supportive evidence given the low volume and exposure conditions occurring for GaAs producing and using sectors. RAC simply overruled this by read across to well-known carcinogenic Arsenic species (e.g. As2O3). Industry as a whole cannot follow this approach and wonders why high quality substance specific multiyear studies should be conducted in future if they can be set aside by unproven read across from a substance with significant different behavior and toxicological profile. This clearly challenges the priority use of existing data. Based on the existing evidence for GaAs a Carc Cat 1A classification is clearly not warranted. 3) Reprotox analysis should be reopened GaAs was also classified for Reprotox effects based on an opinion of the French CA. Checking the original references, industry discovered that the studies used to conclude the classification were presumably accidentally misquoted by France. This led to the opposite classification as that indicated by the data. Although not foreseen in this consultation phase industry urges ECHA taking into account the scientific comments brought in by the toxicologists acting on behalf the Freiberger Compound Materials GmbH which is a German medium sized company and one of few world-market active producers of GaAs wavers. Taking into account critically the data from original papers a clear effect on fertility at low doses in the absence of other toxic effects cannot be assumed. This clearly contradicts to the proposed Reprotox Cat 1B classification. We would like to emphasize that industry wants REACH to be a correct, credible and efficient risk management tool for the safe manufacture and use of substances, including GaAs. Given the arguments listed above we believe that an in-depth review of all available data, including the registration file and not limited to the carcinogenic endpoint will result in a more adequate classification and labeling proposal.	on occupational epidemiological studies please see response to Germany / Christian Eckert / ZVEI / Industry or trade association in the beginning of this document. Regarding your comment on toxicity to reproduction, please see response to France / Thomas Pearsall / European Photonics Industry Consortium / Industry or trade association in the beginning of this document.
21/04/2011	United Kingdom / Iwan Davies / IQE plc / Company-Manufacturer	*ECHA comment: The attached document (IQE Gallium Arsenide Classification-ReadAcross-LH.pdf) is copied below.* **IQE plc response to Gallium Arsenide Classification: Read Across Analysis** IQE plc analysis of the Read Across approach used on Gallium Arsenide Classification by the ECHA/RAC during 2009/2010 before arriving at its Opinion on 25th May 2010. Dr. JI Davies B.Sc. (Lond.), ARCS, MRSC IQE Group Technology Director 21st April 2011 **The Harmonised Classification of Gallium Arsenide at Community level by the European Chemicals Agency; ECHA/RAC/CLH-0000000792-73-03/F** IQE plc is submitting the following report and comments in respect of the above classification process for Gallium Arsenide. IQE is firmly established as the leading global supplier of advanced Gallium Arsenide and Indium Phosphide compound semiconductor wafers with products that cover a diverse range of applications, supported by an	Thank you for your comments, including the attempt to perform an analogue approach evaluation of gallium arsenide in-line with CLP/OECD Guidance. Regarding your comment on use please see response to France / Thomas Pearsall / European Photonics Industry Consortium / Industry or

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		innovative outsourced foundry services portfolio that allows the Group to provide a 'one stop shop' for the wafer needs of the world's leading semiconductor manufacturers. IQE uses advanced crystal growth technology (epitaxy) to manufacture and supply bespoke semiconductor wafers ('epi-wafers') to the major chip manufacturing companies, who then use these wafers to make the chips which form the key components of virtually all high technology systems. IQE is unique in being able to supply wafers using all of the leading crystal growth technology platforms. Our products are found in many leading-edge consumer, communication, computing and industrial applications, including a complete range of wafer products for the wireless industry, such as mobile handsets and wireless infrastructure, Wi-Fi, WiMAX, base stations, GPS, and satellite communications; optical communications, optical storage (CD, DVD), laser optical mouse, laser printers & photocopiers, thermal imagers, leading-edge medical products, barcode, high efficiency LEDs and a variety of advanced silicon based systems. The demand for the supply of compound semiconductors has seen rapid growth, fuelled largely by the increasing demand for feature rich handsets and smartphones. IQE's strategy of investment in worldwide manufacturing bases offers customers the security of supply and the ability to increase capacity in line with demand. IQE recognises the inherent toxic nature of some of the materials used in the semiconductor industry and as a result, employs a high degree of safety-enhanced and high-integrity equipment features to ensure that hazardous materials are not exposed to personnel. In recognising that Gallium Arsenide possesses some toxic properties, the Proposal being considered here to classify it as a Carcinogenic Category 1A is unjustified and unscientific, based on the evidence presented. The following report addresses the Read-Across approach utilised to reach the judgment offered by RAC/ECHA in its Opinion Document referred to in the above title. On behalf of IQE plc Dr. J. Iwan Davies, Group Technology Director **Executive Summary** A second 45-day Public Consultation on the harmonised classification and labelling under Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) and Classification, Labelling and Packaging (CLP) guidelines, of Gallium Arsenide is currently ongoing, terminating on 25th April 2011. There was minimal negative feedback to the European Chemicals Agency (ECHA) on the 1st Consultation in Jun/Jul 2009. The Risk Assessment Committee (RAC)/ECHA published its Opinion Document in May 2010 and decided to upgrade the category for carcinogenicity, based on read across from other arsenic compounds listed as carcinogens in category 1A in CLP Annex VI, Table 3.1. The new classification was:- **Carc. 1A – H350 (May cause cancer)** **Repr. 1B – H360F (May damage fertility)** **STOT Rep. 1 – H372 (Causes damage to the respiratory and haemotopoietic system and testes through prolonged and repeated exposure)** Owing to a combination of lack of awareness, ignorance and generally poor publicity, the GaAs industry has become more aware of the situation during the last 6 months or so. Efforts are underway through international working groups	trade association in the beginning of this document. Regarding your comments on read-across, please see point 1) of the Annex to RCOM (Additional response to comments). For RAC evaluation of Carter et al. (2003) please see point 6) of the Annex to RCOM (Additional response to comments). Regarding your comments to the IARC monograph, we would like to mention that Tokar et al. (2010) confirms the validity and result of the gallium arsenide longterm NTP study (NTP, 2000). The F344/N rat is known to have high background incidences of certain types of tumors including testicular interstitial cell tumors and mononuclear cell leukemia, and was discontinued from use by NTP because of this. Regarding your comment on effects from particles, please see point 3) of the Annex to RCOM (Additional response to

Date	Country/ Person/ Organisation/ MSCA	Comment	RAC response
		and committees, individual companies, stakeholders, public and political bodies to gather as much information as is possible to support the move to downgrade or to have fully reviewed the classification of GaAs, using a wider breadth of scientific, toxicological and statistical information. The challenge to the GaAs industry would be two-fold. Firstly, the toxicological data would be reviewed for its validity and accuracy, with eminent experts in the field being employed to assist with such activities. Secondly, the approach and mechanisms used by ECHA to proceed to its classification would be cross-examined. Comments and reports, pertinent to both activities, are required to be posted onto ECHA's website by the 25th April 2011 deadline. This review aims to discuss the toxicology, procedures and mechanisms surrounding this classification process. It also seeks to argue the case for a more robust and thorough review of the science (chemistry and toxicology) and how the information can be used more sensibly and accurately within the REACH/CLP classification mechanisms. **GaAs Classification Timeline, Processes & Mechanism** **Timeline** o A French Competent Authority delegation submitted an Annex XV dossier to the European Chemicals Agency (ECHA) in **May 2009** as a "Proposal for Harmonised Classification and Labelling: Gallium Arsenide". o The original classification proposed by the French delegation was:- **Carc. 2 – H351 (Suspected of causing cancer)** **Repr. 1B – H360F (May damage fertility)** **STOT Rep. 1 – H372 (Causes damage to organs)** o The 1st Public Consultation **June/July 2009**; responses received from several Member States and two relevant responses from Freiberger and Recapture Metals, both from Germany. Both commented on the interference of this consultation period with that required to **Register** their substances under REACH regulations. They were already producing dossiers for this purpose and did not find the time to simultaneously compose purposeful comments within the short 45-day period. o On **25th May 2010**, following several RAC Meetings and perusal of the data, literature citations and use of read-across methodology, the RAC published three documents. An "**Opinion to...**, "**Background Document to...** and "**Response to Comments Document to.. the proposed harmonised classification and labelling at Community level of Gallium Arsenide".** o In this Opinion Document, the RAC had revised the original classification to:- **Carc. 1A – H350 (May cause cancer)** **Repr. 1B – H360F (May damage fertility)** **STOT Rep. 1 – H372 (Causes damage to the respiratory and haemotopoietic system and testes through prolonged and repeated exposure)** and followed up with scientific grounds for the Opinion o On **11th March 2011**, ECHA issued a News Alert, announcing a 2nd Consultation period, ending on 25th April 2011.	comments). Regarding your comment on occupational epidemiological studies please see response to Germany / Christian Eckert / ZVEI / Industry or trade association in the beginning of this document. Regarding your comments on threshold for carcinogenicity, please see point 2) of the Annex to RCOM (Additional response to comments). Regarding your comments on the metabolic pathway of gallium arsenide and other arsenic compounds, please see point 5) of the Annex to RCOM (Additional response to comments). Regarding comments on bioavailability, please see point 4) of the Annex to RCOM (Additional response to comments). Regarding your comments on the Rosner and Carter et al. papers, please see the Annex to RCOM (Additional response to comments).

Date	Country/ Person/ Organisation/ MSCA	Comment	RAC response
		Discussion of the RAC Opinion and REACH/CLP Methodology used The RAC reconfirmed the ReproToxicity and Specific Organ Toxicity gradings, but upgraded the classification for carcinogenicity with the following comments:- □ None of the studies of cancer in the semiconductor industry were informative. □ Gallium arsenide was only carcinogenic in female rats (not male or either sex of mouse). □ Carc. Cat 2 was appropriate based on this animal study. □ There was no human epidemiological data for carcinogenicity of Gallium Arsenide available. □ Owing to the increased sensitivity of humans to As-carcinogenicity, it was decided to use data from studies of As-contaminated drinking water and copper smelting environments, due to arsenic oxides(s) – these are already Carc 1A in Annex VI, Table 3.1. □ The process of **Read-Across** was used and applied to GaAs, supported by toxicokinetic data. It described a metabolic pathway from the apparent dissolution of GaAs and similar to that of the already-classified As-compounds. □ By applying **Weight of Evidence** and **Read-Across**, justification for upgrading the category for GaAs to Carc 1A was made by taking the carcinogenicity of other similar (metabolic pathway) As-compounds into relevant consideration. The **read-across** method is one of the techniques used by ECHA (and OECD – Organisation for Economic Cooperation and Development) for filling in of gaps in data when comparing chemicals within a series or grouping. This is covered in more detail in Appendix 1. **Discussion of the Read-Across Approach and RAC Opinion** The justification by the RAC is clearly based, almost exclusively, on the detection *in vivo* of metabolites in ***some*** studies on animals exposed to inhalation and/or ingestion of fine GaAs particles. These metabolites are similar/identical to those found in epidemiological studies on humans, known to have been exposed to arsenic oxides through contaminated drinking water or copper smelting processes. The RAC/ECHA, according to its Opinion Document of May 2010, has read-across the endpoint data for carcinogenicity from arsenic trioxide and arsenic pentoxide to its proposed classification for GaAs – based exclusively on the observation of similar metabolites in blood and tissues. **IQE Evaluation and Concerns on Read-Across** A complete list of those arsenic-related compounds currently in Table 3.1 of Annex VI of the CLP legislation is shown in Appendix 2. Some of these compounds have been removed for this current evaluation of the read-across method, whilst others have been retained, initially in order to ascertain whether they form a chemical category or analogue approach as is outlined in the guidance by CLP/OECD. The chemicals removed from the full table and the reasons are as follows:-	

Date	Country/ Person/ Organisation/ MSCA	Comment	RAC response
		Triethyl arsenate and t-butyl arsine - organometallic compounds Lead Hydrogen Arsenate - lead compound (Pb cation) The remainder of the compounds have been collated in Table 1, which has been constructed along the principles of an ***analogue approach*** in CLP/OECD guideline documentation. GaAs does not sit comfortably in an arsenic compound ***chemical category*** – these are groups of compounds sharing a clear trend in data, whether physico-chemical, human health or environment properties and endpoints. Whilst chemical categories such as groups of i) varying carbon chain length organic compounds or ii) inorganic compounds sharing a common cation and oxidation state, exist in case-studies quoted by OECD/REACH, there is not any such convincing evidence for the arsenic compounds in Table 1. The favoured approach for a minimal range of compounds is therefore, the analogue approach, where a ***limited*** number of chemicals exist. The ***proposed*** classification of GaAs from the RAC Opinion is entered into the Table in red for illustrative purposes. The comments below are derived from an evaluation of this Table, based on the ***analogue approach***:- □ The Table has been presented in order of increasing oxidation state of arsenic from GaAs and arsine at –III, through Arsenic at 0 and then to the oxides and their respective acids at III and V. □ Of the series of arsenic compounds already classified to CLH, only arsine, arsenic, arsenic trioxide and pentoxide (and their acids) are remotely relevant – the others are organic or other metallic compounds □ The oxides plus their hydrated forms are added here in an attempt to evaluate whether a coherent grouping can be formed – with a view to making any form of read-across a more robust activity, based on a wealth of relevant and reliable data. □ In GaAs, Gallium is therefore, *normally* considered the cation and arsenic the anion in this context, although some workers report GaAs as a covalent compound □ To that end, the trioxide and pentoxide, with oxidation state at +III and +V respectively show that the arsenic is overwhelmingly the "cation" – arsenic is a metalloid and an element of extreme versatility, showing this large range of oxidation states. □ The physico-chemical properties are summarised thus:- o GaAs is much more insoluble in water than the oxides (*c.f.* <<1g/L against 37-660g/L). Data for arsenic (and arsine) are similar to GaAs. o The melting point of GaAs is very high at 1238:C (*c.f* 312/315:C for the oxides) o The crystalline structure and appearance of GaAs is quite different to the oxides, grey and metallic (as in arsenic) as opposed to white, hygroscopic crystals/powders for the oxides. o Gallium arsenide and arsenic are generally denser than the oxides. □ There is not therefore, a credible series of compounds from which to easily extrapolate properties and endpoints to GaAs and given the fact that arsine is a gas, the only close analogue is ***possibly*** arsenic. □ It is clear from the Table that the ONLY read-across endpoint is the proposed Carc. Cat. 1A from the oxides to GaAs. There has been no attempt to simultaneously re-classify arsenic, if indeed it were relevant, (with Carc 1A), as might be expected if the read-across methodology were a robust and credible process.	

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		The classification for repeated dose (STOT) and ReproToxicity are clearly not read-across and must have derived from the original animal experiments, principally from the National Toxicity Program [NTP 2000]. To this end, much of the evidence presented thus far appears to downgrade, without total justification, the effect of gallium on toxicity *etc*. More effort appears to be concentrated on read-cross of the As-species. Given the STOT and ReproToxicity endpoints, gallium may well have a role to play in the toxic mechanisms. Overall, it would appear that the read-across process has been performed to a limited extent, maximising on expert judgement but minimising on weight of evidence and ***known*** negative results from both animal and human epidemiological studies.	

Date	Country/ Person/ Organisation/ MSCA	Comment	RAC response

	TARGET	~~ANALOGUE ???~~	POSS. ANALOGUE	~~ANALOGUE ???~~	No data	~~ANALOGUE ???~~	~~ANALOGUE ???~~
CAS No.	1303-00-0	7784-42-1	7440-38-2	1327-53-3	13464-58-9	1303-28-2	7778-39-4
EC No.	215-114-8	232-066-3	231-148-6	215-481-4	Not in ESIS	215-116-9	231-901-9
Chemical Formula	GaAs	AsH_3	As	As_2O_3	$As(OH)_3$	As_2O_5	H_3AsO_4
Chemical Name (IUPAC)	Gallium Arsenide	Arsine	Arsenic	Diarsenic trioxide	Arsenious Acid	Diarsenic pentoxide	Arsenic Acid
Physico-Chemical data							
Melting Point (°C)	1238	-117	615 (sublm)	312	-	315 (decomposes)	35
Boiling Point (°C)	-	-63	-	465	-	-	160 (decomp)
Molecular Weight (g/mol)	144.6	78.0	74.9	197.8	125.9	229.8	141.9
Density (g/cm³)	5.32	0.0049 (gas); 1.64 (-64°C)	5.73	3.74	-	4.32	2.5
Water Solubility (g/L) @~20°C	<<1	0.7	<<1	37	-	660	167
Arsenic Oxidation state	-3	-3	0	3	3	5	5
Appearance	Grey, cubic crystals	Colourless gas	Metallic grey	White solid	Aqueous solution	White powder (hygro)	White crystals (hygroscopic)
Crystalline State	Zincblende	(trigonal pyramidal)	Trigonal	Cubic/monoclinic	(pyramidal)		(tetrahedral)
Environmental Toxicity							
Acute Toxicity to Environment		Aqua Acute 1, H 400 Very toxic to aquatic life	Aqua Acute 1, H 400 Very toxic to aquatic life	Aqua Acute 1, H 400 Very toxic to aquatic life		Aqua Acute 1, H 400 Very toxic to aquatic life	Aqua Acute 1, H 400 Very toxic to aquatic life
Chronic Toxicity to Environment		Aqua Chronic 1, H410 Very toxic to aquatic life with long lasting effects	Aqua Chronic 1,H410 Very toxic to aquatic life with long lasting effects	Aqua Chronic 1,H410 Very toxic to aquatic life with long lasting effects		Aqua Chronic 1,H410 Very toxic to aquatic life with long lasting effects	Aqua Chronic 1, H410 Very toxic to aquatic life with long lasting effects
Mammalian Toxicity							
Acute Oral			Acute Toxicity 3, H301 Toxic if swallowed	Acute Toxicity 2, H300 Fatal if swallowed		Acute Toxicity 3, H301 Toxic if swallowed	Acute Toxicity 3,H301 Toxic if swallowed
Acute Inhalation		Acute Toxicity 2, H373 May cause damage to organs through prolonged or repeated exposure	Acute Toxicity 3,H331 Toxic if inhaled			Acute Toxicity 3, H331 Toxic if inhaled	Acute Toxicity 3, H331 Toxic if inhaled
Acute Dermal				Skin Corr. 1B, H314 Causes severe skin burns/eye damage			
Repeated Dose	STOT RE 1, H372 Causes Damage to the respiratory and haemotopietic system and testes through prolonged or repeated exposure	STOT RE 2, H400 Very toxic to aquatic life					
Genetic Toxicity							

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		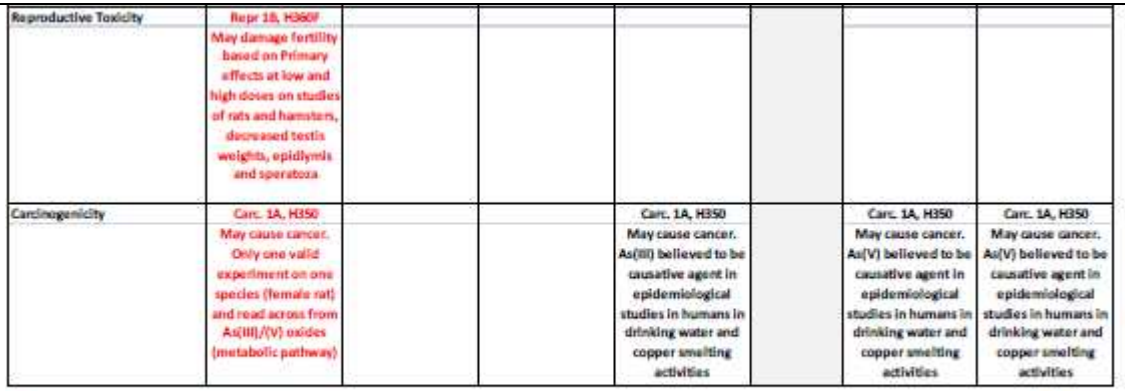	

Reproductive Toxicity	Repr 1B, H360F May damage fertility based on Primary effects at low and high doses on studies of rats and hamsters, decreased testis weights, epidlymis and speratoza						
Carcinogenicity	Carc. 1A, H350 May cause cancer. Only one valid experiment on one species (female rat) and read across from As(III)/(V) oxides (metabolic pathway)			Carc. 1A, H350 May cause cancer. As(III) believed to be causative agent in epidemiological studies in humans in drinking water and copper smelting activities		Carc. 1A, H350 May cause cancer. As(V) believed to be causative agent in epidemiological studies in humans in drinking water and copper smelting activities	Carc. 1A, H350 May cause cancer. As(V) believed to be causative agent in epidemiological studies in humans in drinking water and copper smelting activities

Table 1 – An attempt to perform an Analogue Approach Evaluation of GaAs in-line with CLP / OECD Guidance

 The Weight of Evidence claim from the RAC Opinion refers to the "metabolic pathway" reference in two studies of GaAs in hamsters and an assumed similarity to that observed in human epidemiological studies from drinking water contamination and copper smelting activities. However, it chooses to ignore and rule out the following:-
o The limited animal data (female rats) for Carcinogenicity would have been barely suitable, according to CLP guidelines, an excerpt from which is given in Appendix 3, for a Carc. Cat 2 rating. New evidence however, see Discussion section below, shows that this study is now invalid, effectively meaning that **no animal evidence** exists.
o The multiple evidence of epidemiological studies in the semiconductor industry in the past 25 years (since the citations in the Opinion document were published) – these are listed in the Discussion section on the IARC/RAC position
o Negative endpoint information is just as valid as positive, again as per the CLP/OECD guidelines

Instead, the Background/Opinion documents continue to quote the IARC contention (2006) that GaAs is part of an overall Group 1 rating for Arsenic Compounds in general. This will be discussed in more detail later.

A further protracted review of the OECD and CLP Guidelines on Chemical Categories and Read-Across demonstrates a number of flaws in the derivation of the Background/Opinion documents.

1. Read-across should only be applicable to even the smallest (analogue) of groupings if the compounds share common structural features and underlying mechanisms of action. Since GaAs is at one end of our "series", extrapolation of the data should not be recommended as there is clearly not a common underlying mode of action.

2. Because the number of chemicals is limited, any conclusion will not be robust and is too heavily reliant on Expert Judgement – much of this is not suitably justified. Also RAC/ECHA has not fully explained which type of Read-Across process was used.

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		3. The influence of the Potency of the chemical for Regulatory Classification was not discussed, given that for CLH and risk management processes, a threshold needs to be quoted. To this end, additional testing is often considered to demonstrate the differences in potency across the "series", which could warrant different classifications. 4. The Quality and Suitability of the methods listed in the Background/Opinion documents should be required to meet current acceptable standards (e.g. OECD). The arguments are based on 1984-87 papers – as stated previously, work conducted since these dates, has been largely ignored. 5. The Weight of Evidence guidance should be based on relevant, reliable and sufficient hazard data for regulatory purposes. It should also be based on the totality of available information, whether experimental or estimated. The wealth of recent data mentioned in 4. above should have come into consideration. 6. **Metabolic Pathway** – this forms the main basis of the argument. The guidance states that it should:- a. Address the common toxicological mechanism for endpoints related to systemic effects. They may not predict local point of entry (skin, lungs) due to the Parent Compound. b. The underlying hypothesis is the sequential metabolism of Parent Compound to downstream blood Primary and Secondary metabolites. The approach is usually reserved for toxicological endpoints. c. The pathway should be detected *in vivo*, with metabolites detected in blood or tissue. d. The recommended level of evidence as standard is DIRECT measurement of Parent Compound, Primary and Secondary metabolites, in blood, *in vivo*. e. A limitation of the approach is that it is only useful for identifying hazards related to systemic blood levels of the Parent and Primary/Secondary metabolites. Other endpoints (skin, respiratory tract) cannot be addressed; these are often related to the physico-chemical properties of the administered chemical and may differ between Parent, Primary and secondary metabolite f. Definite data on the metabolism should be provided *e.g.* time course data for both Parent and metabolites. g. Determine whether the metabolites are formed in ***appreciable*** levels in blood and tissue and determine basic toxicokinetic parameters for the Parent Compound h. Other studies using the Parent Compound should be examined for similar toxicity. Toxicokinetic experiments should have robust summaries, detailing relative blood levels. 7. **Commentary on Metabolic Pathway Argument** – considering the points stated in 6 a-h above, as taken from the CLP/OECD guidance notes, it would appear that the metabolic pathway assumption used in the ECHA/RAC Background and Opinion documents of May 2010 is too simplistic and lacks a certain amount of justification. Challenging arguments include:- a. No proof or evidence on how GaAs dissolves and the resultant As-moiety bio-transforms from a (–III) oxidation state to the (III/V) inorganic As species and thereafter to the arsenical metabolites, in the quoted references. b. There is no ample evidence of detection of the Parent compound in blood or tissues as per the recommended standard, not is there evidence of appreciable levels of the metabolites in the same medium. c. There appear to be no obvious hazards and endpoints due to systemic effects for which the metabolic pathway	

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		approach is well suited. d. Where the metabolic pathway is not suited, such as at the points of entry into the body, appreciable toxicological effects have occurred e.g. the lungs acting as a point of contact for particulates **Discussion of IARC/RAC Position** The IARC monograph of 2006 is bereft of modern studies but does mention a very good review by Carter *et al* (2003). In addition, the RAC Background document also quotes the updated IARC Monograph published in the Lancet (2009). This document is a brief and not particularly informative update and makes no mention of GaAs, maintaining its earlier position on Arsenic Compounds in General. It mentions, but contains no proof, that Dimethylarsinic acid metabolite (DMA) is carcinogenic to animals and furthermore, the updated IARC opinion groups the metabolites DMA and MMA as Group 2B – "***possibly carcinogenic to humans***". Returning to the IARC monograph of 2006, the Final Evaluation states that there is "***inadequate evidence***" in humans and "***limited evidence***" in animals for the carcinogenicity of GaAs. In the final paragraph of this 2006 monograph, the IARC Working Group agreed that for GaAs, there was "***no data of cancer in humans***", and is at best a "***weak carcinogen in animals***". The IARC continues to adopt an extremely conservative approach for GaAs, by retaining it in Group 1 based on the **potential** to cause cancer on account of two mechanisms. The first is the observation of a small release of inorganic arsenic from the breakdown of GaAs at its distribution sites and the second is the observation of lung cancer in female rats. The first mechanism, namely the **metabolic pathway**, is discussed at length later on. The second issue discussed by the IARC [2006] in its Overall Evaluation to retain GaAs within the Group 1 "*carcinogenic to humans*" category will be discussed next. It is suggested by the IARC *2006+ that "*the gallium moiety may be responsible for the lung cancers observed in the study of female rats*". Recent evidence has emerged that the F344/N rat has been discontinued from use in Toxicity Studies, King-Herbert and Thayer [2006]. The chronic inflammatory effects of intracheally instilled particles are probably more responsible for the neoplastic transformations observed in animal species, than the carcinogenic effects of GaAs. There is some evidence of pulmonary effects due to the inhalation of GaAs particles, Webb *et al* [1986, 1987] where histopathological evidence was used to assess inflammatory responses and where also pneumotoxicant activity was discussed. Many workers agree that the arsenic species more readily dissolves and that much of the gallium is retained in the lung for long periods or expectorated by pulmonary clearance and then rapidly excreted in the faeces. Other mechanisms, such as the effect on the lungs of particle exposure in itself and its potential to cause cancer *c.f.* other particles like silica, NTP [2000], have also been recognised. Some report the Gallium Arsenide particles as being "*roughly spherical*" Webb *et al* [1984], whilst other reports show them to be "*cubic, columnal or pyramidal*", Yamauchi *et al* [1986]. A study by Tanaka *et al* [2004] between the intermetallic semiconducting compounds, indium arsenide (InAs), gallium arsenide (GaAs) and aluminium gallium arsenide (AlGaAs) on intratracheal instillations in hamsters is very informative. It recognises the potential effect on the lungs of rats in the form of lung tumours due to non-fibrous solid particles (*e.g.* titanium dioxide, diesel soot, carbon black and talc) as described by Nikula [2000]. Also it and its other related studies showed the effect of the counter-ion (i.e. not arsenic) on lung damage by these intermetallic	

Date	Country/ Person/ Organisation/ MSCA	Comment	RAC response
		semiconducting compounds. Indium arsenide appeared to have the greater toxic effect on the lungs by forming more prolific pulmonary lesions and leading to a greater loss in body weight andincrease in lung weight compared with GaAs and AlGaAs, Tanaka *et al* [2003, 2004]. Comparisons have also been made between InAs, GaAs and InP, where pulmonary lesions were found in InAs and InP, but ***not*** in GaAs, Tanaka [2004], Tanaka *et al* [2003] and Yamazaki *et al* [2000]. What all studies are agreed upon is that the differences in toxic manifestation are more likely due to the dissolved counter-ion and not arsenic itself and that the physical nature of the particles contributes to the toxic response. Similar observations in varying counter-ion effects in other gallium and indium containing semiconducting compounds were reported by Morgan *et al* [1997]. All suggest that the biological effects of these semiconducting materials warrant further investigation. Chitambar [2010] discusses the role played by the counter-ion gallium and its role in organ toxicity other than the lung. He also outlines in this paper the widespread use of gallium compounds in anti-cancer treatments, but also acknowledges the requirement for a better understanding of the mechanisms of action. Also key in the IARC and RAC position is the notion that all the epidemiological information from the semiconductor industry was "***not informative***" or there was "***no human data available***" on the carcinogenicity of GaAs. Many publications have discussed the exposure to GaAs and the biological monitoring of staff, *e.g.* Yamauchi *et al* [1989], Sheehy and Jones [1993], Morton and Mason [2006], Park *et al* [2010] and Morton and Leese [2011]. These publications show the changing exposure levels to As in differing operations within the plants, and clearly show that there is some uptake of As-related species within the body. However, epidemiological studies exist from publications within the last decade, some of which look at human data in semiconductor industries back to the 1960-70s, Boice *et al* [2010], Nichols and Sorahan [2005], Beall *et al* [2005] and Darnton *et al* [2010]. These have largely been ignored by RAC in their Background/Opinion documents. None show any evidence of workplace exposure to As within the semiconductor industry and any increasing risk of contracting cancer. Both major points raised in this paragraph are tied together by the more than probable existence of a **threshold for carcinogenitic effects** of GaAs. The RAC Background Document assumes that the "***risk of cancer increases linearly with dose***" and justifies this by referring to EPA guidelines. Schoen *et al* [2004] highlighted updated versions of these guidelines (Draft 2003, finally published 2005, http://cfpub.epa.gov/ncea/cfm) which allow for greater incorporation of mode of action considerations in dose-response, relying less on assumptions of linearity at low doses. Schoen *et al* continue by saying that current risk methodologies are likely to overestimate the potency of arsenic owing to its non-linear mode of action. It is highly likely that any threshold is **far in excess** of any exposure during GaAs production. This position is also supported by Cohen *et al* [2006], where evidence points to non-linear dose-response relationship for the biological processes involved in the carcinogenicity of arsenicals. The use of the previously mentioned US EPA updated 2005 guidelines, using a margin of exposure model (http://www.epa.gov/cancerguidelines), is highly recommended. The RAC Background document refers to the linear relationship based on a much earlier model last updated in 1998 (http://www.epa.gov/ncea/iris/subst/0278.htm). Taking all the above points into consideration and with dwindling robust evidence, it would seem appropriate for the IARC, and ECHA/RAC, to delay the classification of the carcinogenic category for GaAs, until such time that further studies improve the understanding of the toxicology and carcinogenicity of this substance. **Metabolic Pathway / Toxicokinetic Discussion**	

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The assumption is based entirely on the dissolution of GaAs in the body into Ga and As "moieties", a conversion into inorganic trivalent (III) arsenite and pentavalent (V) arsenate and thereafter, by biotransformation through various enzymatic oxidative/reductive methylation reactions to arsenicals. These are the monomethylated (MMAV and MMAIII) and dimethylated (DMAV and DMAIII) arsenical metabolites. A depiction of a series of arsenic species, important to toxicity, including their oxidation states, is shown below and is provided by Carter *et al* [2003]

Arsenic species important in toxicity

Name (formula)	Chemical form	Comment
$As(OH)_3$, arsenious acid, often called arsenite	Oxidation state, AsIII	Aqueous solution species for +III pKa = 9.2, 12.1, 13.4.
H_3AsO_4, arsenic acid usually called arsenate	Oxidation state, AsV	Aqueous solution species for +V at pH 7.4 is −2 charged anion ($HAsO_4^{-2}$) pKa = 2.22, 6.98, 11.5.
AsH_3, arsine	Oxidation state, As(−III) Hydride (H^-)	Most reduced form of arsenic, slightly soluble in water.
CH_3–As(O)$(OH)_2$ monomethylarsonic acid, (MMAsV)	Oxidation state is +V.	Methylated metabolite of AsII, metabolized to dimethylarsinic acid
CH_3–$As(OH)_2$ monomethylarsonous acid (MMAsIII)	Oxidation state is +III.	Reduced metabolite of MMAsV
$(CH_3)_2$–As (O)(OH) dimethylarsinic acid, (DMAsV)	Oxidation state is +V.	Dimethylated metabolite of AsIII and methylated metabolite of MMAsIII, pKa = 6.2.
$(CH_3)_2$–As (OH) dimethylarsinous acid, (DMAsIII)	Oxidation state is +III.	Reduced metabolite of MMAsV
GaAs, gallium arsenide	Oxidation state of As is 0 to −III.	Synthetic compound with no acid–base behavior

It was stated by the RAC that such species had been found in early toxicological studies and to support its view, it cited ***three*** key references in particular. Two were concerned with the biotransformation of GaAs in hamsters (considered more suitable because their urinary metabolic profile resembles that of humans following inorganic exposure) by Rosner and Carter [1987] and Yamauchi *et al* [1986]. The other was an excellent toxicochemical review by Carter *et al* [2003] – same author as above. Typical reaction mechanisms within this metabolic pathway, are shown below as taken from Carter *et al* [2003]. This pathway is also generally supported by a number of authors reporting in the last decade, Thomas *et al* [2001], Hughes *et al* [2002], Vahter [2002] and Cohen *et al* [2006].

Arsenic oxide metabolism by mammalian methylators

1. Reduction–oxidation
   $H_3AsO_4 \leftrightarrow As(OH)_3$
   AsV AsIII
2. Oxidative methylation
   $As(OH)_3 \rightarrow CH_3AsO(OH)$
   AsIII MMAsV
3. Reduction–oxidation
   $CH_3AsO(OH)_2 \leftrightarrow CH_3As(OH)_2$
   MMAsV ↔ MMAsIII
4. Oxidative methylation
   $CH_3As(OH)_2 \rightarrow (CH_3)_2AsO(OH)$
   MMAsIII DMAsV
5. Reduction–oxidation
   $(CH_3)_2AsO(OH) \rightarrow (CH_3)_2As(OH)$
   DMAsV DMAsIII

Date	Country/ Person/ Organisation/ MSCA	Comment	RAC response
		Whilst these ***three key citations*** (Yamauchi *et al* [1986], Rosner and Carter [1987] and Carter *et al* [2003]) in the RAC Background document are used as ***primary evidence*** for the detection of MMA and DMA metabolites in GaAs "breakdown" as found in the drinking water and copper smelting studies associated with arsenic oxides, some comments within the papers are revealing. The information contained within demonstrates that the situation with GaAs is quite different from arsenic (III/V) oxides, arsenites and arsenates (collectively known as Inorganic-As or In-As by most workers):- **Yamauchi et al papers** Yamauchi, Takahashi and Yamamura [1986] – "**With the data from the present study, it should not be defined whether the chemical species of the arsenic released from GaAs is inorganic As (III) or As(V); hence it is described aggregately as inorganic arsenic in the present paper**" and **"It was further shown that the concentrations of inorganic arsenic, MAA and DMAA detected in organs and tissues were low and that these species of arsenic disappeared rapidly therefrom"** and **"oral GaAs proved extremely less deleterious** (than other arsenic compounds)**"**. These comments probably raise concerns regarding several of the guideline recommendations for Read-Across, principally those of the detection of a Parent Compound, appreciable quantities of metabolite (in blood/tissues), the Potency of the chemicals and the resultant effect on threshold values. On analysing the paper, some concerns are raised on the seemingly low levels of arsenic-related species when hamsters were subjected to oral doses of GaAs. To that end, a comparison was made to a similar paper by Yamauchi and Yamamura [1985] where hamsters were subjected to an **oral** dose of arsenic trioxide. The paper states that hamsters have a very similar urinary metabolic rate to humans (*c.f.* Buchet *et al* [1981]). It is justifiable to compare these two Yamauchi *et al* papers as the experimental conditions were identical and arsenic trioxide is the primary chemical the RAC chose as its main vehicle for Read-Across. For the purposes of the study, In-As is the total inorganic arsenite (III) and arsenate (V) content. Several observations and questions/concerns are apparent when comparing the two studies:- 1. The **background arsenic level** in excreted urine was measured in hamsters ***before*** administration of As2O3 and GaAs respectively. However, the levels and proportions differed between the two studies. The As2O3 study showed 1.69µg As/day (In-As 43%, MAA 2%, DMAA 12% and TMA 43%) whereas the GaAs study showed 0.89µg As/day (In-As 9%, MAA 1%, DMAA 23% and TMA 66%). The worrying feature is the much larger proportion of In-As in the urine of hamsters during the As2O3 study – this will become clearer and appear more relevant later. 2. A comparison was made only between roughly equal doses of GaAs and As2O3, normalised and corrected for equimolar arsenic. 3. Species detected were In-As, monomethyl arsonic acid (MAA), dimethyl arsenic acid (DMAA) and trimethylarsenic (TMA). TMA was only detected following As2O3 administration, probably in the liver. No TMA was detected after GaAs ingestion. However, the paper does point out that the amount of TMA did not differ significantly from the control value and was "**statistically insignificant**". It is noteworthy at this point that the amount of TMA measured after As2O3ingestion is generally greater than the combined In-As+MAA+DMAA total following GaAs ingestion.	

Date	Country/ Person/ Organisation/ MSCA	Comment	RAC response
		4. The totals of In-As, MAA and DMAA measured following GaAs ingestion were consistently of the order of the background urine values for each species (considered statistically insignificant for TMA following As2O3 ingestion). One minor exception was that DMAA was ~ 4 times its background value on Day 1 after GaAs ingestion. Conversely, the same species after As2O3 ingestion were often up to several hundred times their background values over the 5-day study. 5. **Urinary Metabolic Trend** – following normalisation and allowance for equimolar amounts, the In-As and metabolite concentrations in As2O3 were ~1000-2000 times the levels found after GaAs ingestion. Most, if not all, metabolic activity (NB – still of the same order as the background levels) after GaAs ingestion had largely disappeared in the urine after 12hr. After As2O3 ingestion, these levels were maintained thus; In-As peaking on Day 1 fell to "control" by Day 3, MAA also peaking on Day 1 was still significant on Day 5 and DMAA, peaking on Day 2 was also significant after Day 5. The conclusion could be two-fold: i) the levels of arsenic species measured following GaAs ingestion were statistically insignificant and ii) inorganic arsenic and its metabolites were both absorbed more easily and were retained within the body longer following As2O3 ingestion. Total urinary excretion after 5 days was only 0.15% of the total As dose for GaAs whilst it was 48.5% of the total As dose after As2O3 ingestion. 6. **Whole Blood Trend** – In-As and its metabolites were of the same order as the control (<0.001µg/ml) in blood following GaAs ingestion but were 1000-2000 times higher (~0.1 – 0.2µg/ml) following As2O3 ingestion. Also the levels were insignificant 12hr after GaAs ingestion but didn't fall to the control level until 72hr after As2O3 ingestion. Also DMAA in plasma was ~1000 times higher for As2O3 than for GaAs 7. **Faecal Excretion Trends** – Following GaAs ingestion, 82% of the **total As dose** was excreted in the faeces after 1 day - the amount after 5 days was 88%. Meanwhile for As2O3, only 2.1% of the total As dose was excreted in the faeces after 1 day, increasing to 11% after 5 days. 8. **Total Excretion After 5 Days** – 88% after GaAs and 59.5% after As2O3. It appears that inorganic arsenic and its metabolites are more easily absorbed, are higher by 3 orders of magnitude in blood and urine and are retained for much longer following As2O3 ingestion than is the case for GaAs ingestion. To this end, it could be argued that the amounts of these species following GaAs ingestion are effectively statistically insignificant. To compare with the case for the arsenic oxides, justification as per the recommended standards for Read-Across in GaAs appears presumptive. This was in respect of potency and thresholds, appreciable (or not) amounts detected and proper identification of species. Furthermore, another article by Yamauchi, Takahashi, Mashiko and Yamamura [1989] throws further light on the subject as in this case, biological monitoring, through inhalation, on humans working in a GaAs factory (as well as a copper smelting establishment) was performed. Whilst it could be demonstrated that there was a higher airborne arsenic concentration (usually in the form of dust particles) in some production areas of a GaAs plant (up to 24µg/m3), compared with 2µg/m3 in inspection areas, the urinary total inorganic + metabolite concentration was essentially unchanged (although the In-As did rise slightly for the production area workers). The highest recorded total urinary arsenic concentration was recorded by office workers at the same plant. However, these were still 10% **lower** than the control, a group of 102 students not exposed to GaAs. It is recognised that TMA measured in the urine of all workers and control is due to arsenobetaine, a harmless organic substance	

Date	Country/ Person/ Organisation/ MSCA	Comment	RAC response
		derived from seafood and is therefore heavily dependent on the diet of subjects. The copper smelter subjects worked in a sulphuric acid plant nearby and the average airborne arsenic concentration was 336µg/m3, greater than 10 times the maximum of the GaAs plant, but typically of the order of > 150 times the typical value (it could be ascertained that those working nearer the smelting activities were exposed to even higher values). It is well known that the inorganic arsenic (III/V) oxides are the primary arsenic-containing agents in such establishments and the levels in the urine of copper workers demonstrated a much increased incidence of In-As, MAA and DMAA of up to 10 times that of the GaAs workers and controls. There is evidence therefore, that despite some minor uptake of environmentally sourced arsenic (GaAs dust) in the GaAs industry, levels of inorganic arsenic and its metabolites in urine were unchanged compared with the controls. This was clearly not the case with an As2O3 rich environment in a sulphuric acid plant close to a copper smelting area. Given that this study was conducted > 20 years ago and major engineering control measures and risk reduction activities are now commonplace in modern semiconductor plants, airborne levels are <2µg/m3 in all areas of plants. Allied to the observation that there has been no uptake within the bodies of GaAs workers in the study above as well as in many epidemiological studies since, it could be concluded from the Yamauchi papers that it is **not relevant** to Read-Across to GaAs from As2O3. The evidence is based on metabolic behaviour and level, the absence of parent species detection and lack of endpoint evidence, whether toxic or carcinogenic, in animals and humans. **Rosner and Carter *et al* papers** Much was discussed in the Background document on the paper by Rosner and Carter [1987] where an intratracheal instillation of GaAs was compared with equimolar quantities of sodium arsenite (III) and sodium arsenate (V) – there is little data on the solubility of these compounds (i.e. in comparison to arsenic trioxide and pentoxide) available in the literature although there is no question they are more soluble than GaAs. In general there is:- 1. Lower absorption (5% of total dose, lower by a factor of 10), a greater lung retention (24% of total dose still left after 4 days against <1% after 1 day) but a greater faecal excretion (27% of total dose after 1 day compared with 10%) for GaAs inhalation compared with the more soluble arsenicals, arsenite and arsenate. 2. As a result of 1. the **bioavailability** of GaAs is <10% that of the soluble arsenicals 3. The ratio of DMAA to In-As is more similar to the profile for arsenite (III), although the much lower solubility of GaAs probably leads to a greater efficiency of methylation producing a higher percentage of DMAA, compared to the much more soluble arsenicals. 4. Much of the faecal excretion (which after 4 days is 46% of the total dose) is thought to be due to expectoration from the lungs. This together with the *in vivo* solubility and large lung retention shows that the particulate nature of GaAs must be considered in assessing the toxic effects. Webb et al [1987] show the effect of particle size on dissolution of GaAs 5. In addition the nature of the As species in the lung is **not determined**. Several points surrounding the quoting of this paper in the RAC Background document are concerning. The first is a potential implication that Read-Across from **arsenic** to GaAs is relevant as arsenic derived from GaAs is converted into As(III), As (V) and a major metabolite DMAA. There is no evidence of GaAs or the intermediate As-species	

Date	Country/ Person/ Organisation/ MSCA	Comment	RAC response
		involved (in this or indeed arguably any other paper) between the dissolution of GaAs and the observation of inorganic-As and its metabolites, albeit at a much reduced level, *in vivo* in animals. Secondly, the discussion section of this paper in the Background document (p. 12) states that arsenic from GaAs absorption ***"was converted to As(III), and As(V), monomethylated arsenicals (MMA-V and MMA-III) and dimethylated arsenicals (DMA-V and DMA-III)"***. Although there is a diagram of the Biotransformation of inorganic arsenic on the same page, this is from another source dated 2001 - there is **no mention of oxidation states of the metabolites in the Rosner and Carter paper**. The speciation of the metabolites MMA-III and DMA-III in urine has only been possible with advances in analytical chemistry since 2000, Le *et al* [2000]. Indeed, the urinary metabolites normally seen are the As-V oxidation state as these are the ones excreted in larger volumes as they cannot bind to other molecules (*e.g.* proteins) in the body in order to traverse cell membranes, Carter *et al* [2003]. It is not clear if the specific arsenic compounds present in urine accurately reflect those in the blood or tissues, Carter *et al* [2003]. Carter *et al* [2003] – "**The gallium arsenide had a lower solubility than any other arsenic compound and it had a disproportionate intensity of lung damage to suggest that the GaAs had a site of contact interaction and that oxidation reactions were important in its toxicity. The urinary metabolites after GaAs exposure were the same as excreted by arsenic oxides but the chemical compounds responsible for the toxic effects of GaAs are different from the arsenic oxides. The review concludes that there is insufficient evidence to equate the different arsenic compounds. There are several differences in the toxicity of the arsenic compounds that will require substantial research**" The conclusion to the analysis of these papers (Yamauchi *et al* and Carter *et al*) quoted in the Background document and in the IARC Monograph [2006] is that there is insufficient evidence that the relatively low levels of metabolites detected in blood and tissues are representative of the species responsible for the toxic effects of GaAs. The direct evidence of the nature of the breakdown species is absent as is a description of a mode of action. The relative effects of the potency of the toxic species and its inevitable relationship to thresholds is also not discussed. These, coupled with the observation of large differences in structure and physico-chemical properties, suggest that the **read-across** process should not have been initiated. Instead, a more comprehensive study of the toxicology, chemistry of already existing information and further studies/analyses on the effects of GaAs on animals should have been undertaken. **Conclusion** Advances in the understanding of the metabolism of arsenic species during the last decade, should have been taken into consideration in the RAC Background/Opinion documents. Recent advances in the detection of metabolites in urine should improve the understanding of this process. Although much evidence of the urinary excretion particularly of methylated As-V species exists, the detection of the methylated As-III species, universally agreed to be the more probable toxic intermediates, in tissues is not yet available. Hence an important target for any future understanding of the biotransformation of arsenic is the detection and quantification of such species in blood and tissues. To that end, what the role of the methylated As-III species is in observed cell toxicity following exposure to inorganic arsenic (trioxide, pentoxide and related compounds) is as yet unknown, Thomas *et al* [2001], Hughes *et al* [2002], Vahter [2002] and Cohen *et al* [2006]. What role Gallium Arsenide, and any of its potential dissolution products, their detection and how they interact is also yet to be determined.	

Date	Country/ Person/ Organisation/ MSCA	Comment	RAC response
		The fairly recent declaration of the non-applicability of F344/N rats to cancer studies effectively removes the last piece of evidence of cancer attributed to GaAs in experimental animal studies. Some workers, notably Huff *et al* [2000], are of the belief that animal studies conducted properly should still demonstrate carcenogenicity, despite the long-standing notion that arsenic is only carcinogenic to humans. This is particularly true for arsenic trioxide where the evidence in animals is equivocal, but very compelling in humans. Indeed, Carter *et al* [2003] tend to agree that until a reliable animal carcinogenesis model is established, it would be more fruitful to study the non-carcinogenic responses. Epidemiological studies where subjects were known to be exposed to high levels of arsenic trioxide and pentoxide showed evidence of carcinogenicity, although a mechanism of action is as yet unknown. Whether GaAs shows the same tendencies as arsenic trioxide, its **primary source analogue** according to the RAC/ECHA in the Read-across process, remains to be seen. It must be concluded however, that there is currently **no evidence of carcinogenicity**, in either animals or humans, due to GaAs. The RAC therefore, in implementing the **Read-Across** method, supported by the **Weight of Evidence** argument, ignored the paucity/absence of animal data, the absence of human evidence and the general principles of toxicology and chemistry associated with the postulated Bio-Transformation of GaAs *in vivo*. The arguments at face value appear tenuous, given the weight of evidence of all the studies on cancer in GaAs-based workplaces, conducted within the semiconductor industry. The derivation of the classification in the RAC Opinion Document of 25th May 2010 appears to break many of the principles laid down in the CLP/OECD Guideline documents and justification reverts to the Weight of Evidence argument, using expert judgement. The **actual** weight of evidence of effectively zero incidences of carcinogenicity during the production and use of GaAs should lead to renewed and properly conducted animal experiments. In the meantime, there should be **no Carcinogenicity Category placed on GaAs**, derived from any Read-Across or any other presumptive arguments. **References** Beall C, Bender TJ, Cheng H, Herrick R, Kahn A, Matthews R, Sathiakumar N, Schymura M, Stewart J and Delzell E, "Mortality among Semiconductor and Storage Device-Manufacturing Workers", J. Occup. Environ. Med., **47**, 996-1014 (2005) Boice Jr JD, Marano DE, Munro HM, Chadda BK, Signorello LB, Tarone RE, Blot WJ and McLaughlin JK, "Cancer Mortality among US Workers Employed in Semiconductor Wafer Fabrication", J. Occup. Environ. Med., **52**, 1082-1097 (2010) Buchet JP, Lauwerys R and Roels H, "Comparison of the urinary excretion of arsenic metabolites after a single oral dose of sodium arsenite, monomethylarsonate or dimethylarsinate in Man", Int. Arch. Occup. Environ. Health, **48**, 781 (1981) Carter DE, Aposhian HV and Gandolphi AJ, "The metabolism of inorganic oxides, gallium arsenide and arsine: a toxicochemical review", Toxicol. App. Pharmacol., **193**, 309-334 (2003) Chitambar CR, "Medical Applications and Toxcities of Gallium Compounds", Int. J. Environ. Res. Pub. Health, **7**, 2337-2361 (2010) Cohen SM, Arnold LL, Eldan M, Lewis AS and Beck BD, "Methylated Arsenicals: The Implications of Metabolism	

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Date	Country/ Person/ Organisation/ MSCA	Comment	RAC response
		Such a grouping usually leads to the exposure of the same metal moiety. Animal models also do not reliably predict effects on humans, hence where hazards are identified on human data, use of read-across can provide a solution. Underlying assumptions for this approach and the basis for this type of category development follow:- □ Hypothesis is based on the presence in all compounds of a common metal ion □ Bioavailability of the metal ion (or its redox form) at target sites in the body determines the occurrence and severity of effects for the read-across □ Supporting information to assess this bio-availability include typical physico-chemical properties – water solubility, degree of dissociation, systemic effects, toxicokinetics □ Care required to select metal compounds for which category approach is relevant □ Read-across from some categories may not be applicable □ Chemical speciation and valency (e.g. Cr3+/Cr6+) may result in different mechanisms □ Organometallic compounds have different modes of action – the ion is not present in the same form as the inorganic – and read-across between the two is NOT recommended □ Metals – difficulties exist in read-across from metal compounds □ Crystalline structures of insoluble metal compounds could affect the hazard profile. Other considerations to the above include:- □ The counter-ion effect (e,g, anion) may mask the effect of the metal ion in e.g. acute toxicity or repeated dose. □ Crystalline structure – could it affect bioavailability □ Particle size – influences deposition behaviour in the respiratory tract **Appendix 2 : As-related compounds already classified (CLH)**	

Date	Country/ Person/ Organisation/ MSCA	Comment	RAC response

Index No	International Chemical Identification	EC No	CAS No	Classification		Labelling		
033-001-00-X	arsenic	231-148-6	7440-38-2	Acute Tox. 3 * Acute Tox. 3 * Aquatic Acute 1 Aquatic Chronic 1	H331 H301 H400 H410	GHS06 GHS09 Dgr	H331 H301 H410	
033-002-00-5	arsenic compounds, with the exception of those specified elsewhere in this Annex	-	-	Acute Tox. 3 * Acute Tox. 3 * Aquatic Acute 1 Aquatic Chronic 1	H331 H301 H400 H410	GHS06 GHS09 Dgr	H331 H301 H410	
033-003-00-0	diarsenic trioxide; arsenic trioxide	215-481-4	1327-53-3	Carc. 1A Acute Tox. 2 * Skin Corr. 1B Aquatic Acute 1 Aquatic Chronic 1	H350 H300 H314 H400 H410	GHS06 GHS08 GHS05 GHS09 Dgr	H350 H300 H314 H410	SVHC
033-004-00-6	diarsenic pentaoxide; arsenic pentoxide; arsenic oxide	215-116-9	1303-28-2	Carc. 1A Acute Tox. 3 * Acute Tox. 3 * Aquatic Acute 1 Aquatic Chronic 1	H350 H331 H301 H400 H410	GHS06 GHS08 GHS09 Dgr	H350 H331 H301 H410	SVHC
033-005-00-1	arsenic acid and its salts with the exception of those specified elsewhere in this Annex	-	-	Carc. 1A Acute Tox. 3 * Acute Tox. 3 * Aquatic Acute 1 Aquatic Chronic 1	H350 H331 H301 H400 H410	GHS06 GHS08 GHS09 Dgr	H350 H331 H301 H410	
033-006-00-7	arsine	232-066-3	7784-42-1	Flam. Gas 1 Press. Gas Acute Tox. 2 * STOT RE 2 * Aquatic Acute 1 Aquatic Chronic 1	H220 H330 H373 ** H400 H410	GHS02 GHS04 GHS06 GHS08 GHS09 Dgr	H220 H330 H373 ** H410	
033-007-00-2	*tert*-butylarsine	423-320-6	4262-43-5	Pyr. Liq. 1 Acute Tox. 2 *	H250 H330	GHS02 GHS06 Dgr	H250 H330	
082-011-00-0	lead hydrogen arsenate	232-064-2	7784-40-9	Carc. 1A Repr. 1A Acute Tox. 3 * Acute Tox. 3 * STOT RE 2 * Aquatic Acute 1 Aquatic Chronic 1	H350 H360Df H331 H301 H373 ** H400 H410	GHS06 GHS08 GHS09 Dgr	H350 H360Df H331 H301 H373 ** H410	SVHC
601-067-00-4	triethyl arsenate	427-700-2	15606-95-8	Carc. 1A Acute Tox. 3 * Acute Tox. 3 * Aquatic Acute 1 Aquatic Chronic 1	H350 H331 H301 H400 H410	GHS06 GHS08 GHS09 Dgr	H350 H331 H301 H410	SVHC

Appendix 3 : CLP Guidance notes for Carcinogenicity Rating

Date	Country/ Person/ Organisation/ MSCA	Comment	RAC response

3.6.2.2 Classification criteria for substances

Substances are classified according to their potential to cause cancer in humans. In some cases there will be direct evidence on the carcinogenicity to humans from epidemiological studies. However, in most cases the available information on carcinogenicity will be primarily from animal studies. In this case the relevance of the findings in animals to humans must be considered.

Annex I: 3.6.2.1. For the purpose of classification for carcinogenicity, substances are allocated to one of two categories based on strength of evidence and additional considerations (weight of evidence). In certain instances, route-specific classification may be warranted, if it can be conclusively proved that no other route of exposure exhibits the hazard.

Table 3.6.1

Hazard categories for carcinogens

Categories	Criteria
CATEGORY 1:	Known or presumed human carcinogens A substance is classified in Category 1 for carcinogenicity on the basis of epidemiological and/or animal data. A substance may be further distinguished as:
Category 1A:	Category 1A, known to have carcinogenic potential for humans, classification is largely based on human evidence, or
Category 1B:	Category 1B, presumed to have carcinogenic potential for humans, classification is largely based on animal evidence.
	The classification in Category 1A and 1B is based on strength of evidence together with additional considerations (see section 3.6.2.2). Such evidence may be derived from: – human studies that establish a causal relationship between human exposure to a substance and the development of cancer (known human carcinogen); or – animal experiments for which there is sufficient (1) evidence to demonstrate animal carcinogenicity (presumed human carcinogen). In addition, on a case-by-case basis, scientific judgement may warrant a decision of presumed human carcinogenicity derived from studies showing limited evidence of carcinogenicity in humans together with limited evidence of carcinogenicity in experimental animals.
CATEGORY 2:	Suspected human carcinogens The placing of a substance in Category 2 is done on the basis of evidence obtained from human and/or animal studies, but which is not sufficiently convincing to place the substance in Category 1A or 1B, based on strength of evidence together with additional considerations (see section 3.6.2.2). Such evidence may be derived either from limited (1) evidence of carcinogenicity in human studies or from limited evidence of carcinogenicity in animal studies.
(1) Note: See 3.6.2.2.4.	

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		Annex I: 3.6.2.2.3. Strength of evidence involves the enumeration of tumours in human and animal studies and determination of their level of statistical significance. Sufficient human evidence demonstrates causality between human exposure and the development of cancer, whereas sufficient evidence in animals shows a causal relationship between the substance and an increased incidence of tumours. Limited evidence in humans is demonstrated by a positive association between exposure and cancer, but a causal relationship cannot be stated. Limited evidence in animals is provided when data suggest a carcinogenic effect, but are less than sufficient. The terms 'sufficient' and 'limited' have been used here as they have been defined by the International Agency for Research on Cancer (IARC) and read as follows: (a) Carcinogenicity in humans The evidence relevant to carcinogenicity from studies in humans is classified into one of the following categories: – sufficient evidence of carcinogenicity: a causal relationship has been established between exposure to the agent and human cancer. That is, a positive relationship has been observed between the exposure and cancer in studies in which chance, bias and confounding could be ruled out with reasonable confidence; – limited evidence of carcinogenicity: a positive association has been observed between exposure to the agent and cancer for which a causal interpretation is considered to be credible, but chance, bias or confounding could not be ruled out with reasonable confidence. (b) Carcinogenicity in experimental animals Carcinogenicity in experimental animals can be evaluated using conventional bioassays, bioassays that employ genetically modified animals, and other in-vivo bioassays that focus on one or more of the critical stages of carcinogenesis. In the absence of data from conventional long-term bioassays or from assays with neoplasia as the end-point, consistently positive results in several models that address several stages in the multistage process of carcinogenesis	

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		should be considered in evaluating the degree of evidence of carcinogenicity in experimental animals. The evidence relevant to carcinogenicity in experimental animals is classified into one of the following categories: – sufficient evidence of carcinogenicity: a causal relationship has been established between the agent and an increased incidence of malignant neoplasms or of an appropriate combination of benign and malignant neoplasms in (a) two or more species of animals or (b) two or more independent studies in one species carried out at different times or in different laboratories or under different protocols. An increased incidence of tumours in both sexes of a single species in a well-conducted study, ideally conducted under Good Laboratory Practices, can also provide sufficient evidence. A single study in one species and sex might be considered to provide sufficient evidence of carcinogenicity when malignant neoplasms occur to an unusual degree with regard to incidence, site, type of tumour or age at onset, or when there are strong findings of tumours at multiple sites; – limited evidence of carcinogenicity: the data suggest a carcinogenic effect but are limited for making a definitive evaluation because, e.g. (a) the evidence of carcinogenicity is restricted to a single experiment; (b) there are unresolved questions regarding the adequacy of the design, conduct or interpretation of the studies; (c) the agent increases the incidence only of benign neoplasms or lesions of uncertain neoplastic potential; or (d) the evidence of carcinogenicity is restricted to studies that demonstrate only promoting activity in a narrow range of tissues or organs. For human studies, the quality and power of the epidemiology studies require expert consideration and would normally lead to a Category 1A classification if data of adequate quality shows causality of exposure and cancer development. IRCSA, Section R.7.7.10.2, further discusses the types of human epidemiology data available and the limitations of the data. Where there is sufficient doubt in the human data then classification in Category 1B may be more appropriate. On the other hand epidemiological studies may fail, because of uncertainties in the exposure assessment and/or limited sensitivity and statistical power, to confirm the carcinogenic properties of a substance as identified in animal studies (WHO Working group, 2000).	
21/04/2011	United Kingdom / Mark Furlong / Wafer Technology Ltd / Company-Manufacturer	p.1. Wafer Technology Ltd is expressing concern at the application of the read-across approach to harmonising the classification and labelling of Gallium Arsenide and the elevating of its carcinogenicity rating to 1A. Physical and chemical evidence has been presented to support the argument that it is not possible to classify Gallium Arsenide in the same way as the oxides of Arsenic as is beimg proposed by the RAC of the ECHA. p 2 and 5. Wafer Technology Ltd is proposing a carcinogenicity rating of no higher than 2 for Gallium Arsenide based on the lack of firm evidence of carcinogenic behaviour in animals and humans. Studies in the workplace and 25 years of experience have not been considered by the RAC of the ECHA, and none of these studies have shown any evidence of increased cancer mortality within the compound semiconductor industry. --- *ECHA comment: attached document (WT letter to ECHA incl RTB.doc) is copied below* 20th April 2011 Dear Sir Wafer Technology Ltd is the only UK based manufacturer of III-V semiconductor materials and exports the vast majority of its output, which includes both Gallium Arsenide (GaAs) polycrystalline material and polished GaAs	Thank you for your comments. Regarding your comments on read-across, please see point 1) of the Annex to RCOM (Additional response to comments). Regarding your comment on experience and studies from the semiconductor industry we refer to our response to comments on occupational epidemiological studies please see response to Germany / Christian Eckert / ZVEI / Industry

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		wafers. GaAs is a fundamental and strategically important material to the compound semiconductor industry and is used in many of today's high-end devices such as smartphones, cellular base stations, LED devices and solar cells. The European Commission, through its Chemicals Agency (ECHA), is currently overseeing the process of registering and classifying this material in accordance with its two keynote pieces of recent chemical legislation. These are namely REACH (Registration, Evaluation, Authorisation and Restriction of Chemicals) EU Regulation 1907:2006 and CLP (Classification, Labelling and Packaging of Chemicals) EU Regulation 1272:2008. The current attempt at harmonizing the classification and labeling of Gallium Arsenide and the movement to elevate its Carcinogenicity Rating to the highest level (Category 1A), is causing considerable concern within the semiconductor industry, particularly as it is based upon the read-across approach. The justification by the Risk Assessment Committee of the ECHA appears to be based, almost exclusively, on the detection *in vivo* of metabolites in ***some*** studies on animals exposed to inhalation and/or ingestion of fine GaAs particles. These metabolites are similar to those found in epidemiological studies on humans known to have been exposed to arsenic oxides through contaminated drinking water or copper smelting processes. The RAC/ECHA has read-across the endpoint data for carcinogenicity from arsenic trioxide and arsenic pentoxide to its proposed classification for GaAs – based exclusively on the observation of similar metabolites in blood and tissues. It is the application of this method, and the lack of a rigorous study of the evidence pertinent to Gallium Arsenide that most concerns us as a company and the industry in general. Gallium Arsenide is not the same as Arsenic Trioxide/Pentoxide in terms of its physcio-chemical properties or oxidation states (for example it is much less soluble in water than the oxides) and therefore cannot be seen to sit comfortably in an Arsenic compound chemical category. By virtue of this, it is not possible to sensibly assign the same carcinogenicity rating to all these Arsenic related compounds. Studies of the metabolic pathway (in animals and humans) suggest strongly that Gallium Arsenide cannot be treated in the same way as the oxides of Arsenic simply because even though the urinary metabolites after GaAs exposure were the same as excreted by the arsenic oxides, the chemical compounds responsible for the toxic effects of GaAs are different from the arsenic oxides. These studies add weight to the argument that the read-across approach is not appropriate in this case. The RAC have used the results of one study that suggested a link between tumour growth in just one rat and GaAs, but chose to ignore the 25 years of experience of the industry where a multitude of studies have not revealed a link between this substance and cancer in humans. We feel strongly that the lack of human evidence (no carcinogenic evidence found in GaAs based workplace studies) and weak animal data does not justify an elevation of the carcinogenicity rating of Gallium Arsenide to Category 1A. Assigning a rating of no higher than category 2 or delaying reclassification would be more appropriate until further studies are undertaken that are relevant to GaAs in the workplace.	or trade association in the beginning of this document. You question the RAC conclusion of the NTP study from 2000. The F344/N rat is known to have high background incidences of certain types of tumors including testicular interstitial cell tumors and mononuclear cell leukemia, and was discontinued from use by NTP because of this. A recent paper by Tokar et al. (2010) was also submitted in the public consultation. This paper supports the conclusions from the rat study (NTP, 2000) and consequently strengthens our previous conclusion on the NTP study in the RAC opinion of 25 May 2010.

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		Appended is a scientific comment in response to the Opinion of the RAC from its document of the 25th May 2010, on the harmonized classification of Gallium Arsenide. Yours faithfully Dr. Mark J. Furlong On behalf of Wafer Technology Ltd Mr. Roy T. Blunt On behalf of Wafer Technology Ltd **REACH – some comments on the 'read across' process based on the chemical and physical properties of GaAs and how it could enter the body.** There is a very good case for contesting the 'read across' conclusion that has linked GaAs to As_2O_3 and the other materials listed. As_2O_3 is a white, relatively volatile powder (sublimes at 193°C) that dissolves readily in water (37 g/litre at 20 ºC - CRC Handbook of Chemistry & Physics 74th Edition 1993-4) or dilute acids or alkalis. In contrast GaAs has totally different physical and chemical properties to As_2O_3. It is an involatile, crystalline, material that looks, to the eye, very much like a metal. GaAs is only chemically dissolved by strongly oxidising acids (concentrated nitric acid or mixes of non-oxidising acids and hydrogen peroxide) or alkali solutions mixed with hydrogen peroxide which, I believe, do not exist in the body. The accepted chemical mechanism of GaAs dissolution is through initial oxidation of the surface to produce gallium and arsenic oxides followed by dissolution of these oxides, leaving a bare GaAs surface which can then be re-oxidised, dissolved, and so on in a continuing process. Without this oxidation stage there is no dissolution of GaAs and thus there is no significant likelihood of bulk GaAs being dissolved in the body. GaAs does form a thin mixed oxide layer (probable composition around 50% Ga_2O_3 – 50% As_2O_3) in air, which is essentially self-limiting in thickness at around 3 nm (experimental value obtained using Spectroscopic Ellipsometry on a GaAs substrate that has been exposed to air for 10 years). This thin oxide layer could itself dissolve in the fluids found in the body (taking water or Gamble's solution – a simulation of lung fluid – as an example) – but the oxide would not regrow – thus only a very tiny amount of dissolved arsenic would be released. As the particle size of the GaAs decreases (generally only particles in the size range below about 10 um diameter are trapped in the lungs) the apparent dissolution would increase because there would be a larger total surface area initially covered with oxide which could dissolve, but the actual GaAs core of the particles would still not dissolve, and will be eventually expressed from the body as particles by expectoration. Although the thickness of this oxide would normally be limited to about 2 nm it is possible that, in some sample powdering processes, the GaAs may reach temperatures significantly above room temperature which would result in thicker oxide layers. This may explain the great variance of results for 'solubility' of GaAs in vitro that has been reported by many authors. It is worth noting that Yamauchi et al (Toxicology 40, 237 – 246, 1986) found that his 'in vitro' solubility results did not agree at all with his 'in vivo' results, concluding that 'GaAs is only slightly soluble in the gastrointestinal tract and the peritoneal cavity'. Equally Carter et al (Toxicology & Appl. Pharmacology 193, 309-334, 2003) state that 'it is clear that highly insoluble arsenide semiconductors were less acutely toxic than equal amounts of arsine or their more soluble arsenious acid products'.	

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		Unfortunately there are no materials which have sufficiently similar chemical or physical properties to GaAs to permit a valid 'read across' even using the so-called 'analogue approach'. Certainly As_2O_3 or lead hydrogen arsenate are not suitable candidates - a possibly better candidate could be arsenic. Arsenic itself (which, like GaAs, looks like a metal to the eye) is not classified as a carcinogen in the UK or EU – however it is classified as such in California. Since arsenic is, itself, insoluble in water the incorporation process in the body is by solution of the natural oxide (As_2O_3) which forms on arsenic when exposed to air. However, in contrast to GaAs, the thickness of the oxide on arsenic does not appear to be self-limiting in thickness. When a sample of arsenic is freshly cut to reveal a shiny surface it rapidly tarnishes in the presence of air as it forms a layer of surface oxide (100% As_2O_3). The fact that this oxide can be observed optically as a tarnished layer indicates that the oxide thickness is many tens of nanometres in thickness (compare GaAs – where the oxide thickness is self-limiting at about 3 nm and only contains 50 % of As_2O_3). Thus, by any reasonable 'read across' assessment GaAs must surely be considered as far less toxic or carcinogenic than arsenic. In actual fact there is no need to use 'read across' arguments when determining the carcinogenicity of GaAs. There is a large literature on this (including many references from the last decade which do not appear to have been considered at all by the IARC or RAC) concerning its effect on rats, mice, hamsters and a number of studies on humans working in the semiconductor industry. The overwhelming conclusion of this work is that there is no significant evidence of any carcinogenic or genotoxicity activity of GaAs. The sole report (NTP/NIH 2000 publication No 00-3951) of carcinogenic toxicity concerns one female rat (out of four in the test group) – however this rat was from the F344/N strain and a later report from the same institution (King-Herbert et al, Toxicologic Pathology 34, 802-5, 2006) stated that this particular strain of rat had been withdrawn from use as it showed high rates of spontaneous tumour growth. The spontaneous tumours were of the same sort that had been observed on the one individual rat during the earlier GaAs test – thus throwing extreme doubt upon the conclusion of the original GaAs carcinogenicity study. It should also be pointed out that a very recent large scale investigation (covering 100,000 workers in total) on cancer mortality amongst US workers in the semiconductor industry (Boice et al, J Occupational & Environ. Medicine 52, 1082-97, 2010) concluded that there was no evidence of increased cancer mortality overall or mortality from any specific form of cancer. To sum up - Classification of GaAs as a Class 1 carcinogen under ECHA/OECD published guidelines requires firm evidence of carcinogenic behaviour in animals or humans – this degree of reliable evidence does not exist. It is very doubtful whether the evidence even justifies a class 2 carcinogen rating. GaAs **cannot** reasonably be regarded as more carcinogenic or toxic than arsenic itself. Roy Blunt B.Sc., ARCS, MRSC, C.Chem 19th April 2011	
21/04/2011	Germany / Birgit Müller / Freiberger Compound Materials GmbH / Company-Manufacturer	Freiberger Compounds Materials GmbH ("Freiberger") submit that the RAC Opinion of May 25, 2010 does not assess all available data and that inaccurate conclusions on classification are reached. We attach two papers (i) listing and discussing additional data and the conclusions based on such additional data ('Bomhard scientific paper'); and (ii) summarizing Bomhard and discussing the legal flaws in relation to classification ('Briefing Paper').	Thank you for your comments. The response also covers the comments from Dr. E.M. Bomhard and coworkers below.

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		In essence, in relation to carcinogenicity, the following additional data should be taken into account: (1) Lung carcinogenicity of small particles (Federico et al. 2007, Valavanidis et al. 2008); (2) Phaeochromocytomas as a sequel of chronic inflammatory stress (Greim et al. 2009, Osaki et al 2002); (3) Non-relevance of the mononuclear cell leukemia in the F344 rat strain (Caldwell 1999, Elwell et al 1996, Lington et al 1997); (4) Levels of MMA or DMA in workplaces of GaAs and semiconductor industry (Morton and Leese 2010; Morton and Mason 2006, FCM 2010); (5) Thresholds for human carcinogenicity (Bates et al. 2004; Brown and Ross, 2002; Lamm et al. 2004, 2006, 2007; Meliker et al. 2010; Mink et al. 2008; Schoen et al. 2004; Snow et al. 2005; Tapio and Grosche 2006); (6) Genotoxicity of arsenic compounds in humans (several new studies, namely Basu et al. 2002; Ghosh et al 2007; Paiva et al. 2008, Vig et al. 1984); (7) New epidemiological studies in semiconductor industry consistently showing no increase of incidences/prevalences of cancer attributable to arsenic or arsenicals (Beall et al. 2005; Bender et al. 2007; Boice et al. 2010; Darnton et al. 2010; Nichols and Sorahan 2005); (8) Bioavailability of arsenic and its metabolites in GaAs production (Yamauchi et al. 1989); (9) Mode of action (ATSDR 2007; Cohen et al. 2006; Schuhmacher-Wolz et al. 2009); (10) New results on human cells demonstrating existence of concentration ranges without any effect (Basu et al. 2002; Ghosh et al 2007; Paiva et al. 2008; Vig et al. 1984); (11) No evidence for an adverse effect of GaAs on chromosomes from experimental data (Gibson et al. 1997; NTP 2000); (12) Additional studies and evaluations (e.g. Kirsch-Volders 2011) are mentioned in Bomhard scientific paper attached. Based on the above, there is neither animal data nor epidemiological data to suggest that GaAs is carcinogenic. The claim that arsenic originating from an exposure to GaAs is metabolized by the human organism to form MMA or DMA through the process of methylation is not supported by existing data either. Therefore, read-across from arsenic is not permissible. On reprotoxic classification, Chitambar 2010 was omitted (no adverse effects on testes or on male fertility). The results on other than fertility parameters after intratracheal instillations into hamsters published by Tanaka et al. (2000), which indicate marked toxicity in other organs than the testes in the Omura et al. (1996b) study have not been included. Thus the reprotox classification is not warranted either. *ECHA comment: The attached document (2011_04_21 Briefing paper) is copied below.* **Gallium Arsenide** **Position ot Freiberger Compounds Materials GmbH on the** **Opinion of the Committee for Risk Assessment proposing harmonized classitication and labeling at the EU level for GaAs adopted 25 May 2010** April 21.2011	Please also the Annex to RCOM (Additional response to comments). Assessment of the hazard properties of GaAs as a substance and risk assessment from exposure related to usage of GaAs in the microelectronic industry are different things. Regarding your comment on toxicity to reproduction, please see response to France / Thomas Pearsall / European Photonics Industry Consortium / Industry or trade association in the beginning of this document. Regarding your comment on RAC disregarding uncertainties expressed by IARC in relation to the gallium moiety, we agree with IARC that the observed findings may be a result of the combination of the two moieties, and that gallium arsenide is a weak carcinogen in experimental animals.

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		I. EXECUTIVE SUMMARY Freiberger Compounds Materials GmbH ("Freiberger")1 submit2, based on scientific3 and legal advice taken, that the Opinion of May 25, 2010(the 'Opinion') of the Committee for Risk Assessment ("RAC") on the proposal for the classification of Gallium Arsenide("GaAs") as carc. cat 1A, reprotox cat 18 (under CLP) is scientifically and legally flawed. lt is not compliant with the rules of Article 13 and Annex XI REACH, as well as the classitication criteria of the CLP Regulation. Freiberger therefore urge RAC to correct its opinion on the classification and labeling of GaAs. Freiberger hereby responds to the re-opened consultation of March 2 011. The present paper contains a summary of the main new scientific evidence and assessment of this evidence laid out in detail in Annexl. In addition, this paper evaluates the available scientific evidence agains the proposed EU classification. II. ANALYSIS 1. RAC relies upon an incomplete data set RAC's Opinion is largely based upon older available data and fails to take into account new quality data generated after the IARC 2006 monograph was drafted. In particular, RAC bases its Opinion on IARC's Monograph No.86 (2006) on classification of GaAs,and IARC'S March 2009 re-confirmation of the classification of arsenic and inorganic arsenic compounds as carcinogenic to humans (group classification). With two exceptions, all literature on toxicology and epidemiology quoted in the 2006 IARC Monograph originates from the 1980s and '1990s. Beyond the IARC monograph RAC mainly references older publications that are listed in the ATSDR (2007) review and in the NTP report (2000),.in particular, epidemiological data on arsenic. However, there are new studies available on, for example, lung carcinogenicity of small particles (Federico et al. 2007, Valavanidis et al, 2008), on phaeochromocytomas as a sequel of chronic inflammatory stress (Greim et al. 2009, Osaki et al 2002), on non relevance of the mononuclear cell leukemia in the F344 rat strain (Caldwell 1999, Elwell et al 1996, Lington et al 1997), on levels of MMA ar DMA in workplaces of the GaAs and semiconductor industry (Mofon and Leese 2010, Morton and Mason 2006, FCM 2010), on thresholds of the carcinogenicity (Bates et al. 2004, Brown and Ross 2002, Lamm et al. 2004,2006,2OO7, Meliker et al. 2010, Mink et al. 2008, Schoen et al. 2004, Snow et al.2005 Tapio and Grosche 2006) and genotoxicity of arsenic compounds in humans (several new studies, namely Basu et al. 2002, Ghosh el al. 2oo7; Paiva el al. 2008, Vig et al. 1984). Additional studies and evaluations on the genotoxicity and mode of action of arsenic compounds are mentioned in Annex I to this Paper (Kirsch-Volders 2011). The combined legal effect of Recital20 (4) and Article 15 of CLP Regulation5 on the Classification of substances requires that classifications are based on the following principles: (a) All available in formation must be collected and used, provided it is of good quality; (b) Whenever new information of good quality becomes available, it must be used too,	Regarding your comment on occupational epidemiological studies please see response to Germany / Christian Eckert / ZVEI / Industry or trade association in the beginning of this document. Regarding your comment on effects from particles, please see point 3) of the Annex to RCOM (Additional response to comments). RAC agrees with IND that due to irrelevance to humans the findings of benign pheochromocytoma of the adrenal medulla should be disregarded when assessing carcinogenicity, with reference to Greim et al. (2009). Please see the opinion (of 1 December 2011). We also agree with IND who claims that the spontaneous incidence of mononuclear-cell leukemia (MCL)6 in Fischer F344 rats is so high that this effect should be disregarded. Please see the Please see the opinion (of 1 December 2011).

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		e.g. the classification must be updated. These principles are in line with Article 114 of the Treaty of the Functioning of the European Union ('TFEU'), which requires the European Commission to take account of any new developments based on scientific facts when it deals with proposals concerning health, safety, environmental and consumer protection, and they are in line with the overall objectives of REACH and CLP, i.e. to provide a high level of human health and environmental protection. 2. lnaccurate conclusions because of use of incomplete data set and inaccurate analysis of data analyzed a) Data regarding carcinogenicity (i) Incomplete assessment of IARC Monograph IARC(2006) acknowledged that on GaAs, there is "inadequate evidence in humans for the carcinogenicity of gallium arsenide'' and "limited evidence in experimental animals'' (Annex 1, page 37 of the RAC Opinion). IARC nevertheless classified GaAs as carc.1A based on the older 1987 group classification of arsenic compounds as carc. 1A arguing that that the in vivo and in vitro evidence suggests that GaAs releases gallium and arsenic moieties, that there is some evidence to suggest that both these moieties may have a cancer potential either independenotly or together and therefore the overall classification is warranted despite a lack of conclusive data or full understanding of the etfects.6. RAC disregards the uncertainties expressed by IARC in relation to gallium. (ii) Incomplete data set Several epidemiologic studies carried out in the semiconductor industry consistently show no increase of incidences/prevalences or cancer attributable or arsenic or arsenicals (Beall et al, 2005; Bender et al. 2007; Boice et al. 2010; Darnton et al. 2010; Nichols and Sorahan 2005). None of these epidemiological studies are referenced in the RAC opinion RAC only refers to older epidemiological studies on arsenic compounds. (iii) New Data on Carcinogenicity of Particles The Fischer F344 rat study (see above) which resulted in tumors in female rats should be reinterpreted based on new data. Most of the changes reported could in fact result from chronic irritation of the lung tissue (Federico et .al 2007; Valavanidis et al. 2008).They are qualitatively similar to effects reported as the typical outcome of exposure to other particles e.g. talc or quartz by inhalation (NTP 2000, Woltf et al. 1988).In particular, the increased occurrence of alveolar-bronchionlar neoplasms (mostly adenomas) in female rats should be considered as the consequence of toxicity to the lung. lt is not to be interpreted as an indication of the primary carcinogenic effect of GaAs: The longer the inflammation lasts, the higher is the resulting risk of cancer formation (Federico et al.2007). The experimental conditions employed by NTP (whole-body exposure, very small particles at concentration causing irritation to the lung) are beyond doubt representing "worst case" scenario. Taking into account the secondary effects caused by the toxicity to the lung, no primary carcinogenic effect of GaAs can be derived.	Regarding your comment on the discontinuance of use of the F344 rat strain in carcinogenicity studies, we believe that the conclusions from the NTP study on gallium arsenide in rats still is valid, as assessed by Tokar et al. in a recent paper (Tokar et al., 2010). By way of response to new developments issue: The RAC opinion was adopted according to the procedure laid down in Art. 37(4) of Regulation No.1272/2008 (CLP Regulation) and in the RAC working procedure on processing of dossiers for harmonised classification and labelling, following a proposal from the Member State. According to Article 37(4) CLP Regulation, all the parties concerned are given the opportunity to comment on the proposal submitted. The public consultation provides the opportunity to ensure that additional information and scientific input from concerned parties (e.g. industry, Member States, the general public and other

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		It is known that the inhalation of particles by humans may cause chronic toxicity to the lung and subsequenatly sa long-term sequela may cause cancer (Valavanidis et al.2008). lncidentally cancer may be caused by any chronic damage to the lung and also other tissues. While this observation could be seen as attributing a certain carcinogenic potential to small particles, it certainly does not justify the general classification of respirable particles of any compositioan as carcinogenic to humans. (iv) Results not relevant to humans The increased occurrence of benign phaeochromocytomas female rats is most likely the resulot of the chronic inflammatory stress and has no relevance to humans (Greim et al.2009, Osaki et al 2002). The increased occurrence of mononuclear cell leukemia in female rats at the highest concentration is also most likely the result to the chronic inflammatory stress in the lung, which through overcompensatinon increases the background incidence at the high dose. Several authors have concluded that this type of tumor is not relevant to human risk (Caldwell, 1999; Elwell et al. 1996; Lington et al. 1997). In 2005, NTP stopped using the F344 rat for any experimental work on toxicity for this (and another) reason. (v) lncorrect classification for carcinogenicity In arriving at its conclusionos on the results of the tests described above, RAC'S methodology was contrary to the requirements of the CLP Regulation: According to Annex1 (Section3.6.2.1.) of the CLP Regulation, carcinogens cat. 1 are classified as follows: o "CATEGORY 1A: KNOWN to have carcinogenic potential for humans; the placing of a chemical is largely based on human evidence. o CATEGORY1 B:P RESUMED to have carcinogenic potential for humans; the placing for a chemical is largely based on animal evidence. The classification in Category 1A or 1B is based on strenglh of evidence together with additional considerations, such evidence may be derived f rom human studies that establish a causal relationship between human exposure to a chemical and the development of cancer (known human carcinogen). Altenatively, evidence may be detived from animal experiment for which there is sufficient evidence to demonstrate animal carcinogenicity (presumed human carcinogen). In addition, on a case by case basis, scientific judgment may warrant a decision of presumed human carcinogenicity derived from studies showing limited evidence of carcinogenicity in humans together with limited evidence of carcinogenicity in experimental animals." (emphases added). First, based on the criteria above, as regards animal tests on GaAs, i.e. the F344 rat study, this according to IARC (2006) (IARC and CLP criteria are similar) represents “l imited" evidence of a carcinogenic effect, because it is the single available animal study with a positive outcome, it concerns only one species and the effects are only in one sex.	stakeholders) can be provided to RAC for the opinion-forming process. Regarding your comments on read-across, please see point 1) of the Annex to RCOM (Additional response to comments). Regarding your comments on mode of action and threshold for carcinogenicity, please see point 2) of the Annex to RCOM (Additional response to comments). IND claims that recent data on the association between hypoxaemia and the occurrence of phaeochromocytomas, highlighting or demonstrating that hypoxaemia was certainly induced as a sequel of the massive lung toxicity. Lung toxicity was present in the NTP-studies at all doses and this toxicity determined the choice of the maximal dose of GaAs used in the 2-year study to 1 mg/m3. At this dose survival rates of exposed males and females rats and mice were similar to those of the chamber

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		Second, there is inadequate evidence in humans for the carcinogenicity of GaAs (IARC 2006). Thus, classification to carc. cat.1B is not justified. Third, as discussed above, there are new data available that provide evidence that the F344 rat study may no longer be relied upon as evidence for carcinogenic effecf relevant to human risk, because it may merely represent evidence in relation to specific target organ toxicity (to the lung) of small respirable particles after repeated (inhalative) exposure. Thus, there is currently, in our opinion, no evidence from either human or animal studies for classification of GaAs as carcinogen even for suspected human carcinogen (carc cat.2).. In the absence of any relevant animal and human data, what is therefore left for RAC to consider is whether it is possible to apply read-across from arsenic compounds. A substance may be read-across from another substance pursuant to Annex XI REACH7 under the following conditions: - structural similarity; - predictability of physicochemical properties, human health effects and environmental effects or environment fate from the reference substance. RAC argues that "arsenic compounds already listed as carcinogen in category 1A produce the same metabolites in mammals as GaAs. Examples given are arsenate (arsenic acid) in drinking water and diarsenic trioxide from ores processed in copper smelters, where epidemiology demonstraters risk of cancer." In addition, RAC uses data derived solely from the bioavailability of arsenicals after oral and intratracheal (i.t.) administratiton to rats and hamsters and data from hamsters indicating a metabolism comparable to other arsenicals known to be carcinogenic to humans. According to RAC, the arsenic bioavailable from GaAs is metabolized to form predominantly dimethylarsinic acid (DMA(V)) through methylation like in the case of other inorganic arsenicals known to be carcinogenic to humans (Rosner and Carter 1986; Yamauchi et al.1986). A mode of action justifying this extrapolation is, however, not presented by IARC. However, no reference is made by RAC to a published Japanese study (on bioavailability of arsenic and its metabolites in GaAs production) (Yamauchi et al. 1989). According to this study, a significant increase (by 24 and 22% respectively) of arsenic concentrations in the urine of exposed workers was recorded at the end of a shift. However, at the same time no increase of the concentration of methylated arsenic species was found. The above results are in line with corresponding studies for the processing of GaAs wafers. The respective studies find in general very low excretion of arsenic mostly on a level barely distinguishable from the reference group. No increased excretion of MMA or DMA in the urine was found in this case either (Farmer et al. 1990; Morton and Leese2010; Morton and Mason 2006, FCM2010).	controls.Body weight gain was only marginally influenced (slightly reduced in male rats and slightly increased in female mice). No clinical findings related to GaAs exposure were observed in either mice or rats. Multiple inflammatory lesions were observed in lungs and was said to occupy less than 5% of the alveolar parenchyma in the 0.1 mg/m3 groups and approximately 10% to 15% or 20% in the highest dose groups in mice and rats, respectively. Furthermore, none of the heamatological data indicate the presence of a clinically significant hypoxemia, although the haematological data are also directly influenced by gallium and arsenic thus complicating the evaluation of the results. IND claims that the apparent qualitative differences with regard to lung carcinogenicity after i.t. instillation to hamsters as well as micronucleus induction in mice in comparative studies with

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		The claim that arsenic originating from an exposure to GaAs is metabolized by the human organism to form MMA or DMA through the process of methylation is thus not supported by existing data. Concluding from the above, read-across is not permissible because of a lack of structural similarity and predictability of human health effects. Even if it is assumed that the arsenic originating from an exposure to GaAs is metabolized by methylation as assumed by RAC, this still leaves the question whether it can be concluded that this hypothesis necessarily implies a carcinogenic potential of GaAs for humans. This conclusion would require that a) the mode of action behind the carcinogenicity of inorganic arsenical is known and b) it would in addition require the assumption that there is not threshold for this mode of action. However, both conditions are not supported by available data either. Several modes of actions to explain the carcinogenicity of arsenic are currently discussed. The most frequently quoted and thus the most likely mechanisms are i) indirect genotoxicity (chromosome aberration), ii) reactive oxygen species, iii) cell proliferation and transformation and iv) hypo-/hypermethylation of the DNA (ATSDR 2007; Cohen et al. 2006; Schuhmacher-Wolz et al. 2009). For the last three modes of action (ii- iv), a threshold definitely has to be assumed. In the case of chromosome aberrations, the majority of publications focus on the induction of micro nuclei. New results on human cells now demonstrate the existence of concentration ranges without any effect (Basu et al. 2002; Ghosh et al 2007;Paiva et al. 2008; Vig et al. 1984). Furthermore, there is no evidence for an adverse effect of GaAs on chromosomes provided in the published experimental data (Gibson et al. 1997; NTP2000). ln addition, a number of more recent epidemiological studies based on quite accurate exposure assessments (essentially studies on drinking water indicate the existence of a threshold for the carcinogenic effects of (other arsenicals) well above the known exposure experienced during the production and processing of GaAs (Bates et al. 2004; Brown and Ross, 2002; Lamm et al. 2004, 2006, 2007; Meliker et al. 2010; Mink et al. 2008; Schoen et al. 2004; Snow et al. 2005; Tapio and Grosche 2006). Thus, whilst read-across to similar chemistry can be helpful surrogates within a weigh of evidence approach, read-across should not be relied upon to such a significant extent in these circumstances because there is strong evidence that the carcinogenicity of arsenicals is likely to have a threshold below which there is no carcinogenic activity. However, RAC did not take any threshold into consideration. b) Data regarding reprotoxicity (i) Omission of findings RAC acknowledges that there is no human data on reprotoxicity. RAC therefore uses short term (2 weeks and 14 weeks) animal studies (see Annex 1 of RAC Opinion at 5.5.2) to derive at its conclusions below. With respect to fertility, RAC has adopted the hypothesis of IARC (2OO6) that gallium is accumulating in the testicular tissue,	various arsenicals, which argue against grouping of inorganic arsenic compounds into one category, have not been dealt with. (please see Annex to RCOM – Additional response to comments) Industry has commented on the apparent lack of in vivo genotoxicity and carcinogenicity of GaAs in contrast to more soluble inorganic arsenic compounds. The negative *in vivo* micronuclei results in the NTP-study for GaAs may be due to the low sensitivity of the mouse to arsenic toxicity and thus that the levels in the bone marrow was not sufficiently high to result in an increase. Furthermore, no similar inhalation studies with other inorganic arsenicals have been performed making the evaluation of the negative GaAs results difficult. Industry has commented on several life-span studies with Syrian hamsters and states that diarsenic trisulfide and GaAs were negative in these studies in contrasts

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		concluding that the findings on testes and spermatogenesis are primary effects observed in the absence of other relevant toxic effects. RAC has not taken into account in this regard the longterm 2 year inhalation study conducted by NTP in 2000 8. This study does not report accumulation in the testiculart issue (nor in blood and serum). No damage to spermatozoa/- testes were found at concentrations up to 1.0 mg/m3 in both mice and rats. (ii) lncorrec interpretation – alleged primary reprotoxic effects According to RAC's Opinion, at page 4 . "No multi-generation studies investigating potential effects of Gallium Arsenide on fertility are available but repeated dose toxicity studies have reported data on reproductive organs. The dossier submitter presented two 8 weeks tracheal instillation studies in rats and hamsters, and two 14 weeks inhalation studies in rats and mice. Several testicular concentration-related modifications, like decreased testis weights, epididymis weights, spermatids counts and spermatozoa motility, have been observed in the whote-body inhalation of Gallium Arsenide in rats and mice. Similar testicular effects have also been reported in rats and hamster following intratracheal instillations. Histopathologic examination of the testis in rat and hamstes revealed a spermiation failure as spermatid retention was observed at post-spermiation stages of bolt species." Thus, repeated dose toxicity is the only basis on which RAC has assessed reprotoxicity. In addition, RAC considers that GaAs is reprotoxic provided that the etfects found in testes at low doses in animals of two species were primary and not secondary to other toxic effects. The RAC Opinion concludes that " the effect on testis is corsidered to be primary, as it is seen as reduced epididymal spermatozoal concentration in mice exposed to 10 mg/m3 without clinically significant reduction in haemoglobin concentration or reduced body weight...clear evidence of effect on fetlility at low doses in the absence of other toxic effects warrants classification for reproductive toxicity. Also at higher doses the effects were Considered to be primary and not resulting from other toxic effects. (…) Due to clear evidence of testicular toxicity in two species, the original proposal to classify Gallium Arsenide as Repr. 1B - H360F (CLP) is suppoted. This is also supported by the potential of gallium to accumulate in rat testis following inhalation exposure (see toxicokinetics section in the Background Document)'' First, as already stated above, we note that according to the NTP 2 year study (2000), no accumulation in the testicular tissue occurs. Second, RAC bases its Opinion on the absence of other toxic effects only on the fact that there was no clinically significant reduction in haemoglobin concentration or reduced body weight. However, this is not clear evidence that the effect is 'primary'. The inhalation studies reported massive effects to the lung at levels affecting fertility parameters and at concentrations as far below these levels. These studies report, in addition, significant haematological changes. Such chronic lung inflammation leads inevitably on hypoxaemi, which in turn causes secondary effects in oxygen dependant tissues, in particular germinal epithelia of the testes producins sperms This means that persistent lung toxicity triggers the effects in the testes and not the gallium or arsenic moieties. Finally, the dose level causing effects cannot be considered as 'low' in light of the accumulation in the lung. Hence, there is thus no clear effect on fertility at low doses and the effect is not primary either.	to the more soluble inorganic arsenic species. However, RAC wants to point out the following: although arsenic trioxide has been shown to be tumourigenic to the lung of hamsters in the study by Ishinishi et al., (1983), only calcium arsenate induced lung tumours, whereas arsenic trioxide and diarsenic trisulfide both were inconclusive when tested in the same experiment (Yamomoto et al., 1987). Likevise, neither GaAs nor arsenic trioxide induced a clear carcinogenic response in the study by Ohyama et al. (1987). Thus, these studies underline that these animal models have low sensitivity to inorganic arsenic induced carcinogenesis. We acknowledge that the small particle size and high consentration in the NTP 2 year study on rats represent an exposure scenario that constitutes a worst case scenario. However there is no deviation from OECD test guideline 451 on this issue.

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		(iii) Incomplete Gallium compounds, e.g .gallium nitrate, are intravenously applied at fairly high dose levels (10 to 25 mg/kg body weight) to treat cancer, hypercalcaemia and metabolic bone diseases. No adverse effects on testes or on male fertility have been reported (Chitambar 2010). RAC did not take this study into account when deriving its conclusions. The results on other than fertility parameters after intratracheal instillations into hamsters published by Tanaka et al. (2000), which indicate marked toxicity in other organs than the testes in the Omura et al. (1996b) study have not been included. With best regards, Birgit Müller REACh Coordinator *ECHA comment: The attached document (2011_04_21 Dr Bomhard et al - On GaAs Toxicology) is copied below.* **Expert Report Gallium Arsenide** **On the Subject of Carcinogenicity and Fertility Effects by Dr. Ernst M. Bomhard** REACh ChemConsult GmbH, Dresden **Prof. Dr. Michael Iatropoulos** Dept of Pathology, New York Medical College Valhalla, NY 10595, USA **Prof. Dr. Gary Williams** Dept of Pathology, New York Medical College Valhalla, NY 10595, USA **TABLE OF CONTENTS** **1. INTRODUCTION 4** **2. NEW RELEVANT SCIENTIFIC EVIDENCE NOT INCLUDED IN THE IARC AND RAC BACKGROUND DOCUMENT 5** **3. IDENTIFIED OMISSIONS IN THE PRESENT BACKGROUND DOCUMENT 6** **4. DATA ON THE TOXICOLOGY AND CARCINOGENICITY OF GALLIUM ARSENIDE: WHAT IS THE OVERALL EVIDENCE? 7** **5. DATA ON THE GENOTOXICITY OF GALLIUM ARSENIDE 10** **6. NEW DATA ON THE SUBJECT OF A THRESHOLD IN THE CARCINOGENICITY OF ARSENIC 11** **7. CONSIDERATIONS ON THE BIOAVAILABILITY OF ARSENIC AND EVIDENCE FOR GALLIUM ARSENIDE 12** **8. EVALUATION OF FERTILITY STUDIES WITH GALLIUM ARSENIDE 14** **9. REFERENCES 15** **10. APPENDIX 1 22** **1. INTRODUCTION**	Regarding your comments on genotoxicity, please see the point 2) of the Annex to RCOM (Additional response to comments). Regarding your comments on bioavailability please see the background document and point 4) of the Annex to RCOM (Additional response to comments).

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		Effective May 25th 2010 the Committee for Risk Assessment (RAC) has proposed the following for the harmonized classification and labeling of gallium arsenide (EC Number: 215-114-8, CAS Number: 1303-00-0) according to the Regulation (EC) No 1272/2008 (CLP Regulation). **Carcinogenicity Cat. 1A** **Reprotoxicity Cat. 1B (RAC, 2010)** The IARC monograph No. 86 (2006) classifying gallium arsenide as a carcinogenic agent to humans appears to be one of the main sources on which RAC has based its May 2010 Opinion with regard to carcinogenicity. Beyond the IARC monograph, the RAC opinion essentially quotes older publications that are listed in the ATSDR (2007) review and in theNTP report (2000), in particular, with regard to the epidemiology of arsenic. With respect to fertility, RAC has adopted the hypothesis of IARC (2006) that gallium is accumulating in the testicular tissue, concluding that the findings on testes and spermatogenesis are primary effects observed in the absence of other relevant toxic effects. IARC classified gallium arsenide as "carcinogenic to humans" solely from data on the bioavailability of arsenicals after oral and intratracheal administration and on data from hamsters indicating metabolism comparable to other arsenicals known to be carcinogenic to humans (i.e. after intratracheal instillation of 5 mg/kg body weight in 0.05 % Tween 80/physiological NaCl; bioavailability of arsenic from gallium arsenide about 10% compared to sodium arsenate and sodium arsenite; Rosner and Carter, 1987). A mode of action justifying this extrapolation was, however, not included in the IARC review. It shall be noted here that except for two papers (Carter et al., 2003; Styblo et al., 2000), all literature on toxicology and epidemiology of gallium arsenide and other arsenicals as well as on the epidemiology in the semiconductor industry quoted in the IARC monograph predominantly originates from the '80 to '90 period. Several new studies on epidemiology and the toxicological mode of action of arsenic have became available after the IARC review and shall be considered in the carcinogenicity assessment. The main aim of this scientific submission for the second consultation is ***to provide RAC with relevant new information published since the IARC evaluation*** and not included in the latest version of the background document to the opinion (January 2010). In addition, this paper aims to provide a weight of evidence assessment for the carcinogenicity and fertility endpoints based on the integrated interpretation of existing and the submitted new evidence. **2 "NEW RELEVANT SCIENTIFIC EVIDENCE" NOT INCLUDED IN THE IARC/ATSDR AND RAC BACKGROUND DOCUMENT** In follow-up of the request for "new relevant information" this section summarizes the new information that became available and that may be relevant for assessing the carcinogenicity and the fertility endpoints for gallium arsenide. • on the evaluation of the NTP studies on gallium arsenide: _ recent data on the carcinogenic effects of particles inducing chronic active lung inflammation indicating that lung tumours are secondary sequelae of the lung pathophysiology and not indicative of a primary carcinogenic effect of	

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		gallium arsenide. _ recent data on the association between hypoxaemia and the occurrence of phaeochromocytomas, highlighting or demonstrating that hypoxaemia was certainly induced as a sequel of the massive lung toxicity. _ recent data on the lack of relevance of phaeochromocytomas for human risk assessment. _ recent data on the irrelevance of mononuclear cell leukemia in F344 rats for human risk assessment _ recent data on a negative HPRT test indicating again a lack of genotoxic/mutagenic activity of gallium arsenide _ recent human data on the genotoxicity of arsenicals at low exposure, which are indicative of a non-linear dose-response relationship, thus indicating a threshold. _ a very recent evaluation of up-to-date knowledge on the question of a threshold in arsenical genotoxicity came to the conclusion that "direct mutagenic effects of arsenic leading to gene mutations and clastogenicity are observed only at higher concentrations" and that "there are good mechanistic arguments to support the idea that there might be a threshold" even if (Kirsch-Volders 2011). • on the interpretation of the metabolism data of gallium arsenide _ recent data in humans exposed to gallium arsenide during production and processing indicate that the metabolic pathway proposed by RAC on the basis of hamster studies is different from carcinogenic arsenicals. _ recent data in humans exposed to inorganic arsenicals by seafood do not support the hypothesis that metabolism of arsenicals to methylated species is a carcinogenic principle. _ on the interpretation of the effects on male fertility parameters • recent data in humans and experimental animals clearly show that chronic lung toxicity leads to hypoxaemia, which in turn affects male fertility parameters i.e. spermatogenesis and testicular morphology. The newly provided information listed above is taken forward into the discussions hereunder, applying a weight of evidence elaboration on the references quoted in the Background document and the information listed above. **3. IDENTIFIED "OMISSIONS" IN THE PRESENT BACKGROUND DOCUMENT** The Background Document used by RAC to support its opinion is largely based on the Annex XV forwarded by the submitting country. It however contains a limited number of omissions which are listed here below. • for example: • the increasing number of epidemiological and mode of action studies and evaluations pointing to a threshold in the carcinogenicity of arsenicals has not been evaluated. • several recent epidemiological studies in the semiconductor industry (all of them without indications of arsenic induced cancers) were evaluated as being not informative (they do not specifically address arsenic exposure) (include references). However several other publications reporting exposure to arsenic in the semiconductor industry are available (include references). • the apparent qualitative differences with regard to lung carcinogenicity after i.t. instillation to hamsters as well as micronucleus induction in mice in comparative studies with various arsenicals, which argue against grouping of inorganic arsenic compounds into one category, have not been dealt with. • the results of a study in workers producing gallium arsenide indicating significantly increased arsenic excretion at shift end but no increase in methylated arsenic species (Yamauchi et al. 1989) have not been included. • the results on male fertility parameters (as well as haematological parameters) have not been put into a perspective with the chronic lung toxicity.	

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		• the results on other than fertility parameters after intra-tracheal instillations into hamsters published by Tanaka et al. (2000), which indicate marked toxicity in other organs than the testes in the Omura et al. (1996b) study have not been included. • the results on other than fertility parameters after intratracheal instillations into rats also pointing to marked toxicity in other organs than the testes have not been taken into account. The consequences of the listed omissions is assessed hereunder and integrated in the overall weight of evidence approach including the newly submitted information. **4. DATA ON THE TOXICOLOGY AND CARCINOGENICITY OF GALLIUM ARSENIDE: WHAT IS THE OVERALL EVIDENCE ?** Up to the present, no reports were found of an individual who was harmed by exposure to gallium arsenide. Accordingly, there are no reports on workers exposed to gallium arsenide showing an increased cancer incidence (IARC, 2006). For gallium arsenide a data set is available covering all important endpoints and containing studies mostly performed to existing guidelines. There exists no other inorganic arsenic compound for which this is the case. Up to now, gallium arsenide is the only inorganic arsenic compound that has been studied by means of long-term exposure (via inhalation) in 2 species (NTP, 2000) In the 2-year inhalation study performed by the NTP (2000), Fischer F344 rats were exposed to gallium arsenide (GaAs) concentrations of 0, 0.01, 0.1 and 1.0 mg/m3. In the 2-year inhalation study on B6C3F1 mice the concentration levels were 0, 0.1, 0.5 and 1.0 mg/m3. The high concentrations were the same in both species, while the mid (5 times) and low (10 times) concentrations were higher in the mouse. All animals were whole-body exposed 6h/d, 5d/w for 105 weeks. The aerosols used had a MMAD ranging from 0.8 to 1.0 µm (at a geometric standard deviation of 1.9 each). No further data characterizing the aerosols (e.g. their surface morphology) were provided. The experimental conditions employed by NTP (whole-body exposure to very small particles at high concentrations causing irritation to the lung) are beyond doubt representing a “worst case” scenario. *Note: A recent cascade impactor analysis of the particle size at various workplaces in gallium arsenide production and processing of the ingots revealed only about 10 to 15 % particles as respirable fraction (2011).* Both rats and mice had **chronic active lung inflammation** (male rats 3/50, 43/50, 50/50, 50/50; female rats 11/50, 46/50, 49/50, 50/50; male mice 1/50, 3/50, 3/50, 12/50; female mice 1/50, 2/50, 11/50, 18/50), with the incidences in rats of both sexes significantly higher compared to mice, although the low dose of gallium arsenide in mice was 10 times higher than the low dose in rats and 5 times higher in the mid dose (the high dose was the same). The species difference is based on the perfusion status (see comments below), which is 33 times greater in mice (Iatropoulos et al. 1996). The other non-neoplastic effects reported were **proteinosis**, **alveolar epithelial hyperplasia** (atypical hyperplasia), and **alveolar epithelial metaplasia** in the lung. All of these changes result from a chronic irritation of	

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		the lung tissue. They are qualitatively similar to those effects reported as the typical outcome of the exposure to other particles e.g. talc (H2Mg3(SiO3)4) or quartz (SiO2) by inhalation (NTP 2000, Wolff et al. 1988). There was an increased occurrence of **alveolar-bronchiolar neoplasms** (mostly adenomas), **mononuclear cell leukaemia** and **benign pheochromocytomas** in female rats. This increased occurrence was not observed, neither in male rats nor in mice(females and males). Some recent and additional data shall be considered when interpreting these results: _ Federico et al. (2007) for example have recently shown that a broad range of chronic inflammatory processes in the lung result in the induction of neoplastic transformation. The longer the inflammation lasts the higher is the resulting incidence of cancer formation. (there are several but needs time e.g. Mossman. Mechanism of action of poorly soluble particulates in overload-related lung pathology. Inhal Toxicol 12, 2000, 141-148) The increased occurrence of alveolarbronchiolar neoplasms (mostly adenomas) in female rats should therefore be seen as the consequence of the primary sustained toxicity of gallium arsenide to the lung and not as an indication of a primary carcinogenic effect. Moreover, Watson and Valberg (1996) showed that the rat turned out to be the most susceptible species with respect to this mechanism of tumorigenesis Gallium arsenide particles apparently have a high potential to cause irritation to the lung and other respiratory tissues, when applied under the experimental conditions of inhalation or i.t. instillation. This is the primary event in both sexes of both species that produces the sustained chronic toxicity to the respiratory tract that interferes with gallium arsenide clearance. Specifically, the mouse lung volume and plasma flow rate ratio are 33 times greater compared to the rat, providing superior perfusion and consequently resulting in the mouse lung possessing a better adaptive capacity to chronic sustained inflammation compared to female rats, which have the smallest capacity, even compared to male rats (Iatropoulos et al, 1996). This is reflected in the incidence and severity of this inflammation, which is equally severe in both sexes. _ Several additional life-span studies with Syrian hamsters not mentioned in the RAC background document should also be mentioned here. The animals were intermittently i.t. treated over a period of 15 weeks. With potassium arsenate and diarsenic trioxide, an increased number of lung tumours were observed. This was not the case for diarsenic trisulfide. Gallium arsenide was also negative but the number of surviving animals was however too small to allow for clear-cut conclusions (Ishinishi et al. 1983; Ohyama et al. 1988; Pershagen et al. 1984; Pershagen and Björklund 1985; Yamamoto et al. 1987). Thus, there seems also to be some evidence for qualitative differences between the various inorganic arsenicals with respect to their potential, to be considered before drawing conclusions _ About the increased occurrence of **mononuclear cell leukemia in female rats** at the highest concentration of GaAs, it shall be stressed that this type of tumor is very common in the F344 rat strain and most likely the result of the chronic inflammatory stress in the lung, which through overcompensation increases the background incidence at the high dose (not yet, came from Gary). Several authors have concluded that this type of tumor (spontaneous/background) is not relevant to human risk (Caldwell, 1999; Elwell et al. 1996; Lington et al. 1997). In 2005, NTP stopped using the F344 rat for any experimental work on toxicity for this (and another) reason. _ The increased occurrence of **benign pheochromocytomas** in female rats is also most likely the result of the chronic inflammatory stress and with no relevance to humans (Greim et al. 2009). Interestingly, a correlation between non-neoplastic chronic lung lesions and pheochromocytomas has been found in 9 NTP 2-year inhalation studies (including the gallium arsenide study) with exposure of male F344 rats to particulate matters (female rats have not been included in this evaluation) (Osaki et al. 2002). A significant correlation between the occurrence of pheochromocytomas and the severity of inflammations and fibrosis was found. The authors pointed out that a	

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		reduction of the surface area available for gas exchange results in systemic hypoxaemia that should be expected under the given circumstances. The decrease in gas exchange then stimulates the secretion of catecholamines by the adrenal medulla. The chronic endocrine hyperactivity of the adrenal medulla finally eventuates in the formation of hyperplasia and neoplasms (Osaki et al. 2002). To summarise, the relevance of the benign pheochromocytomas and mononuclear cell leukemia in the female rats for the human can been questioned. And with regard to the effects on the lung and respiratory tract tissues, the significant inflammation, hyperplasia and metaplasia (extensive and sustained - for 105 weeks-) caused by the inhalation of gallium arsenide most probably represent the primary toxic effect. No primary carcinogenic effect of gallium arsenide can easily be inferred from the NTP observations as a) there was only evidence of carcinogenic activity in female rats and not in male and female mice or in male rats and b),.there was clear evidence of alveolar-bronchiolar neoplasms (mostly adenomas) in female rats, however there was extensive evidence of chronic pulmonary and upper respiratory tissue inflammation, hyperplasia and neoplasia. There are also indications that there may be differences between the various inorganic arsenicals with respect to the potential to cause tumours. Epigenetic carcinogens acting through cytotoxicity are generally accepted to have cancer thresholds at exposures below which they do not elicit the cellular and tissue effects that lead to carcinogenicity (Barlow et al, 2005; Dybing et al, 2002; Williams et al, 1996; Williams, 2008). It shall be noted here as well that the NTP study was used by NIOSH: as evidence of neoplasia was present only in the female rat high dose (1 mg/m3 group), a ceiling value of 0.002 mg/m3 for gallium arsenide in the workplace (ACGIH Worldwide®, 2003) was recommended. This being said, it is known that the inhalation of particles by humans may cause chronic toxicity to the lung and subsequently as a long-term sequel may cause cancer (Valavanidis et al. 2008). Incidentally cancer may be caused by any chronic damage to the lung and also other tissues. While this observation could be seen as implying a certain carcinogenic potential to small particles, it certainly does not justify in any way the general classification of respirable particles of any composition as carcinogenic to humans. **5. EVALUATION OF DATA ON THE GENOTOXICITY OF GALLIUM ARSENIDE** Results from four different assays are available (Ames, HPRT, MNT in vitro; MNT in vivo). In the Ames test (preincubation method) gallium arsenide was applied to the *S. typhimurium* stems TA97, TA98, TA100, TA102 and TA1535 at concentrations up to 10000µg/ml. No gene mutation was observed (Zeiger et al. 1992, cited in NTP 2000) with and without metabolic activation by means of rat or hamster S9-mix (at concentrations up to 30%).A gallium arsenide extract (at a loading of 200 mg/ml in DMSO for 72 h at 37 °C, with shaking) was applied to L5178Y lymphoma cells of mice at concentrations ranging from 250 to 2000 µg/ml. The experiment was performed with and without metabolic activation by a rat-S9 mix. In no case a mutation at the HPRT-locus of the L5178Y cells was observed by the microtiter fluctuation technique (Stone, 2010). Gallium arsenide was also tested as part of a series of experiments studying the induction of micronuclei in Syrian hamster embryo (SHE) cells. In this series of experiments within the NTP program, NTP tested a totality of 16 chemicals, which were under investigation for carcinogenicity at that time. The concentrations ranged from 2.5 to 10 µg/ml; treatment period was 24 h. Concentrations of 10µg/ml were clearly cytotoxic. In contrast to the (positive) reference substance, colchicine, no micronuclei were induced by gallium arsenide (Gibson et al. 1997). It shall be noted here that hamsters have been reported to be more similar to humans than rats with respect to the metabolism of arsenic (Rosner and Carter 1987).	

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		The frequency of micronuclei in erythrocytes was analyzed in samples of peripheral blood taken from 10 mice (in 2 concentrations only 9 animals) of each of the tested concentrations (0.1 – 75 mg/m3) used in NTP's 14–week study. A total of almost 200,000 normochromatic erythrocytes was evaluated. No indication of any exposure related effect was found (NTP 2000). In conclusion, none of the studies addressing the different endpoints yielded evidence for a genotoxic effect of gallium arsenide. While numerous studies on gene mutation with other arsenicals also do not show positive effects, most studies on chromosomal damage (clastogenicity) or aneugenic effects do show positive effects in vitro as well as in vivo. Diarsenic trisulfide administered orally in 4 different experiments (at doses of 100, 160, 500 and 500 mg/kg body weight) with CBA mice did not increase the incidence of micronuclei in polychromatic erythrocytes in any of the experiments. However, only with diarsenic trisulfide, amounts of arsenic could be detected in the blood (390 – 900 ng/ml, at a detection limit of approximately 100 ng/ml). For all the other tested substances (sodium and potassium arsenite and diarsenic trioxide all administered intraperitoneally at doses up to 10 mg/kg body weight) the concentration of arsenic in the blood was below the detection limit. Despite this a significant and even marked increase of micronuclei was detected with those other substances (Tinwell et al.1991). These findings highlight that obviously the proof of the bioavailability of arsenic originating from inorganic arsenicals does not allow deriving any conclusion about the occurrence or non-occurrence of any genotoxicity effect typical for arsenic. **6. NEW DATA ON THE SUBJECT OF A THRESHOLD IN THE CARCINOGENICITY OF ARSENIC** A number of more recent epidemiological studies based on quite accurate exposure assessments (essentially studies on drinking water) indicates the existence of a threshold for the carcinogenic effects of (other) arsenicals well above the known exposure experienced during the production and processing of gallium arsenide (Bates et al. 2004; Brown and Ross, 2002; Lamm et al. 2004, 2006, 2007; Meliker et al. 2010; Mink et al. 2008; Schoen et al. 2004; Snow et al. 2005; Tapio and Grosche 2006). New data on the genotoxicity (predominantly on the formation of micronuclei) of (other) arsenicals in humans are also indicative of a threshold at a level that is by far not reached during gallium arsenide production or processing (Basu et al. 2002; Ghosh et al 2007; Paiva et al. 2008; Vig et al. 1984). In a very recent evaluation of the actual database on genotoxic effects and possible thresholds of gallium arsenide and arsenicals in general, Kirsch-Volders (2011) (see Annex 1) summarized that "direct mutagenic effects of arsenic leading to gene mutations or clastogenicity are observed only at higher concentrations, except when arsenic is tested in comutagenesis experiments. Arsenic is working essentially as an indirect mutagen leading to chromosome breakage or aneuploidy, by inhibiting proteins involved in DNA repair, mitotic machinery, methylation processes and other genotoxicity-related pathways." She recommended the micronucleus assay, which is covering both clastogenic and aneugenic events, for the assessment of the hazard and risk of arsenic genotoxicity and concluded that "there are good mechanistic arguments to support the idea that there might be a threshold for genotoxic effects but there is insufficient experimental evidence...".	

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		Various (some of them are very extensive) epidemiological studies carried out in the semiconductor industry consistently show no increase of incidences/prevalences of cancer attributable to arsenic or arsenicals (Beall et al. 2005; Bender et al. 2007; Boice et al. 2010; Darnton et al. 2010; Nichols and Sorahan 2005). Overall, all the above data provide strong evidence for the existence of a threshold for the toxic, genotoxic and carcinogenic effects of arsenic (though the exact value still needs to be quantified). There remains hardly any doubt that there is no scientific justification for a linear extrapolation of effects to the low non-toxic levels of exposure relevant to gallium arsenide production or processing. Recent studies conducted in industry did not show an increase of incidence/prevalence of cancer attributable to arsenic or arsenicals. **7. CONSIDERATIONS ON THE BIOAVAILABILITY OF ARSENIC AND EVIDENCE FOR GALLIUM ARSENIDE** RAC also justifies its opinion on the classification of gallium arsenide by the argument that arsenic becomes bioavailable after oral or intratracheal (i.t.) instillation to hamsters. According to RAC, the arsenic bioavailable from gallium arsenide is metabolized to form predominantly dimethylarsinic acid (DMAV) through methylation,as in the case of other inorganic arsenicals known to be carcinogenic to humans (Rosner and Carter 1986; Yamauchi et al. 1986). With this reasoning RAC also adopts the previous arguments of IARC (IARC 2006). It shall be noted here that in the hamsters experiments the solubility of gallium arsenide was enhanced by using Tween 80 or a phosphate buffer. Despite this the absorption rate for i.t. instillation amounted to only 5-10%. The absorption rate for oral administration stayed below 1%. No reference was made in the RAC document/in IARC to a published Japanese study on bioavailability of arsenic and its metabolites in gallium arsenide production (Yamauchi et al., 1989). The study analysed the situation in the production and the processing of gallium arsenide ingots at the end of a shift. It monitored inorganic arsenicals, methylarsonic acid (MMAV), DMAV and trimethylarsinic compounds in urine. A significant increase (by 24 and 22% respectively) of arsenic in the urine of exposed workers was recorded at the end of a shift. However, at the same time no increase of the concentrations of methylated arsenic species was found (Yamauchi et al. 1989). The above results are in line with corresponding studies for the processing of gallium arsenide wafers. The respective studies found in general very low excretion of arsenic mostly on a level barely distinguishable from the reference group. No increased excretion of MMA or DMA in the urine was found in these either (Farmer et al. 1990; Morton and Leese 2010; Morton and Mason 2006). The claim that arsenic originating from an exposure to gallium arsenide is metabolized by humans to form MMA or DMA through the process of methylation is thus not supported by existing data. However, even if it could be assumed that the arsenic originating from an exposure to gallium arsenide is metabolized by methylation, this still leaves the question whether it can be concluded that this hypothesis necessarily implies a carcinogenic potential of gallium arsenide for humans. This conclusion would require both a)that the mode of action for the carcinogenicity of inorganic arsenicals is known and b)the assumption that there is no threshold for this mode of action. Both conditions are not supported by the available data:	

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		Several modes of actions to explain the carcinogenicity of arsenic are currently discussed. The most frequently quoted and thus the most likely mechanisms are i) indirect genotoxicity (chromosome aberration), ii) formation of reactive oxygen species, iii) increased cell proliferation and transformation and iv) hypo-/hypermethylation of the DNA (ATSDR 2007; Cohen et al. 2006; Schuhmacher-Wolz et al. 2009). For the last three modes of action (ii- iv) a threshold definitely has to be assumed. In the case of chromosome aberrations, the majority of publications focus on the induction of micronuclei. New results on human cells now demonstrate the existence of concentration ranges without any effect (Basu et al. 2002; Ghosh et al 2007; Paiva et al. 2008; Vig et al. 1984). The levels of exposure to arsenic discussed in these studies are well above those relevant to the manufacturing and processing of gallium arsenide (Farmer et al. 1990; FCM 2010; Morton and Leese 2010; Morton and Mason 2006). Furthermore there is no evidence for an adverse effect of gallium arsenide on chromosomes provided in the published experimental data (Gibson et al. 1997; NTP 2000). Further evidence for the argument that the bioavailability of arsenic originating from inorganic arsenicals dose not necessarily cause the effects typical for arsenic is provided by the study of Tinwell et al. (1991) on diarsenic trisulfide. For this substance, Tinwell did not observe the induction of micronuclei typical for other inorganic arsenicals despite bioavailability. It is well known that seafood contains larger amounts of trimethylated arsenic species and arsenosugar. These arsenic compounds are generally deemed toxicologically inert. It is however important to note that up to 4% of the arsenic contained in seafood is present in the form inorganic arsenical compounds (Borak and Hosgood, 2007). In some cases this value is actually exceeded (Norin et al. 1985). Therefore populations with a high consumption of seafood have a relatively high intake of inorganic arsenic. As a result not only small amounts of inorganic arsenic and MMA are excreted, but also an increased excretion of DMA at concentrations of up to 100 µg arsenic/l in urine was reported for these populations (Borak and Hosgood 2007; Heinrich-Ramm et. al. 2002; Heitland and Köster 2008; Wei et al. 2003). No evidence is known to date identifying an increased risk of cancer or any other disease caused by arsenic for populations with high consumption of seafood. All data published on DMA excretion of workers in the gallium arsenide industry show levels substantially below 100 µg arsenic/l urine (Farmer and Johnson, 1990; Morton and Leese 2010; Morton and Mason 2006). In summary there is no sufficient evidence • that exposure to gallium arsenide results in an increased level of methylated arsenic species in the human body • that the metabolism of arsenic to methylated arsenic species provides a plausible mode of action to derive a carcinogenic potential for the respective arsenical and • that the data on gallium arsenide gave evidence for any of the postulated modes of action. Based on all the above presented data, it is inappropriate, based on bioavailability of insignificant amounts of arsenic of MMA, to classify gallium arsenide as “carcinogenic to humans”. **8. EVALUATION OF FERTILITY STUDIES WITH GALLIUM ARSENIDE** Four studies reveal effects on spermatozoa and testes: two studies in rats and hamsters with 16 i.t. instillations each,	

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		two 14-week inhalation studies on rats and mice (Omura et al. 1985, 1986a,b; NTP 2000). The weekly administered dose in the i.t. studies was 7.7 mg/kg/d in both cases. The concentrations in the inhalation studies were in both studies: 0, 0.1, 1.0, 10, 37 and. 75 mg/m3, (6 h/d, 5 d/w). Effects reported in the i.t. studies were essentially related to the stages of spermatogenesis, the morphology of spermatozoa and their motility. In the inhalation study of rats, slight effects on the motility of spermatozoa were observed at 10 mg/m3. Minimal testicular atrophy was recorded at 37 mg/m3, whereas this effect was moderate to severe at 75 mg/m3. In the inhalation study in mice hypospermia and testicular atrophy were found at concentrations at or above 10 mg/m3. The i.t. studies do not mention any findings related to other organs. However ,Tanaka et al. (2000) who reported further details on the hamster study performed by Omura et al. (1996b), mentioned decreased body weights, massive effects on the lung and kidney damage., Other data from studies on rats by other authors using comparable experimental conditions(single or repeated i.t. instillation at comparable dose levels), observed marked lung toxicity (Goering et al. 1988; Webb et al. 1984, 1986, 1987). In the 14-week inhalation study, in rats, effects on the lung at 0.1 mg/m3 and above as well as haematological effects (microcytic anemia) at 10 mg/m3 and above were observed. In mice, the 14-week inhalation study revealed effects on the lung at 1.0 mg/m3 and above as well as haematological effects (microcytic anemia) at 10 mg/m3 and above. It shall be noted that no adverse effects on spermatozoa or testes were reported in the 2-year inhalation studies (reference) in mice and rats at concentrations up to 1.0 mg/m3 . One of the two reasons for RAC's decision to classify gallium arsenide as a reprotoxicant Cat. 1B was "clear effects on fertility at low doses in the absence of other toxic effects…" This is however not substantiated by the available data. A plausible explanation for the observed effects on spermatozoa and testes is provided by the fact that all studies without exception report severe damage to the lung. This damage of the lung induces a persistent hypoxaemia (see also Osaki et al. 2002). It is well known that hypoxaemia of various causes (high altitude exposure, diseases of the lung) has adverse effects on spermatozoa and the function and morphology of testes. This applies to humans as well as to laboratory animals. (Aasebo et al. 1993; Donayre et al. 1968; Farias et al. 2005, 2010; Gasco et al. 2003; Gosney 1984,1987; Liao et al. 2010; Semple et al. 1984; Shevantaeva and Kosyuga, 2006; Verrati et al. 2008). The other rationale given by RAC „This is also supported by the potential of gallium to accumulate in rat testis following inhalation exposure" is at variance with the conclusions of the NTP report: Gallium and arsenic concentrations in the lung tissue reached their peak value of more than 100 µg/g after a 6-month exposure to gallium arsenide at a concentration of 1.0 mg/m3. For comparison, a concentration of 0.50 µg gallium/g and 1 µg arsenic/g respectively was detected in the testicular tissue. Furthermore, a marked decrease of the gallium and arsenic concentrations in the lung tissue occurred after 6 months. According to the authors this was due to an increased activity of macrophages. At a concentration of 0.01 mg/m3 (still causing lung tissue irritation) there were no traces of gallium detectable in the testes at any time and the concentration of arsenic was at the level of the controls. The absence of any detectable gallium concentration in the testicular tissue at the exposure level closest to the actual situation at the work station, i.e. 0. 01 mg/m3, does not support the assumption of an accumulation relevant for classification. Presumably the NTP judgment is based on the observation that compared to the accumulation in the lung the increase of the gallium and arsenic concentration in the testicular tissue is insignificant.	

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		In summary there is no effect of gallium arsenide on male fertility relevant to classification and labeling. **Note:** Gallium compounds, e.g. gallium nitrate, are intravenously applied at fairly high dose levels (10 to 25 mg/kg body weight) to treat cancer, hypercalcaemia and metabolic bone diseases. No adverse effects on testes or on male fertility have been reported (Chitambar 2010). **9. REFERENCES** Aasebo et al. Reversal of sexual impotence in male patients with chronic obstructive pulmonary disease and hypoxemia with long-term oxygen therapy. J Steroid Biochem Mol Biol. 46, 1993, 799-803. ACGIH Worldwide®, 2003 Documentation of the TLVs® and BEIs® with other Worldwide Occupational Exposure Values, Cincinnati, OH. ATSDR. Agency for Toxic Substances and Disease Registry. Toxicological profile for arsenic. August 2007. Barlow et al. Introduction pp 15-17 in Risk assessment of substances that are both genotoxic and carcinogenic, EFSA/WHO International Conference with support of ILSI Europe, Brussels, Belgium, 2005, pp 1-286. Basu et al. Enhanced frequency of micronuclei in individuals exposed to arsenic through drinking water in West Bengal, India. Mutat Res 416, 2002, 29-40. Bates et al. Case-control study of bladder cancer and exposure to arsenic in Argentina. Am J Epidemiol 159, 2004, 381-389. Beall et al. Mortality among semiconductor and storage device-manufacturing workers. J Occup Environ Med 47, 2005, 996-1014. Bender et al. Cancer incidence among semiconductor and storage device workers. Occup Environ Med 64, 2007, 30-36. Boice et al. Cancer mortality among US worker employed in semiconductor wafer fabrication. J Occup Environ Med 52, 2010, 1082-1097. Borak and Hosgood. Seafood arsenic: implications for human risk assessment. Regul Toxicol Pharmacol 47, 2007, 204-212. Brown and Ross. Arsenic, drinking water, and health: a position paper of the American Council on Science and Health. Regul Toxicol Pharmacol 36, 2002, 162-174. Caldwell. Review of mononuclear cell leukemia in F-344 rat bioassays and its significance to human risk: a case study using alkyl phthalates. Reg Toxicol Pharmacol 30, 1999, 45-53. Carter et al. The metabolism of inorganic arsine oxides, gallium arsenide, and arsine: a toxicochemical review. Toxicol Appl Pharmacol 193, 2003, 309-334. Chitambar. Medical applications and toxicities of gallium compounds. Int J Environ Res Public Health 7, 2010, 2337-2361. CLH-GaAs, 2009. Annex XV report, Proposal for harmonised classification and labelling. Substance Name: GALLIUM ARSENIDE, EC Number: 215-114-8, CAS Number: 1303-00-0, Submitted by: France, Date: May 2009, Version: 2 Cohen et al. Methylated arsenicals: the implications of metabolism and carcinogenicity studies in rodents to human risk assessment. Crit Rev Toxicol 36, 2006, 99-133. Darnton et al. A further study of cancer among the current and former employees of National Semiconductor (UK)	

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		1.2.1 Definitions of thresholds A threshold dose for a specific genotoxic effect of a substance may generally be described as the dose below which the substance does not induce the effect, although it has the potential to induce it. Such a definition can be used in the context of various genetic endpoints — from early DNA effects (e.g., DNA adducts, DNA damage) to mutations. As a practical requirement of using such a general definition one should always explain what is specifically meant in a given context, especially the genetic endpoint must be specified. When discussing specific data, it would be helpful to differentiate between **true** and **practical** threshold doses. According to Lutz (1998), a true threshold dose may be defined as a point in the dose–response curve where a slope 0 changes into a slope >0. For situations where the substance under investigation acts incrementally by a mechanism which has a (variable) background rate, a true threshold will not be found. However, a practical threshold dose can be set where the linear part of the dose–response curve is hidden within the background variability. Threshold doses must be distinguished from 'no observed adverse effect levels' (NOAELs) which depend on the sensitivity of a test system to detect a specific effect. Furthermore, NOAELs refer to 'adverse' effects, whereas thresholds may be defined for effects without knowledge of their consequences. Thresholds can often be assimilated to NOELs, as far a true non-genotoxic dose range for a given genotoxic effect is demonstrated; however thresholds are considered to have "nonlinear dose responses", and in the case of NOELs "non-linear" responses are not always "thresholded". *1.2.2 Indications for thresholded mutagenic effects require mechanistic evidence* For many years it has been commonly accepted that risk assessments of genotoxic chemicals are based on linear models for extrapolating low dose effects from experimental data. Some authors name it a dogma, paradigm or a historical issue. In fact the underlying assumption is the absence of a threshold for the induction of mutations and is scientifically based on the concepts that i) some DNA lesions are not repaired, have no chance to be repaired (induced in late interphase) or are misrepaired and are therefore mutagenic; ii) a single mutation can be responsible for cell transformation. Although these concepts are still valid, recent developments indicate the existence of **biologically meaningful** threshold effects for some types of mutagenic events. Indeed as far as non-DNA interactive mutagens (**indirect mutagens)** are concerned, when several targets need to be triggered to induce the genotoxic endpoint (e.g. inhibitors of tubulin polymerization). The first experimental demonstration of a threshold was provided for aneuploidy induction *in vitro* in human lymphocytes (Elhajouji et al., 1995, 1997) and in mouse oocytes (Kirsch-Volders et al., 2003), and *in vivo* in rat and mice peripheral blood (Cammerer et al., 2010) exposed to spindle poisons. Extrapolation *in vivo* to germ cells where the organization of chromatin and the efficiencies of the cell cycle and spindle checkpoints may differ between both meiotic divisions and between sexes remains difficult. It was further hypothesized that threshold responses might also be expected from DNA-interactive mutagens (**direct mutagens**) when their interaction with DNA is dependent on particular mechanisms, namely bioavailability, metabolic activation, scavengers of oxidative damage and DNA repair (Kirsch-Volders et al., 2000; Jenkins et al., 2005) (Figure 2). Recent papers analyzed these hypotheses, in particular Jenkins et al. (2005) who came to the evidence of the presence of a genotoxic threshold for O6G- and N7G-inducing alkylating agents in mutagenesis/chromosome damage. The authors considered that the contribution of DNA repair was the essential mechanisms responsible for this threshold. However it would be scientifically unjustified to consider that all DNA lesions are susceptible to be repaired and therefore thresholded responses be expected for all DNA-interactive	

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		mutagens. As far as DNA adducts are concerned, the important adducts for induction of mutations are those which I) avoid immediate repair, ii) misrepair during replication, iii) are repaired within an exon. It is therefore crucial to have specific methodologies to assess the relevant adducts and to understand the corresponding mechanisms of DNA repair. **2. Genotoxicity of Gallium Arsenide (Risk Assessment Committee, 2010)** The genotoxicity data available for GA are scarce and clearly reported in the RAC Background document, 2010 (p25-26): _ single Ames test with and without S9 according to OECD 471 guideline : negative (Zeiger et al., 1992 cited in NTP, 2000) _ single *in vitro* micronucleus (MN) assay in SHE with cytochalasin B without S9, no OECD guideline available at that time: negative (Gibson et al., 1997) _ single *in vivo* MN assay in peripheral blood after inhalation, according to OECD guideline 474 (except absence of positive control): negative (NTP, 2000) I was informed about a very recent HPRT study in MLCells, performed according to current GL, which was also negative (Stone V., 2010 unpublished results). My concern for these genotoxicity studies are related to the low solubility of GA and the size of the particles (mentioned only for the *in vivo* assay 0.9 to 1.3 µm), possibly close to the nanosize. With our present knowledge about the genotoxicity of small sized particles and its implications for *in vitro* and *in vivo* genotoxicity testing the protocols applied at that time are not adequate (Gonzalez et al., 2008, 2011). In particular nanoparticles are almost not taken up by *Salmonella* and in the *in vitro* MN assay cytochalasin-B should not be added together with the particles to avoid block of endocytosis (actin block by cytochalasin-B). The kinetic for uptake and translocation of these small particles through the lung is also a major problem; MN analysis in the lung epithelial cells (at the target site) should be recommended. All these shortcomings might explain the negative data. *In summary we cannot base our conclusions on the available genotoxicity data of gallium arsenide. First, they are too limited. Second, additional information on physico-chemical characteristics of the particles are needed. Moreover, new experiments performed according to the recently designed protocols for the testing of poorly soluble particles should be advised. Therefore we will base our discussion on the genotoxicity modes of action of Arsenic species and Gallium.* **3. Genotoxicity of Gallium** To the best of our knowledge, no data on genotoxicity of gallium is available. The only information which might be relevant for potential genotoxicity is that 1) Gallium can interfere with calcium uptake; the element is a potent inhibitor of protein synthesis (Hoyes et al., 1992); 2) Gallium also appears to inhibit DNA synthesis by action on ribonucleotide reductase (Riaz et al., 1995); and 3) cytopathological effects of Gallium include nuclei with irregular outlines and heterochromatin (Yang and Chen, 2003). **4. Genotoxicity of Arsenic: Gene Mutations, Clastogenicity and Aneugenicity** (for review see Basu et al., 2002; Kligerman and Tennant, 2007; Klein et al., 2007; Gebel, 2001) The trivalent arsenic is considered as more toxic than the pentavalent form. Several data supports the idea that arsenic is not a strong inducer of gene mutations which appear only at higher concentrations. Clastogenesis could be a potentially genotoxic modes of action for arsenic compounds. Several studies report increased chromosome	

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		aberrations in lymphocytes of humans exposed to arsenic in drinking water. However, similar to the gene mutagenesis studies reported, arsenite and the trivalent metabolites are clastogenic only at highly toxic. It has been suggested that the increased number of mitotic figures, recorded in classic cytogenetic assays as mitotic index and used as indicators of "cell viability", may rather imply a cell cycle blockage at G2/M. Since cells with accumulating chromosomal aberrations at G2/M may not be viable in the long term, the relevance of this kind of data for carcinogenic risk assessment remains unclear. Indirect genotoxic mechanisms may include aneuploidy, oxidative stress and inhibition of DNA repair, many of which have clearly been seen after treatment with arsenic compounds. Co-mutagenicity/synergestic effects of arsenic with several direct acting mutagens are well known and can probably be attributed to DNA repair inhibition. At lower arsenic concentrations, aneuploidy is seen. Micronuclei (MN) are induced *in vivo* in mice treated with arsenite and are detected in exfoliated bladder cells, buccal cells, sputum cells and lymphocytes from arsenic exposed humans. An analysis of MN induced by arsenite shows that at low (relatively non-toxic) doses, arsenite acts as an aneugen by interfering with spindle function and causing MN with centromeres, while at high dose it acts as a clastogen, as indicated by MN formation without centromeres. In Chinese hamster V79 cells, 10 μM arsenite (not a very toxic concentration in these cells) disrupted mitotic spindles and induced persistent aneuploidy that was maintained even 5 days after its removal. This may be a possible explanation for the "delayed mutagenesis" noted after long-term exposure to low (non-toxic) concentrations. *In summary, direct mutagenic effects of Arsenic leading to gene mutations or clastogenicity are observed only at higher concentrations, except when arsenic is tested in co-mutagenesis experiments. Arsenic is working essentially as an indirect mutagen leading to chromosome breakage or aneuploidy, by inhibiting proteins involved in DNA repair, mitotic machinery, methylation processes and other genotoxicity-related pathways. Therefore the MN assay which is covering both clastogenic and aneugenic events might be recommended to assay the hazard and risk of arsenic genotoxicity.* **5. Genotoxic Modes of Action of Arsenic Species.** Various modes of action have been proposed for arsenic carcinogenicity: _ induction of oxidative stress _ disruption of tubulin polymerisation _ induction of genetic damage _ diminished DNA repair _ altered DNA methylation patterns _ suppression of tumor suppressor protein p53 _ biomethylation, _ enhanced cell proliferation Of particular importance for thresholded effects of genotoxicity are the following mechanisms: _ *Induction of oxidative and nitrosactive stress and damage (for review see Jomova et al. 2011)* Many mechanistic studies of arsenic toxicity have suggested that reactive oxygen species and reactive nitrogen species are generated during inorganic arsenic metabolism in living cells. Arsenic induces morphologic changes in mitochondria integrity and a rapid decline of mitochondrial membrane potential. Mitochondrial alterations are considered to be primary sites where an uncontrolled random formation of superoxide anion radical occurs. Cascade mechanisms of free radical formation derived from the superoxide radical combined with a decrease in cellular	

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		oxidant defence by treatment with glutathione-depleting agents results in an increased sensitivity of cells to arsenic toxicity. Experimental results based on both *in vivo* and *in vitro* studies of arsenic-exposed humans and animals suggest the possible involvement of increased formation of peroxyl radicals (ROO•), superoxide anion radical (O2 •–), singlet oxygen (1O2), hydroxyl radical (•OH), hydrogen peroxide (H2O2), dimethylarsenic radical [(CH3)2As•], blood nonprotein sulfhydryls and/or oxidant-induced DNA damage (Flora et al., 2007). The exact mechanism responsible for the generation of all these reactive species has yet to be fully elucidated, but some studies have proposed the formation of intermediary arsine species. In addition to reactive oxygen species, arsenic exposure can initiate the generation of reactive nitrogen species (RNS). Several contradictory results describing arsenicinduced production of NO• have been reported, one of which concluded that there was no arsenic-induced increase in NO• generation in hepatocytes and human liver cells, which inhibited inducible NO synthase gene expression in cytokine-stimulated human liver cells and hepatocytes. However, in another study, arsenite was said to inhibit inducible NO synthase gene expression in rat pulmonary artery smooth muscle cells. A third study with low levels of arsenite (<5 μM) similarly recorded no change in intracellular concentration of Ca(II), nor any NO• generation, according to results from EPR spectroscopy. _ *Disruption of spindle tubulins and aneuploidy* Effects of As2O3 on the spindle were reported already in 1986 (Kirsch-Volders, 1986) in primary human fibroblasts and more recently confirmed and reviewed by Kligerman et al., 2005; Kligerman and Tennant, 2007). In the latter, new evidence was provided that reduced glutathione (GSH) can chemically reduce inactive pentavalent arsenicals to trivalent arsenicals which can disrupt tubulin polymerization, and that reactive oxygen species (ROS) are most likely not involved in tubulin disruption. Chromosome instability and karyotype evolution, either through the production of stable chromosome aberrations or the induction of aneuploidy are driving forces in the induction of cancer. Chromosome aberration (CA) induction and spindle disruption leading to aneuploidy are important aspects of the mode of action for arsenic-induced cancer. CA induction likely is produced through the action of ROS, while aneuploid induction may involve direct binding of arsenicals to thiol groups. _ *Methylation* Another important action of low dose arsenite treatment is effects on DNA methylation. It is now well established that altered DNA methylation of many genes, either in their promoter regions or within exons, are important in carcinogenesis, that DNA methylation changes begin early in the carcinogenesis process. It was also shown that methylation of critical targets (tubulins, DNA repair enzymes) may have indirect mutagenic effects (Figure 3). _ *Inhibition of DNA repair by arsenic species and/or metabolites: (for review; see Nollen et al., 2011)* With respect to DNA repair inhibition, several studies point to an interaction of arsenic with various DNA repair pathways, which may in turn decrease genomic integrity. Hartwig, already in 1998, observed that arsenic (III) was inhibiting the NER incision step and in 2002 wrote that As (III) deserves special attention, as it inactivates only PARP, but does so at very low concentration starting from 10nm. Especially nucleotide excision repair (NER) is strongly inhibited by arsenic. Surveying the impact of arsenic on NER, numerous studies have shown that inorganic arsenic inhibits repair of bulky DNA adducts induced by UV-irradiation or benzo[a]pyrene in cultured cells and laboratory animals; additionally arsenite has been shown to down-regulate expression of some NER genes in cultured human cells. In humans, arsenic exposure via drinking water was correlated in a dose dependent manner to decreased expression of some NER genes and diminished repair of lesions in lymphocytes. More recently, Nollen et al. (2011) reported that arsenite and its metabolite monomethylarsonous acid (MMA(III))	

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		strongly decreased expression and protein level of Xeroderma pigmentosum complementation group C (XPC), which is believed to be the principle initiator of global genome NER. This led to diminished association of XPC to sites of local UVC damage, resulting in decreased recruitment of further NER proteins. Additionally Xeroderma pigmentosum complementation group Eprotein (XPE) expression was reduced, which encodes for another important NER protein and similarly to XPC is regulated by the activity of the transcription factor p53. In summary, the data demonstrate that in human skin fibroblasts arsenite and even more pronounced MMA(III) interact with XPC expression, resulting in decreased XPC protein level and diminished assembly of the NER machinery. _ *Genomic dose- reponses (Gentry et al., 2010)* Recently, a comprehensive literature search was conducted by Gentry et al. (2010) to identify information on gene expression changes following exposures to inorganic arsenic compounds. This information was organized by compound, exposure, dose/concentration, species, tissue, and cell type. A concentration-related hierarchy of responses was observed, beginning with changes in gene/protein expression associated with adaptive responses (e.g., preinflammatory responses, delay of apoptosis). Between 0.1 and 10 μM, additional gene/protein expression changes related to oxidative stress, proteotoxicity, inflammation, and proliferative signalling occur along with those related to DNA repair, cell cycle G2/M checkpoint control, and induction of apoptosis. At higher concentrations (10–100 μM), changes in apoptotic genes dominate. Comparisons of primary cell results with those obtained from immortalized or tumorderived cell lines were also evaluated to determine the extent to which similar responses are observed across cell lines. Although immortalized cells appear to respond similarly to primary cells, caution must be exercised in using gene expression data from tumor-derived cell lines, where inactivation or overexpression of key genes (e.g., p53, Bcl-2) may lead to altered genomic responses. Data from acute *in vivo* exposures are of limited value for evaluating the doseresponse for gene expression, because of the transient, variable, and uncertain nature of tissue exposure in these studies. The available *in vitro* gene expression data, together with information on the metabolism and protein binding of arsenic compounds, provide evidence of a mode of action for inorganic arsenic carcinogenicity involving interactions with critical proteins, such as those involved in DNA repair, overlaid against a background of chemical stress, including proteotoxicity and depletion of nonprotein sulfhydryls. The inhibition of DNA repair under conditions of toxicity and proliferative pressure may compromise the ability of cells to maintain the integrity of their DNA. *In summary, As and its compounds are mutagenic. They do induce gene mutations and clastogenicity, but show an inability to induce them at low concentrations. They do induce oxidative damage, inhibition of DNA repair and interference with spindle microtubules (aneuploidy) which are potential genotoxic mode of actions described in II, as suggestive for thresholded modes of action.* *The critical questions are now:* *1) at what concentrations do we see direct (?) DNA damage* *2) why no induction of gene mutations and clastogenic effects at low concentrations* *3) what happens at low doses?* **6. Genotoxicity at Low Doses, in Particular in Human Lymphocytes.**	

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		Studies of populations outside the US exposed to arsenic in drinking water show increases in cancer only at relatively high concentrations, that is, concentrations in drinking water of several hundred micrograms per litre (µg/l). Studies in the US of populations exposed to average concentrations in drinking water up to about 190 µg/l do not provide evidence of increased cancer. Consideration of arsenic's plausible mechanisms and evidence from epidemiological studies support the use of non-linear methods, either via biologically based modelling or use of a margin-of-exposure analysis, to characterize arsenic risks (Schoen et al, 2004). The question here is whether there is experimental support for non-linear doseresponse to genotoxic stress. There has been much controversy about the shape of the arsenic response curve to genotoxicants, particularly at low doses. In brief, some of the results/opinions related to a non-linear genotoxic response, ranging from sublinear to thresholds: _ Hormesis. at 0.1 to 1µM arsenite: protective effect treatment against oxidative stress and DNA damage in human keratinocytes and fibroblast cell lines, including increased transcription, protein levels and enzyme activity of several BER repair genes (DNA polymerase beta and DNA ligase 1) (Snow et al., 2005). Several modes of action, including generation of oxidative stress, perturbation of DNA methylation patterns, inhibition of DNA repair, and modulation of signal transduction pathways, have been proposed to characterize arsenic's toxicity. All of the proposed mechanisms are likely to be non-linear at low does. It is probable that these mechanisms do not act in isolation, but overlap, and contribute to the complex nature of arsenic-induced carcinogenesis (Schoen et al., 2004; Rudel et al., 1996, Andrew et al., 2006). The data available do not indicate that As's genotoxicity can clearly be characterized by a sublinear dose-response relationship. It is more likely that the variety of different types of dose response curves is caused by differing cell types, various biological endpoints studied, and experimental scatter. However, this conclusion does not necessarily mean that a threshold of toxic action of As is not existent nor does it allow the inference that As's carcinogenicity may not underlie a sublinear dose-response relationship (Gebel, 2001). Predictivity for risk assessment is better when starting from human primary cells. As far as genotoxic effects in humans is concerned, data are available in lymphocytes and fibroblasts both *in vitro* and *in vivo*. However I regret not having the extensive data file of the last IARC monograph (issue 100) which is not yet available. Therefore I refer to one review (Basu et al., 2001) and some additional papers found in Table 1. *In vitro* and *in vivo* experimental animals' lowest effective doses are reported and summarized for several endpoints, and in particular alkaline Comet assay, chromosome aberrations, SCE and MN induction in human lymphocytes. However since these experiments were not designed to asses thresholds they are not adequate to provide strong information. *In vivo* in humans, some of the recent available data on exposure and early genetic changes are illustrated in Table 1. Positive results are reported in chronic exposure. Occupational exposure is more difficult to interpret since the workers are exposed to different metals. Drawing conclusions would require a meta-analysis of the whole data set which is out of scope of the present report. *In summary to me, there are good mechanistic arguments (see part 4.) to support the idea that there might be a threshold for genotoxic effects but there is insufficient experimental evidence that this is correct.* Adequately designed *in vitro* and *in vivo* experiments should be recommended. *A meta-analysis of the whole data set describing early genetic effects in vitro human in lymphocytes and epidemiological studies may also help defining lowest effect levels*	

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		7. Proposal for Future Studies Designed to Define Potential Thresholds for Genotoxic Effects First, thresholds need to be demonstrated *in vitro* by assessing genotoxicity in a broad range of low concentrations: _ in relevant cell types (proficient for DNA repair, apoptosis, p53), and preferentially in human primary cells to allow easier extrapolation to the *in vivo* situation _ with very sensitive and validated methods, covering the endpoints which are relevant for As mutagenesis. In casu, chromosome aberrations with chromosome painting or MN assay with FISH for pancentromeric (aneuploidy by chromosome loss or clastogenicity) or chromosome specific probes (aneuploidy by non-disjunction) (Elhajouji et al., 1995, 1997, 2011; Decordier et al.,2011; Cammerer et al., 2009) _ including chronic exposure protocols. Studies could be initiated in tissue culture exposing diploid cells to low concentrations of arsenicals over several cell generations. At prescribed periods of time, chromosome preparations could be made, and chromosome paints applied to determine evidence for the induction of whole chromosome numerical changes or stable chromosome aberrations, as well as the induction of chromosome instability _ in co-mutagenicity experiments with other known mutagens _ using high throughput methodologies allowing screening on a broad range of concentrations: image analysis (Decordier et al., 2009, 2011) and flow sorting (Dertinger et al. 2011; Avlasevich et al. 2011) Second, *in vivo* threshold studies in rodents (MN) should also be addressed with new sensitive methodologies allowing high throughput screening on a broad range of concentrations (Cammerer et al., 2009; 2010). Last but not least, in humans an accurate risk assessment should take into account sensitive populations (e.g. children) and the role of genetic polymorphisms in the expression of genotoxic changes induced by Arsenic. As an interesting example, the paper by Sampayo-Reyes et al. (2010) can be cited here. The authors used the comet assay to evaluate DNA damage in i-As–exposed inhabitants of the north of Mexico. The environmental monitoring and the exposure assessment were done by measuring both drinking water arsenic (As) content and total urinary As. In addition, the studied population was genetically characterized for four different glutathione *S*transferase omega1 (*GSTO1*) polymorphisms (Ala140Asp, Glu155del, Glu208Lys, and Ala236Val) and the As (+3 oxidation state) methyltransferase (*AS3MT*) Met287Thr polymorphism to determine whether such variants influence As-related genotoxicity. As content in the drinking water of the population was found to range between 1 and 187 μg/l, with a mean concentration value of 16 μg/l. The total urinary As content of the exposed individuals was found to be correlated with the As content in drinking water, and subjects were classified as low (< 30 μg As/g creatinine), medium (31–60 μg As/g creatinine), and highly exposed (> 61 μg As/g creatinine). A positive association was found between the level of exposure and the genetic damage measured as percentage of DNA in tail ($p < 0.001$), and *AS3MT* Met287Thr was found to significantly influence the effect ($p < 0.034$) among children carrying the 287Thr variant allele. Altogether, their results evidenced that people living in Ascontaminated areas are at risk and that *AS3MT* genetic variation may play an important role modulating such risk in northern Mexico, especially among children. **8. Conclusions** *One cannot base conclusions on the available genotoxicity data of gallium arsenide. First, they are too limited. Second, additional information on physico-chemical characteristics of the particles are needed. Moreover, new experiments performed according to the recently designed protocols for the testing of poorly soluble particles should be advised. Therefore we will base our discussion on the genotoxicity modes of action of Arsenic species and*	

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		Gallium.Direct mutagenic effects of Arsenic leading to gene mutations and clastogenicity are observed only at higher concentrations, except when arsenic is tested in comutagenesis experiments. Arsenic is working essentially as an indirect mutagen leading to chromosome breakage or aneuploidy, by inhibiting proteins involved in DNA repair, mitotic machinery, methylation processes and other genotoxicity-related pathways. Therefore the MN assay which is covering both clastogenic and aneugenic events might be recommended to assess the hazard and risk of arsenic genotoxicity. There are good mechanistic arguments to support the idea that there might be a threshold for genotoxic effects but there is insufficient experimental evidence that this is correct. Thresholds need to be demonstrated in vitro and in vivo by assessing genotoxicity in a broad range of low concentrations with the high throughput methodologies developed recently, in relevant cell lines and animal models. A meta-analysis of the whole data set describing early genetic effects in vitro in human lymphocytes and epidemiological studies, taking into account genetic polymorphisms, might help defining lowest effect levels. **9. References** Andrew A.S., Burgess J.L., Meza M.M., Demindenko E., Waugh M.G., Hamilton J.W., Karagas M.R. (2006). Arsenic exposure is associated with decreased DNA repair *in vitro* and in individuals exposed to drinking water arsenic. Environmental Health Perspectives 114:1193- 1198 Avlasevich S., Bryce S., De Boeck M., Elhajouji A., Van Goethem F., Lynch A., Nicolette J., Shi J., Dertinger S. (2011). Flow cytometric analysis of micronuclei in mammalian cell cultures: past, present and future. Mutagenesis 26:147-152 Basu A., Mahata J., Gupta S., Giri A.K. (2001). Genetic toxicology of a paradoxical human carcinogen, arsenic : a review. Mutation Research 488:171-194 Basu A., Mahata J., Roy A.K., Sarkar J.N., Poddar G., Nandy A.K., Sarkar P.K., Dutta P.K., Banerjee A., Das M., Ray K., Roychaudhury S., Natarajan A.T., Nilsson R., Giri A.K. (2002). Enhanced frequency of micronuclei in individuals exposed to arsenic through drinking water in West Bengal, India. Mutation Research 516:29-40 Biggs M.L., Kalman D.A., Moore L.E., Hopenhayn-Rich C., Smith M.T., Smith A.H. (1997). Relationship of urinary arsenic to intake estimates and a biomarker of effect, bladder cell micronuclei. Mutation Research 386:185-195 Cammerer Z., Elhajouji A., Kirsch-Volders M., Suter W. (2009). Comparison of the peripheral blood micronucleus test using flow cytometry in rat and mouse exposed to aneugens after singledose applications. Mutagenesis 22:129-34 Cammerer Z., Schumacher M.M., Kirsch-Volders M., Suter W., Elhajouji A. (2010). Flow cytometry peripheral blood micronucleus test in vivo: determination of potential thresholds for aneuploidy induced by spindle poisons. Environmental and Molecular Mutagenesis 51:278-284 Decordier I., Papine A., Plas G., Roesems S., Vande Loock K., Moreno-Palomo J., Cemeli E., Anderson D., Fucic A., Marcos R., Soussaline F., Kirsch-Volders M. (2009). Automated image analysis of cytokinesis-blocked micronuclei: an adapted protocol and a validated scoring procedure for biomonitoring. Mutagenesis 24:85-93 Decordier I., Mateuca R., Kirsch-Volders M. (2011). Micronucleus assay and labeling of centromeres with FISH technique. Methods in Molecular Biology 691:115-36 Decordier I., Papine A., Vande Loock K., Plas G., Soussaline F., Kirsch-Volders M. (2011). Automated image analysis of MN by IMSTAR for biomonitoring. Mutagenesis 26:163-168 Dertinger S.D., Torous D.K., Hayashi M., MacGregor J.T. (2011) **Flow cytometric scoring of micronucleated erythrocytes: an efficient platform for assessing** *in vivo* **cytogenetic damage. Mutagenesis 26:139-145** Elhajouji A., Van Hummelen P., Kirsch-Volders M. (1995). Indications for a threshold of chemically-induced	

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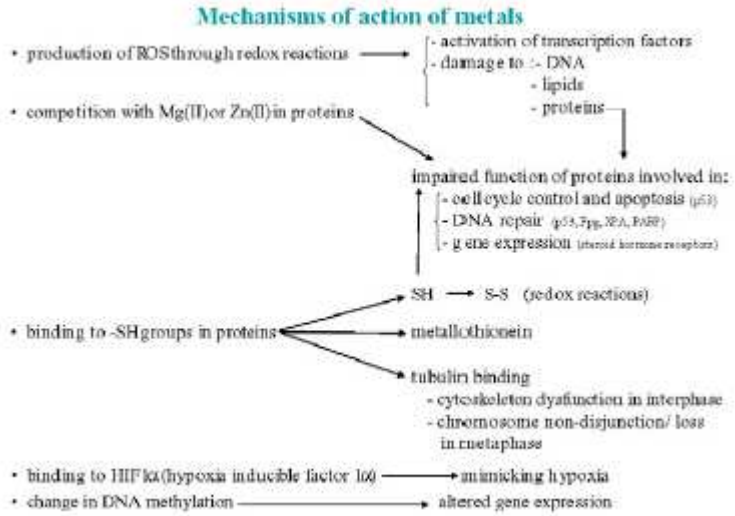
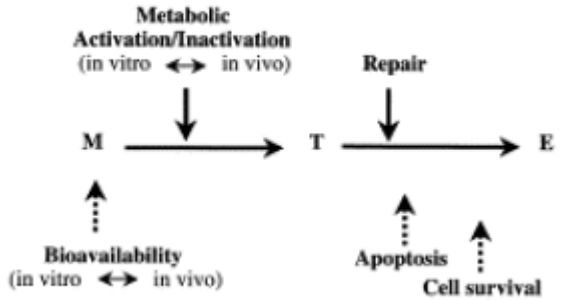
		Tables and figures ***Figure 1:*** *The most important mutagenic processes described such far for metals (Mateuca et al. 2006).*  ***Figure 2****: Factors that might modulate the final effect at the level of the analyzed endpoint (E) after an initial interaction between the mutagen (M) and its target (T). The dose–response relationship is expected to be a superposition of a number of dose–response curves for the various effects and modulations (Kirsch-Volders et al. 2000).*  	

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Figure 3: *Major genetic and epigenetic events involved in the process of carcinogenesis.*

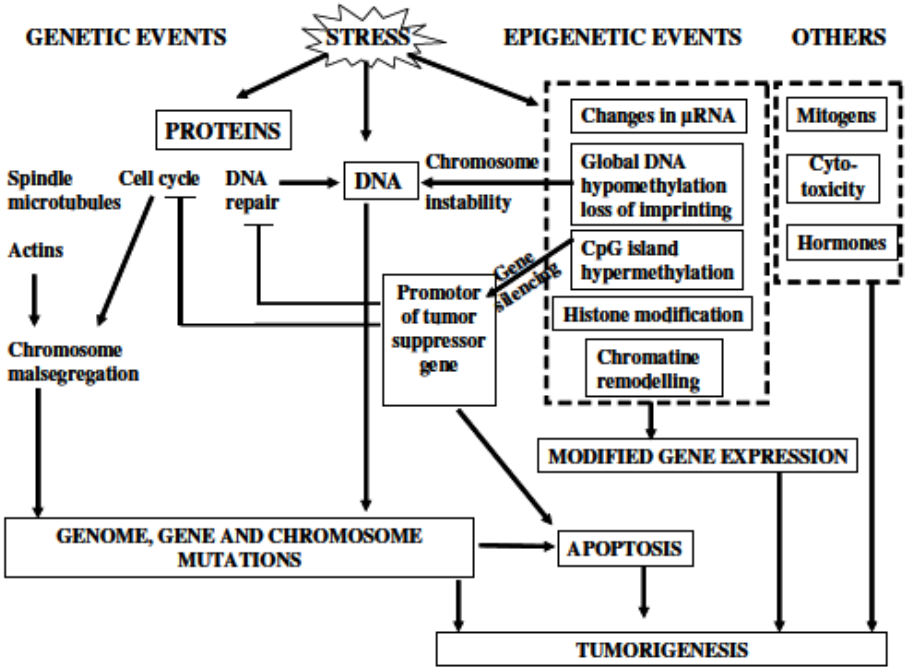

Table 1 *Recent available data on exposure and early genetic changes of arsenic in vivo in humans*

Number of exposed indiv.	Number of controls	Exposure level	Cell type	Comet	SCE	CA	MN	Reference
104	86	0,05 ppm drinking water	lymphocytes			neg		Vig et al., 1984
89	83				neg			
232	no controls	15 µg/l -670 µg/l drinking water	exfoliated bladder cells				strongest correlation with urinary index	Biggs et al., 1997
45 (arsenicism)		368,11 µg/l in drinking water	oral mucosa				pos	Basu et al., 2002
	21	5,49 µg/l in drinking water	urothelial cells lymphocytes				pos pos (with Cyto-B)	
25 Bowen's patients	matched controls	64-800µg/l in drinking water				pos		Ghosh et al., 2007

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		105 (smelting plant) | 52 internal reference group (employees from the same plant) 50 external reference group (working in cupper mine) | lymphocytes | neg (with Cyto-B), but co-exposure to other metals | Paiva et al., 2008	
21/04/2011	United States / Detlef Badorrek / RF Micro Devices / Company-Manufacturer	*ECHA comment: The attached document (RFMD ECHA letter.pdf) is copied below.* Re: Comments on the Proposal for Harmonized Classification and Labeling of Gallium Arsenide The Harmonized Classification and Labeling case of Gallium Arsenide is of particular concern to RF Micro Devices, Inc (RFMD). RFMD is a global leader in the design and manufacture of high-performance semiconductor components. The cornerstone of our technology is the GaAs semiconductor produced in our Greensboro, North Carolina (USA) and United Kingdom facilities. RFMD's products enable worldwide mobility, provide enhanced connectivity and support advanced functionality in the cellular handset, wireless infrastructure, wireless local area network (WLAN), CATV/ broadband and aerospace and defense markets. As one of the largest GaAs semiconductor wafer manufacturing facilities in the world RFMD is rightfully concerned with any ill-conceived classification of GaAs that threatens our core technology and that of an entire industry. Not using the most up to date studies, using improper test subjects and employing inaccurate read across techniques are three examples which make us question this case and prompts our commentary.	Thank you for your comments. Regarding your comment on occupational epidemiological studies please see response to Germany / Christian Eckert / ZVEI / Industry or trade association in the beginning of this document. For RAC evaluation of Carter et al. (2003) and bioavailability please see point 4) of the Annex to RCOM (Additional response to comments). Regarding your comment on the discontinuance of use of the F344 rat strain in carcinogenicity studies, we believe that the conclusions from the NTP study on gallium arsenide in rats still is valid, as assessed by Tokar et al. in a recent paper (Tokar et

[6] synonyme LGLL (Large Granular Lymphocyte Leukemia)

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		GaAs behaves differently from other As compounds and acts differently than elemental As, as far as carcinogenicity is concerned (Carter etal, 2003). We have been manufacturing GaAs wafer and the electronics based on them for 15 years and we are aware of epidemiological studies that have been performed in the GaAs semiconductor industry (Bender et al). These studies did not indicate increased cancer risks attributable to the As exposure. This does not support the accumulation of As in workers involved in this industry. It appears to us that this negative data was not considered when the read across approach was taken to link the carcinogenicity of As_2O_3 with GaAs since these two compounds behave very differently with different oxidation states and water solubility (GaAs: <<1 g/L, As2O3: 660 g/L). Carter et al 2003 stated "It is clear that highly insoluble arsenide semiconductors were less acutely toxic than equal amounts of arsine or their more soluble arsenious acid products". The oft-quoted Carter review draws an unambiguous conclusion with respect to GaAs stating "there is insufficient evidence to equate the different arsenic compounds." The Carter et al review is cited in a number of instances by the RAC without extensive elaboration giving the impression that the Carter review supports the proposed classification of GaAs. However, a reading of the paper leads to quite different conclusions. In addition, to the Carter et al review the Yamauchi (1986) paper commented that "The low solubility and poor oral absorption may make this compound [gallium arsenide] less toxic that other inorganic arsenic compounds." Neither of these papers supports the RAC opinion on the proposed classification of GaAs and should have been instrumental at arriving at a much different opinion.	al., 2010).

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		Studies have shown that the rat is an inappropriate animal from which to draw conclusions about As carcinogenicity in humans (Carter et al, Vahter et al). To quote from Carter et al 2003, "It is not possible to use animal data as a model for humans or for the rat to serve as a model for other laboratory animals. It was a surprise when the results from long- term animal studies did not model humans". It is of concern when the opinions and conclusions of subject matter experts are not openly considered when determining the carcinogenicity of GaAs in humans. In fact recent evidence has emerged that the F344/N rat has been discontinued from use in Toxicity Studies, King-Herbert and Thayer [2006]. It appears that the chronic inflammatory effects of particles are probably more responsible for the neoplastic transformations observed in animal species, than the carcinogenic effects of GaAs. In conclusion we request that the proposed classification of GaAs be reviewed taking into account all the available recent evidence in order to arrive at an appropriate classification. RFMD throughout our wafer fabrication operations has done the due diligence and put safe handling and disposal measures in place to protect our employees. This was done by having a thorough understanding of the compound we are working with and the studies that provide guidance in its use and handling. RFMD requests that the RAC apply the same procedural due diligence to reach a conclusion that is supported by all the scientific evidence available. Respectfully,  Detlef S. Badorrek, RoHS Green Group RF Micro Devices, Inc. 7628 Thorndike Road Greenboro, NC, 27409 USA References Beall et al. Mortality among semiconductor and storage device-manufacturing workers. J Occup Environ Med 47, 2005, 996-1014. Bender et al. Cancer incidence among semiconductor and storage device workers. Occup Environ Med 64, 2007 30-36.	

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22/04/2011	France / Corporate Services / Company-Downstream user	*ECHA comment: The attached document (11-0863 ECHA - Harmonizing classification and labelling – Answer to the public consultation issued on 25th May 2010.pdf) is copied below. There is a confidentiality claim for this comment.*	Noted.
26/04/2011	United States / John Sharp / TriQuint Semiconductor, Inc. / Company-Manufacturer	*ECHA comment: The attached document (TriQuint FPM Comments on GaAs Dossier 25-Apr-2011.pdf) is copied below.* April 25, 2011 European Chemicals Agency Annankatu 18, P.O. Box 400 Fl-00121 Helsinki, Finland Greetings: Attached, please find supplemental comments from TriQuint Semiconductor, Inc. on the Proposal for Harmonised Classification and Labelling of Gallium Arsenide submitted by France. These comments were submitted separate from TriQuint's earlier comments on the Gallium Arsenide comments, due to the fact that they concern some of the same topics that were addressed in the 2009 IPC comments to ECHA regarding this classification. After review of the Response to Comments by the RAC, TriQuint does not think that the RAC gave these comments the due diligence hoped for. These comments concern the effect of fine particulate matter and how that has confounded the data regarding the classification of gallium arsenide with regards to carcinogenicity. Herewith, we offer our comments on the Carcinogenicity classification and the impacts of fine particulate matter. Signed for and on behalf of TriQuint Semiconductor, Inc.: Date: 25-Apr-2011 John Sharp Corporate Product Compliance Manager **Gallium Arsenide** **Position of TriQuint Semiconductor, Inc. on the Opinion of the Committee for Risk Assessment proposing harmonized classification and labeling at the EU level for GaAs adopted 25 May 2010** **Executive Summary** TriQuint Semiconductor, Inc., based on scientific and legal advice, submits that the Opinion of May 25, 2010 of the Risk Assessment Committee on the proposal for the classification of Gallium Arsenide (GaAs) as Carc. Cat. 1A is not	Thank you for your comments. Assessment of the hazard properties of GaAs as a substance and risk assessment from exposure related to usage of GaAs in the microelectronic industry are different things. Regarding your fine particulate matter-considerations, please see point 3) of the Annex to RCOM document (Additional response to comments). We acknowledge that the small particle size and high consentration in the NTP 2 year study on rats represent an exposure scenario that constitutes a worst case scenario.

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		supported by the most recent scientific data. TriQuint urges RAC to correct its opinion on the classification and labeling of gallium arsenide. Specifically, TriQuint requests the RAC to respond to the following with supporting data: 1. How do the dossier authors and the RAC think that particle size effects have been accounted for in the RAC opinion, as stated in the RAC response to the IPC (2009) comments? There has been no distinction made for various sizes of gallium arsenide particles. Therefore, the dossier authors and the RAC must believe that all sizes of gallium arsenide particles are of equal health risk. 2. Why are the exposure scenarios used in the toxicological studies cited by the dossier authors and the RAC relevant, but the most probably exposure scenario for the general public and sensitive populations is not relevant? 3. Do the dossier authors and the RAC believe that particle size is irrelevant to the toxicology of particles? If so, why is there concern about nanomaterials? Does this mean that there will be no EU regulation of nanomaterials, since particle size is irrelevant? **Part I: IPC Comments on Fine Particulate Matter impacts from July 2009** In its comments in July 2009, IPC commented: Surprisingly, none of the investigators in the National Toxicology Program, 2000 study or the IARC Working Group seemed to wonder about the health effects of exposing experimental animals to the particulate matter loads in the tests, and whether the physical nature of the particulate matter itself could cause some of the effects noted regardless of the chemical nature of the particles. IPC went on to show through a detailed analysis of the particle size distribution used in the NTP (2000) study, that most of the effects noted in the NTP (2000) study could be due to the nature of the Fine Particulate Matter (FPM) used in the study. In its response to the IPC comments on the effects of the inhalation of FPM, dossier authors and the RAC responded: *Comment (FR): In the General remarks on the substances considered made by the Working Group for the International Agency for Research on Cancer (IARC) Monograph Volume 86 (see pp 33), it is noted: "Most of the materials evaluated in this volume are poorly soluble solid materials that are deposited in particulate form in the lung, where they may be retained for long periods of time. In this respect, they should be considered as 'particulate toxicants', the toxic effects of which are regulated not only by their chemical composition but also by their particle size and surface properties." Therefore, the physical nature of the particulate matter were taken into account. RAC-(co-)rapporteurs: NTP states in the report that "at no time during the 14-week or 2-year studies were the lungs considered to be in an overload situation."* These are the only comments on IPC's analysis of the impacts of FPM. **Part II: TriQuint response to the RAC Response to IPC Comments** TriQuint would like to respond to the lack of RAC comments and expand on the IPC position. The comment: "*Most of the materials evaluated in this volume are poorly soluble solid materials that are deposited in particulate form in the lung, where they may be retained for long periods of time. In this respect, they should be considered as 'particulate toxicants', the toxic effects of which are regulated not only by their chemical composition but also by*	However there is no deviation from OECD test guideline 451 on this issue. RAC agrees with IND who claims that the spontaneous incidence of mononuclear-cell leukemia (MCL)7 in Fischer F344 rats is so high that this effect should be disregarded. Please see the opinion (of 1 December 2011). Regarding your fine particulate matter-considerations, please see point 3) of the Annex to RCOM (Additional response to comments) Regarding your comments on threshold for carcinogenicity, please see point 2) of the Annex to RCOM (Additional response to comments) Regarding your comments on read-across, please see point 1) of the Annex to RCOM (Additional response to comments). For justification of RACs considerations, please see the opinion (of 1

[7] synonyme LGLL (Large Granular Lymphocyte Leukemia)

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		their particle size and surface properties." Therefore, the physical nature of the particulate matter were taken into account." is inaccurate. If the "physical nature of the particulate matter were taken into account", the subject of this classification would be "Fine Particulate Gallium Arsenide, with a MMAD of 0.8 microns or less", not simply "gallium arsenide". The size of the particles used in the NTP (2000) study has been demonstrated to cause the symptoms that are shown by the animal test subjects. These symptoms would have shown up, regardless of the chemical composition of the substance. Crushed rocks would have given the same outcome. The only necessary characteristics are that the particles are fine particulate matter (< 1 micron) and poorly soluble. When particulate matter is being tested, it is immaterial how many mg/kg of body weight of a substance are given to the test subject. The actual weight of the substance has little to do with how the substance behaves chemically. What does matter is the concentration of active surface sites on the particles. A good proxy for the concentration of active surface sites is the surface area of the particles. For example, if a 1 mm3 cube of gallium arsenide is considered, it has a length, width, and thickness of 1 mm. Since gallium arsenide crystals are cubic at small sizes, this sample would have a surface area of 6 mm2, and a mass of 5.32 mg. If we continuously "halve" the dimensions of the sample of gallium arsenide in a series of steps (except for the yellow highlighted row, which was calculated for the discussion below), we obtain the following data: **Table 1. Particle Size vs Total Surface Area** **Table 1. Particle Size vs Total Surface Area** Particle size, mm | Particle size, microns | MMAD, microns | Single Particle volume, mm3 | Sfc Area per Particle, mm2 | # of Particles | Total Sfc Area, mm2 | Total Mass of GaAs, mg 1.0000000 | 1000 | 2306.513 | 1 | 6 | 1 | 6 | 5.32 0.5000000 | 500 | 1153.256 | 0.125 | 1.5 | 8 | 12 | 5.32 0.2500000 | 250 | 576.628 | 0.015625 | 0.375 | 64 | 24 | 5.32 0.1250000 | 125 | 288.314 | 0.001953125 | 0.09375 | 512 | 48 | 5.32 0.0625000 | 62.500 | 144.157 | 0.000244141 | 0.0234375 | 4096 | 96 | 5.32 0.0312500 | 31.250 | 72.079 | 3.05176E-05 | 0.005859375 | 32768 | 192 | 5.32 0.0156250 | 15.625 | 36.039 | 3.8147E-06 | 0.001464844 | 262144 | 384 | 5.32 0.0078125 | 7.8125 | 18.020 | 4.76837E-07 | 0.000366211 | 2097152 | 768 | 5.32 0.0039063 | 3.9063 | 9.010 | 5.96046E-08 | 9.15527E-05 | 16777216 | 1536 | 5.32 0.0019531 | 1.9531 | 4.505 | 7.45058E-09 | 2.28882E-05 | 134217728 | 3072 | 5.32 0.0009766 | 0.9766 | 2.252 | 9.31323E-10 | 5.72205E-06 | 1073741824 | 6144 | 5.32 0.0004883 | 0.4883 | 1.126 | 1.16415E-10 | 1.43051E-06 | 8589934592 | 12288 | 5.32 0.0003468 | 0.3468 | 0.800 | 4.17256E-11 | 7.21805E-07 | 23966106642 | 17299 | 5.32 0.0002441 | 0.2441 | 0.563 | 1.45519E-11 | 3.57628E-07 | 68719476736 | 24576 | 5.32 0.0001221 | 0.1221 | 0.282 | 1.81899E-12 | 8.9407E-08 | 5.49756E+11 | 49152 | 5.32 0.0000610 | 0.0610 | 0.141 | 2.27374E-13 | 2.23517E-08 | 4.39805E+12 | 98304 | 5.32 0.0000305 | 0.0305 | 0.070 | 2.84217E-14 | 5.58794E-09 | 3.51844E+13 | 196608 | 5.32 0.0000153 | 0.0153 | 0.035 | 3.55271E-15 | 1.39698E-09 | 2.81475E+14 | 393216 | 5.32 0.0000076 | 0.0076 | 0.018 | 4.44089E-16 | 3.49246E-10 | 2.2518E+15 | 786432 | 5.32 0.0000038 | 0.0038 | 0.009 | 5.55112E-17 | 8.73115E-11 | 1.80144E+16 | 1572864 | 5.32 From Table 1, it can easily be seen that all of these particle sizes have the exact same total gallium arsenide mass, 5.32 mg. However, if the particle size of approximately 0.800 micron MMAD (which is equal to the 0.8 micron MMAD used in the NTP (2000) study – highlighted in yellow in Table 1) is reviewed, it can quickly be seen that the surface	December 2011). For RAC evaluation of Carter et al. (2003) (as well as Yamauchi 1986) please see point 6) of the Annex to RCOM (Additional response to comments). Regarding your comment on occupational epidemiological studies please see response to Germany / Christian Eckert / ZVEI / Industry or trade association in the beginning of this document.

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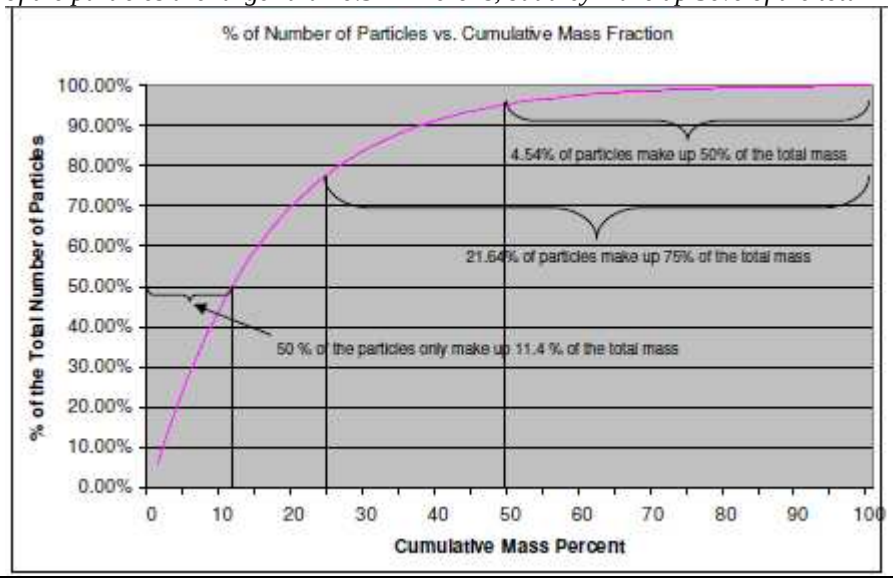
		area of 5.32 mg of this particle size has 2883X the surface area of a 1mm3 cube of gallium arsenide: $\frac{17299mm^2}{6mm^2} = 2883X$ and thus 2883X the number of active surface sites for reactions. Obviously, 5.32 mg of gallium arsenide with an MMAD of 0.800 microns will have a much higher impact that 5.32 mg of gallium arsenide in a 1mm3 cube. IPC examined the particle size distribution very thoroughly in their IPC 2009 comments: *In Table J6 (p. 297 of National Toxicology Program, 2000 study), it is shown that the Mean Mass Aerodynamic Diameter (MMAD) of the gallium arsenide particles was 0.8 microns, with a Geometric Standard Deviation (GSD) of 1.9 in the 2-year rat tests. Similar MMAD and GSD were used in the two-year mice study (Table J7, p 298). The MMAD and GSD were similar for the various aerosol concentrations of 0.01, 0.1, and 1.0 mg/m3. For the sake of discussion, we will assume the MMAD = 0.8 microns and GSD = 2.0. As the MMAD is an "aerodynamic" diameter, not the actual particle diameter, the MMAD has to be divided by the square root of the density of gallium arsenide to get the Stoke's diameter of the particle (0.8 microns / (5.32gr/cm3)^0.5 = 0.347 microns). Since gallium arsenide is heavy, a smaller particle will behave like a much larger particle. The Stoke's diameter is related to the actual diameter by the sphericity, _. Gallium arsenide crystals are cubic in form and _ = 1.0, equal to a sphere. Therefore, we will use the term particle diameter in this discussion, rather than Stoke's diameter. It is erroneous to assume that there is an "average" particle that is 0.347 microns in diameter. An MMAD of 0.8 microns equivalent to a particle diameter of 0.347 microns means that half the mass is in particles larger than 0.347 microns and half the mass is in particles smaller than 0.347 microns. For this particular size distribution (0.8 micron MMAD, GSD = 2.0), only 4.5% of the particles are larger than 0.347 microns, but they make up 50% of the total mass of particles (Figure 1).*  	

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		Figure 1. Particle Size Distribution vs. Cumulative Mass Percent *The point is that the majority of the particles are much smaller than the MMAD of 0.8 microns (particle diameter of 0.347 microns). This smaller particle size also means that the smaller particles have much more surface area available for interactions with tissues and organs (Figure 2).* **Therefore, actual mass-based concentration is immaterial to the discussion of how much of any fine particulate matter does it take to cause impacts. When the inhalation or ingestion of particulate matter is investigated, it is critical that the particle size distribution is taken into account.** **Why is this important?** This is important because Fine Particulate Matter has been demonstrated to cause cancer and other effects that are shown in the lungs of the rats in the NTP (2000) study (see IPC 2009 comments for details, (pages 2 and 3). Recently, studies have shown that small particles less than 0.3 microns (Yamashita et al, 2011) can also cross the placental barrier of pregnant mice and have neurotoxic effects on offspring. Approximately 92.5% of the particles and almost 50% of the weight of the particles in the NTP (2000) study are less than 0.3 microns. The particles in the NTP (2000) study are small enough that they can pass into the blood from the lungs. Also, the large surface area of the particles breathed in by the rats allows a tremendous amount of surface area for reaction with lung tissues. TriQuint reiterates the IPC (2009) comments, by restating that the particle sizes used in the NTP (2000) study have zero relevance to the form of gallium arsenide that will be encountered by any consumer. In its response to the IPC (2009) discussion of exposure scenarios, the dossier authors and the RAC responded: *Comment (FR): These information will be useful in subsequent phase; However, only the part regarding the route of exposition is taken into account for C&L dossiers. RAC (co-) rapporteurs: The exposure scenarios are interesting and relevant for risk assessment, but not relevant for classification and labelling.* These statements do not make logical sense. Of course exposure scenarios are relevant for classification and labeling. **The classification of chemicals substances is BASED upon exposure scenarios.** Does anyone on the RAC think that the outcomes of a study will be the same if the gallium arsenide is ingested vs. inhaled? Will there be a difference if the rats inhale 0.1 mg/m3 vs 10 mg/m3? Will there be a difference if the same air concentration is used, but the particle size of the gallium arsenide is 1 mm in diameter vs. 0.00015 mm in diameter? These are all exposure scenarios. It is misleading to state that exposure scenarios are irrelevant for classification. The entire process of studying chemical toxicology is built on exposure scenarios. How those scenarios are constructed is the main determinant of the outcomes of the toxicological studies. If it is truly believed by the RAC and the rapporteurs that exposure scenarios are irrelevant to classification, then all of the studies cited in the classification of gallium arsenide should be discarded, as they all are based on exposure scenarios. If members of the scientific community truly believed that the particle size distribution did not matter to toxicology, why is there concern in the EU regarding nanomaterials? In the recent RoHS recast, the rapporteur worked very hard to regulate nanomaterials in Electronic and Electrical Equipment (EEE). Risk assessment work is going on around the world, regarding the health hazards of nanomaterials. **Summary**	

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		Contrary to their response to IPC, the dossier authors and the RAC are not accounting for the effects of the particle size distribution in the studies cited in the carcinogenicity classification of gallium arsenide. The particle sizes used in the toxicological studies used in the dossier and RAC opinion are orders of magnitude smaller than those that will be encountered by the general population (including sensitive populations). The sizes of the particles used in the studies are capable of causing many of the same health effects as are cited in the dossier, regardless of the chemical composition of the particles. IPC (2009), Comments on GaAs Dossier, submitted 22-Jul-2009. National Toxicology Program (2000) *Toxicology and Carcinogenesis Studies of Gallium Arsenide (CAS No. 1303-00-0) in F344/N Rats and B6C3F1 Mice (Inhalation Studies)* (NTP Technical Report 492), Research Triangle Park, NC. Yamashita, et al (2011), *Silica and titanium dioxide nanoparticles cause pregnancy complications in mice,* Nature Nanotechnology, Advance Online Publication, 03-Apr-2011	
26/04/2011	United States / John Sharp / GaAs Industry Team / Company-Manufacturer	*ECHA comment: The attached document (GAIT Comments on GaAs Carcinogenicity Classification_25-Apr-2011.pdf) is copied below.* April 25, 2011 European Chemicals Agency Annankatu 18, P.O. Box 400 Fl-00121 Helsinki, Finland Greetings: IPC – Association Connecting Electronics – is pleased to offer the following comments on the Proposal for Harmonised Classification and Labelling of Gallium Arsenide submitted by France. IPC is a global trade association that represents all facets of the electronic interconnection industry, including design, printed board manufacturing and electronics assembly. Printed boards and electronic assemblies are used in a variety of electronic devices that include computers, cell phones, pacemakers, and sophisticated missile defense systems. As a member-driven organization and leading source for industry standards, training, market research and public policy advocacy, IPC supports programs to meet the needs of an estimated $1.7 trillion global electronics industry. An important part of the electronics supply chain is the semiconductor industry, which provides all printed boards and electronics assemblies with components needed for a product to function properly. Gallium arsenide is an essential chemical used in the manufacture of component chips that are necessary for all electronics products. Submitted on behalf of the Gallium Arsenide Industry Team (GAIT), which consists of representatives of: Anadigics, Inc. Astrium (EADS) Avago Technologies, Ltd. AXT, Inc. Azur Space Solar Power GmbH	Thank you for your comments. Regarding your comments on considerations of the various arsenic species and the performed read-across, please see point 1) of the Annex to RCOM (Additional response to comments).

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		Epic Associates Freiberger Composite Materials IPC IQE plc OSRAM RF Micro Devices, Inc. Rockwell-Collins Texas Instruments, Inc. TriQuint Semiconductor, Inc. United Monolithic Semiconductors, GmbH WIN Semiconductors Corp. **Gallium Arsenide** **Position of the Gallium Arsenide Industry Team (GAIT) on the Opinion of the Committee for Risk Assessment proposing harmonized classification and labeling at the EU level for GaAs adopted 25 May 2010** **Executive Summary** The Gallium Arsenide Industry Team (GAIT), based on scientific and legal advice, submits that the Opinion of May 25, 2010 of the Risk Assessment Committee on the proposal for the classification of Gallium Arsenide (GaAs) as Carc. Cat. 1A is not supported by the most recent scientific data. GAIT urges RAC to correct its opinion on the classification and labeling of gallium arsenide. Specifically, GAIT requests the RAC to respond to the following with supporting data: 1. The most recent papers cited in the IARC monograph (with the exception of the NTP (2000) study), unequivocally state that the various arsenic species with their different valence states need to be considered separately. It is not possible to extrapolate from one species of arsenic compound to another, without a detailed review of the chemistry. Even the recent update of the IARC study on gallium arsenide still ignores the most recent studies concerning the limited toxicity of gallium arsenide. How do the dossier authors and the RAC think that the most recent studies support their classification proposal, especially Yamauchi et al (1986) and Carter et al (2003)? 2. The NTP (2000) study shows incidence of carcinogenicity only to female Fischer F344 rats and not to male Fischer F344 rats, nor to mice (male or female), nor to male hamsters. Detailed studies have shown that the F344 strain of rat is especially sensitive to spontaneous incidence of MCL, and that rate of incidence has steadily increased since the 1970s to levels that are shown in the NTP (2000) study. Studies that show evidence of MCL to only female rats of this strain are not sufficient evidence of carcinogenicity. 3. The dossier authors and the RAC have not properly accounted for the effects of the Fine Particulate Matter that was used in the NTP (2000) study, which forms the basis of the opinion of the RAC that gallium arsenide is carcinogenic. Why do the dossier authors and the RAC think that the particulate matter distribution is unimportant in determining the carcinogenicity potential for gallium arsenide, when Fine Particulate Matter has been scientifically demonstrated to cause similar effects to those in the female mice of the NTP (2000) study? 4. The most recent research does not support a linear extrapolation relating arsenic exposure to carcinogenic potential. There is no basis for the rapporteurs' contention that because gallium arsenide can presumably be metabolized to DMAV, gallium arsenide should be classified as a Carcinogen 1A. There is also no data supporting the rapporteurs'	

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		contention that there is no threshold level for gallium arsenide exposure or exposure to DMAV. The studies cited by the rapporteurs are out of date, as EPA has now changed to using a Margin of Exposure (MOE) process, which shows that DMAV is highly unlikely to be of toxicological concern at plausible human exposures. How do the dossier authors and the RAC think that there is no threshold level for exposure to gallium arsenide? 5. The rapporteurs did not perform a proper "read across" process. They did not analyze the physicochemical characteristics of the analogues they chose to compare to gallium arsenide. They did not perform any of the subsequent steps to properly use the read-across method that are recommended in the OECD (2007) guidance document on the grouping of chemical substances. In addition, the papers that are being cited by the rapporteurs as evidence that gallium arsenide is carcinogenic do not support such a classification. The authors of these papers uniformly think that gallium arsenide is much less toxic than the inorganic arsenic oxide compounds that the rapporteurs have chosen to read-across from. How can the dossier authors and the RAC justify "read across" when they have not performed the most basic steps in the recommended "read across" process? 6. The GAIT has worked with six toxicologists to develop new information for consideration by the RAC, including leading arsenic toxicity specialists. This new information does not support the dossier authors' proposed classification, or the RAC opinion on that classification. How do the dossier authors and the RAC justify their opinion, when it is opposite to the most recent studies by the most knowledgeable scientists on arsenic toxicity? **Part I: The RAC opinion and its basis** The RAC has adopted the opinion that gallium arsenide should be classified and labelled as follows: **Classification & labelling in accordance with the CLP Regulation:** Carc. 1A - H350 Repr. 1B - H360F3 STOT RE 1 - H372, **Specific concentration limits:** None **M-factors:** None **Notes:** None **Labelling: GHS08**, **GHS09; Dgr; H350** May cause cancer, **H360F** May damage fertility, **H372** Causes damage to the respiratory and haematopoietic system and testes through prolonged or repeated exposure. From the RAC Opinion: None of the epidemiological studies of cancer in the semiconductor industry were informative with regard to GaAs. The dossier submitter has presented robust 105 weeks inhalation studies in rats and mice (NTP, 2000) and a 15 weeks intratracheal instillation study in hamster (Ohyama et al., 1988). Gallium arsenide was carcinogenic only in female rats after inhalation. This was observed as alveolar/bronchiolar adenoma or carcinoma. The dossier submitter had proposed that gallium arsenide was to be classified as Carc Cat 3 (Directive 67/548/EEC) based on the animal studies. In the public consultation a wish to classify gallium arsenide in agreement to IARC (group 1), proposing Carc Cat 1 instead of Carc Cat 3 (Directive 67/548/EEC) was raised. RAC agreed that an evaluation of carcinogenic effects of gallium arsenide solely based on results from animal studies is insufficient, especially since animals are less sensitive than humans to the carcinogenic effect of arsenic. It was decided to include information from human studies (results of epidemiological studies of carcinogenicity from	

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		exposure to arsenic compounds in copper smelters and from drinking water) on arsenic compounds listed as carcinogens in category 1A in CLP Annex VI and apply read-across to GaAs. A read-across approach is further supported by toxicokinetic data describing the formation of similar arsenic metabolites following GaAs exposure as those formed following exposure to classified arsenic compounds. It was agreed that the carcinogenicity of arsenic and arsenic compounds is of relevance to gallium arsenide and must be taken into account. In conclusion, there is no human data for gallium arsenide per se, but substantial documentation of carcinogenicity in humans of arsenic and arsenic compounds is available, as evaluated by IARC and briefly discussed in the BD. Gallium arsenide is also carcinogenic in female rats after inhalation and would fulfil the criteria for Carc. 2 (CLP), if assessed overlooking carcinogenicity from arsenic and arsenic compounds in humans. By applying weight of evidence and based on read-across from other arsenic compounds listed as carcinogen category 1A in Annex VI of CLP and with reference to the IARC grouping of Arsenic and arsenic compounds as well as gallium arsenide in group 1 ("carcinogenic to humans"), RAC recommends to classify gallium arsenide as a Carc. 1A – H350 according to CLP. **Summation of new information submitted by members of GAIT** 1. GAIT members have expended considerable funds and effort obtaining information for submittal regarding the proposed carcinogenicity classification of gallium arsenide. GAIT has obtained the services of six toxicologists, who are experts in the toxicology of arsenic compounds and carcinogenicity (Dr. Ernst Bomhard, Dr. Gary Williams, Dr. Sam Cohen, Dr. Kirsch-Volders, Dr. H. Vasken Aposhian, and Dr. Michael Iatropoulos). The comments from these toxicologists are submitted separately from these GAIT comments. 2. The expert toxicologists unanimously agree that the dossier authors and the RAC have not considered the most recent studies involving gallium arsenide and arsenic compounds. The dossier authors and RAC have relied almost exclusively on the IARC opinion that since gallium arsenide contain arsenic, and some arsenic compounds have proven to be carcinogenic, that therefore gallium arsenide deserves the highest carcinogenicity classification. The most recent studies show that this assumption by the IARC is wrong. Even when the IARC cited a recent paper (such as the Carter et al, 2003 paper), the IARC did not include the conclusions of the Carter (2003) paper, which stated that chemical valence had to be considered when trying to compare arsenic species. GAIT members have reminded ECHA that all available information must be collected and used, provided it is of good quality and that when new information of good quality becomes available, it must be used and the classification updated. 3. In their comments, GAIT members have shown that the dossier authors and the RAC did not apply the "read across" method properly. The OECD Guidance on Grouping Chemicals was not followed, even at the most basic level. The dossier authors did not even complete the second recommended step of evaluating the physicochemical characteristics of the various arsenic compounds to determine if there was any basis for "reading across" the toxicity from other species to gallium arsenide. If the guidance by the OECD had been followed, it would have quickly been seen that it was inappropriate to read across the carcinogenicity classification from other arsenic compounds to gallium arsenide. 4. GAIT members' comments have shown that the rat species (Fischer F344) used in the dossier authors most substantive paper (NTP, 2000)) are subject to spontaneous mononuclear cell leukemia (MCL), on the order of that found in female rats in the NTP (2000) study. The rate of spontaneous MCL occurrence has continued to rise since the introduction of this species in the early 1970s. Numerous investigators have concluded that the rat is an inappropriate	

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		species to be used to determine carcinogenicity risks for humans, especially for arsenic compounds. At a 2005 workshop, participants advised the NTP to discontinue using the current F344/N strain due to the recent issues with fertility, seizure activity, and chylothorax (King-Herbert and Thayer (2006)). 5. GAIT members have pointed out numerous times that there are no studies that show any cancer risks in the semiconductor industry. The IARC, the dossier authors, and the RAC use the phrase "None of the epidemiological studies of cancer in the semiconductor industry were informative with regard to GaAs", which means that no one has ever found a link between the GaAs industry and cancer. On the other hand, GAIT members have pointed out several studies that show no additional risk of cancer due in the GaAs industry. See Point #7 for a list of studies that show no additional risk of cancer. 6. The dossier authors cite studies such as the Carter et al (2003) paper and the Yamauchi et al (1986) paper several times in their dossier, leading to the impression that these papers support the proposed classification of gallium arsenide as a Carcinogen 1A. In fact, the conclusions of these papers are: a. Yamauchi et al (1986) – "The low solubility and poor oral absorption may make this compound [gallium arsenide] less toxic than other inorganic arsenic compounds." b. Carter et al (2003) – "It is concluded that only arsenic compounds or solution species in the same oxidation state should be compared. Further, the arsenic compounds in an exposure should be measured before use in dose–response and risk assessment determinations. Clearly, even the papers cited by the dossier authors do not support the dossier authors' proposed classification. 7. GAIT members have pointed out the age and irrelevance of some of the exposure data used by the dossier authors. For example in Section 2.1 "Identified Uses" of the Background Document, the authors cite a 1981 estimate of the number of semiconductor manufacturing plants and workers in the US. This is indicative of the age and irrelevance of much of the dossier's information: a. This data is 30 years old, it's from another country, and it covers the entire semiconductor industry – not the small section of the semiconductor industry that is focused on the manufacture of gallium arsenide products. b. There is more updated data, both from the US and the EU on semiconductor manufacturing. Please see Beall et al (2005), Bender et al (2007), Boice et al (2010) Darnton et al (2010), and Nichols and Sorahan (2005). c. Much data was presented in the Background Document on exposure to inorganic arsenic oxides (see pages 32-36) in smelters and drinking water. As pointed out by the expert toxicologists who reviewed the BD and the RAC opinion, this information is irrelevant to gallium arsenide. 8. GAIT members have pointed out the RAC's dismissal of the effects of subjecting test animals to the Fine Particulate Matter that was used in the NTP (2000) study. Many new study reports have been listed (Federico et al (2007), Valavanidis et al (2008), Yamashita et al (2011). Many studies have documented increased incidence of cancer with increased exposure to Fine Particulate Matter, and this effect has confounded the ability to use the NTP (2000) study as any indication of increased cancer risk. GAIT members have spent much time, effort, and funds to demonstrate the error in the dossier authors' classification proposal and the RAC opinion of May 25, 2010. While citing statements within the latest studies on arsenic toxicology, the dossier authors and the RAC ignored the fundamental conclusions of these papers – that you cannot assume that all arsenic compounds behave similarly. The NTP (2000) study that forms the basis of the data for the dossier is not indicative of carcinogenicity risk to humans. The aerosol suspension of Fine Particulate Matter and the use of the Fischer F344 rats, with known spontaneous incidence of Mononuclear Cell Lukemia (MCL) makes the	

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		determination of cancer risk problematic. It may be that the "read across" method can be used in the future. But it will need to be used carefully, and not indiscriminately. The OECD guidance should be carefully followed when using the "read across" method. Thank you for your consideration. For any questions regarding these comments, please contact Stephanie Castorina at IPC (Stephanie.castorina@ipc.org), or John Sharp at TriQuint Semiconductor (john.sharp@tqs.com). Aposhian, H. Vasken, PhD, (2011) *Reactions to and recommendations for modifying the Background document to the Opinion proposing harmonized classification and labelling at Community level of gallium arsenide ECHA/RAC/CLH-0000000792-73-03-A1 Which was adopted 25 May 2010*, manuscript prepared by Dr. Aposhian for submission to ECHA/RAC on April 18, 2011. Arnold, L.L., van Gemert, M., Eldan, M., Nyska, A., and Cohen, S.M. Submitted. *Dimethylarsinic acid: Results of chronic toxicity/oncogenicity studies in Fischer F344 rats and B6C3F1 mice.* Beall C, Bender TJ, Cheng H, Herrick R, Kahn A, Matthews R, Sathiakumar N, Schymura M, Stewart J, Delzell E. (2005) *Mortality among semiconductor and storage device-manufacturing workers.* J Occup Environ Med. 47(10):996-1014. Bender TJ, Beall C, Cheng H, Herrick RF, Kahn AR, Matthews R, Sathiakumar N, Schymura MJ, Stewart JH, Delzell E. (2007) *Cancer incidence among semiconductor and electronic storage device workers.* Occup Environ Med. 64(1):30-6. Boice, John D., Jr, ScD, Marano, Donald E., P.E., CIH,; Munro, Heather M., MS,; Chadda, Bandana K., MPH; Signorello, Lisa B., ScD; Tarone, Robert E., PhD; and McLaughlin, Joseph K., PhD, *Cancer Mortality Among US Workers Employed in Semiconductor Wafer Fabrication*, Journal of Occupational and Environmental Medicine, Vol 52 (11), November 2010, pp 1082-1097. Carter, D. E.; Aposhian, H. V.; and Gandolfi, A. J.; (2003), *The metabolism of inorganic arsenic oxides, gallium arsenide and arsine: a toxicological review*, Toxicol and Applied Pharmacol, 193, pp 309-334. Cohen, Samuel M.; Arnold, Lora L.; Eldan, Michal; Lewis, Ari S.; and Beck, Barbara D. (2006), "*Methylated Arsenicals: The Implications of Metabolism and Carcinogenicity Studies in Rodents to Human Risk Assessment*," Critical Reviews in Toxicology, Vol 36, pp 99-133. Darnton, Andrew; Wilkinson, Sam; Miller, Brian; MacCalman, Laura; Galea, Karen; Shafrir, Amy; Cherrie, John; McElvenny, Damien; Osman, John, (2010), *A further study of cancer among the current and former employees of National Semiconductor (UK) Ltd., Greenock,* HSE Books, Sudbury, Suffolk. IARC. (2004) *Some drinking-water disinfectants and contaminants, including arsenic.* IARC Monogr Eval Carcinog Risks Hum*:* **84:** 1–477. IARC (2006) Monograph *Cobalt in Hard Metals and Cobalt Sulfate, Gallium Arsenide,Indium Phosphide and Vanadium Pentoxide"*, World Health Organization, International Agency for Research on Cancer, Vol. 86. IARC (2009), *Special Report: Policy – A review of human carcinogens – Part C: metals, arsenic, dusts, and fibres,* Lancet, Vol. 10, pp 453-454. IPC (2009), Comments on GaAs Dossier, submitted 22-Jul-2009. King-Herbert A and Thayer K,(2006), "*NTP Workshop: Animal Models for the NTP Rodent Cancer Bioassay: Stocks and Strains – Should we Switch?"*, Toxicol. Path., **34**, 802-805.	

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26/04/2011	United States / Steve Aden / Avago Technologies Wireless (U.S.A) Manufacturing Inc. / Company-Downstream user	Avago Technologies comments regarding the proposed classification of gallium arsenide are included in the attached file; (Avago_comments_letterhead.pdf) Thank you for the opportunity to comment on this important matter. *ECHA comment: The attached document (Avago_comments_letterhead.pdf) is copied below.* Greetings; Avago Technologies is a leading designer, developer and global supplier of a broad range of analog semiconductor devices with a focus on compound III-V semiconductor-based products. Avago Technologies is committed to conducting its business in an ethical, socially responsible and environmentally sustainable manner. It is Avago Technologies policy to responsibly manage the use of hazardous materials in our operations and products, and promote recycling or reuse of our products. REACH applies within the European Union and therefore directly impacts manufacturers and importers within the European Union. In practice, however, its impact is global. The information that EU importers and manufacturers will need to receive from their non-EU suppliers is crucial for their ability to comply with the REACH requirements and the continued use of these substances. Avago Technologies is concerned with the proposal for harmonised classification labeling and packaging of gallium	Thank you for your comments. Assessment of the hazard properties of GaAs as a substance and risk assessment from exposure related to usage of GaAs in the microelectronic industry are different things. Response to comments from Dr. H. Vasken Aposhian is given earlier in this document, in response to comments submitted by you on

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		arsenide, adopted 25 May 2010. Careful review of the "Background document to the Opinion proposing harmonised classification and labelling at Community level of gallium arsenide", (ECHA 2010), raises serious questions about the data which was chosen for inclusion as well as the data which was not included. In addition, the heavy reliance on the use of the read across method, risks oversimplification of the differences between chemical compounds. The proposed carcinogenicity classification of 1A is one of the strictest, and should therefore be based on the most rigorous of scientific analysis, considering all of the existing scientific data. **The proposed classification was justified based on testing of a non-representative species;** Dr. H. Vasken Aposhian of the Department of Molecular and Cellular Biology of the University of Arizona, USA, is an internationally recognized expert in arsenic toxicology and metals toxicology whose bibliography includes over 130 published papers. Dr. Aposhian co-authored two of the papers referenced by the RAC in the background document to the RAC opinion. Dr. Aposhian recently prepared a critique of the background document to the RAC opinion; "Reactions to and recommendations for modifying The Background document to the Opinion proposing harmonised classification and labelling at Community level of gallium arsenide ECHA/RAC/CLH-0000000792-73-03/A1". Dr. Aposhian's critique has been submitted to ECHA, separately, on 20 April 2011. In his critique, Dr. Aposhian stated that; **"The rat is an atypical model for how the human body processes or metabolizes inorganic arsenic".** Dr. Aposhian's discussion of the problems with the use of rats continues, with citations from other investigators in the following excerpt from his critique; **(Beginning of excerpt from H.V. Aposhian.)** **----------** "Thus, it is surprising that the rat was used exclusively in 8 of the 11 examples on pages 8 to 11 of Section *5.1* "Toxicokinetics (absorption, metabolism, distribution and elimination) of the Committee for Risk Assessment RAC Annex 1, Background document to the Opinion proposing harmonised classification and labelling at Community level of gallium arsenide." As stated in *Arsenic in Drinking Water* published in 1999 by the National Research Council/the U.S. National Academy of Sciences: Page 155 "The rat also methylates inorganic arsenic efficiently, but a major portion of the DMA produced is retained in the erythrocytes (Odanaka et al. 1980; Lerman et al. 1983), giving rise to a slow urinary excretion of DMA and **a tissue-distribution pattern that is different from that in most other species** (Vahter et al. 1984). **In addition, the rat shows an extensive biliary excretion of arsenic, about 800 and 37 times more than the dog and rabbit, respectively** (Klaassen 1974)." (bold type made by present author) Page 160 **"In the rat, arsenic is retained in the blood considerably longer than in other species** because of the accumulation of DMA in the red blood cells, apparently bound to hemoglobin (Odanaka et al. 1980; Lerman and Clarkson 1983; Vahter 1983; Vahter et al. 1984). The accumulation of arsenic in the rat erythrocytes was first reported more than 50 years ago (Hunter et al. 1942)." (bold type made by present author) Carter et al. 2003 clearly state on Page 315- "*Human data and animal data* **"It is not possible to use animal data as a model for humans or for the rat to serve as a model for other laboratory animals.** It was a surprise when the results from long- term animal studies did not model humans. ……	21/4/2011. Regarding your comment on occupational epidemiological studies please see response to Germany / Christian Eckert / ZVEI / Industry or trade association in the beginning of this document. Regarding your comments on read-across, please see point 1) of the Annex to RCOM (Additional response to comments).

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		The problem with early data from animals was that rats were used. Previous scientific committees have stated that they did not recommend rats for arsenic oxide disposition studies." (bold type made by present author) Carter et al. 2003 page 325 state that "The 2-year exposure showed increased alveolar/ bronchiolar neoplasms in female rats. This finding is important and the lung appears to be acting as a point of contact toxicant for particles. **Unfortunately, the rat is not recommended for arsenic studies;** only the females responded and there were no other As or Ga species tested for comparison." (bold type made by present author.)" ---------- **(End of excerpt from H.V. Aposhian.)** **Relevant epidemiological studies were apparently not considered;** The RAC background document cites epidemiology from arsenate in drinking water and diarsenic trioxide from ores processed in copper smelters, but fails to include recent substantial epidemiological studies from the semiconductor industry. Section 2.1 of the RAC background document states; "**Exposure to gallium arsenide occurs predominantly in the microelectronics industry** where workers are involved in the production of gallium arsenide crystals, ingots and wafers, in grinding and sawing operations, in device fabrication, and in sandblasting and clean-up activities (Harrison, 1986; Webb et al., 1984)." At least five epidemiological studies have been performed in the semiconductor industry, in recent years, (Beall et al. 2005; Bender et al. 2007; Boice et al. 2010; Darnton et al. 2010; Nichols and Sorahan 2005). These studies do not suggest increased risk of cancer due to real world exposure scenarios in the semiconductor industry. From the industry perspective, it is very difficult to understand how the committee can exclude the epidemiological studies which are so directly related to those that they state to have the greatest risk of exposure. In section 5.7.4, the RAC background document appears to justify the exclusion of the epidemiological studies in the semiconductor industry based on a statement from IARC, 2006; "None of the epidemiological studies of cancer in the semiconductor industry were informative with regard to GaAs (IARC, 2006)." At least three of the recent epidemiological studies from the semiconductor industry could not have been considered by IARC in 2006, since they occurred after that date, (Bender et al. 2007; Boice et al. 2010; Darnton et al. 2010). Similarly, two of these studies occurred after IARC 2009 and therefore could not have been considered in 2009, (Boice et al. 2010; Darnton et al. 2010). Since these studies were also not listed in the references for the RAC background document, they were apparently not considered by the RAC. These epidemiological studies from the semiconductor industry are therefore new information, and should be considered by the RAC. In addition to being new, the epidemiological studies from the semiconductor industry are clearly relevant, in that they are focused on real world exposure scenarios for the population that the RAC has stated to have the greatest risk of exposure. **Read across was used to compare chemically dissimilar compounds;** Section 5.7.5 of ECHA's background document states; "No human data is available on carcinogenicity of gallium arsenide. Gallium arsenide was carcinogenic in female rats after inhalation. Based on these findings in animals gallium arsenide fulfil the criteria for classification as Carc. Cat. 3; R40 (Directive 67/548/EEC) and Carc. 2 – H351 (CLP)."	

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		The RAC background document justifies their 1A recommendation primarily based on read across from arsenic in drinking water and diarsenic trioxide from smelters; Section 5.7.5 of ECHA's background document states; "Examples given are arsenate (arsenic acid) in drinking water and diarsenic trioxide from ores processed in copper smelters, where epidemiology demonstrates risk of cancer. Based on read-across to arsenic and other arsenicals GaAs should be classified as carcinogenic category 1A (CLP)." While the RAC background document refers to the Carter et al (2003) paper, "The metabolism of inorganic arsenic oxides, gallium arsenide, and arsine: a toxicochemical review", the analysis seemingly ignores one of the key points from the conclusion of the same paper; *"It is concluded that only arsenic compounds or solution species in the same oxidation state should be compared. Further, the arsenic compounds in an exposure should be measured before use in dose–response and risk assessment determinations."* None of the chemical compounds mentioned in section 5.7.4 of the RAC background document contain arsenic in the same oxidation state as it occurs in gallium arsenide. It is not obvious that arsenic in a (-3) oxidation state would behave comparably to the other compounds containing arsenic in (+3) or (+5) oxidation states. Even if some of the same metabolites are observed, a chemist would not expect comparable dissolution rates, nor all of the same intermediate compounds, nor the same quantitative distribution of reaction products. The other compounds mentioned in section 5.7.4 are much more chemically similar to each other, than they are to gallium arsenide. This extrapolation casts doubt on the use of read across for gallium arsenide. **Summary;** Avago Technologies appreciates the opportunity to comment on this important matter. We understand that the committee for risk assessment does not perform economic analysis during the classification process. It is not our purpose to discuss the economic analysis in this comment. Gallium arsenide is a highly specialized human made material with unique properties which have enabled an extraordinary array of useful technologies. While the material is specialized and used in relatively limited quantities, its application is ubiquitous and has enabled fundamental changes in wireless communications and energy efficient LED lighting. These are not economic issues which simply favor some companies over others. The technologies enabled by gallium arsenide have already changed how people live and communicate and offer great potential for further strides in energy efficiency. The classification should certainly be based on scientific considerations, but it is important to simultaneously understand the gravity of a hasty or unjustified classification. An incorrect classification of gallium arsenide would impose an unnecessary burden on a key industry which continues to enable advancements in wireless communication and energy conservation. Avago Technologies urges the committee to reconsider the heavy reliance on the use of data from Fisher F344/N rats, which are known to have problems, and to consider the epidemiological studies from the semiconductor industry, which are directly relevant to the proposed classification. In addition, the use of read across seems inappropriate to classify gallium arsenide when the arsenic constituent of this compound exists in an oxidation state which is completely dissimilar to all of the compounds in the comparison group. We encourage the committee to place greater weight on the full set of available scientific data, and avoid the risk of oversimplification which is inherent in the use of read across for chemically dissimilar compounds. Sincerely,	

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		James S. Aden Materials Scientist Avago Technologies, Wireless Semiconductor Division **References;** Aposhian H.V. 2011. Reactions to and recommendations for modifying The Background document to the Opinion proposing harmonised classification and labelling at Community level of gallium arsenide ECHA/RAC/CLH-0000000792-73-03/A1, manuscript submitted to ECHA comments web site 4/20/2011. Beall et al. Mortality among semiconductor and storage device-manufacturing workers. J Occup Environ Med 47, 2005, 996-1014. Bender et al. Cancer incidence among semiconductor and storage device workers. Occup Environ Med 64, 2007 30-36. Boice et al. Cancer mortality among US worker employed in semiconductor wafer fabrication. J Occup Environ Med 52, 2010, 1082-1097. Carter, D. E., Aposhian, H. V., and Gandolfi, A. J. (2003). The metabolism of inorganic arsenic oxides, gallium arsenide and arsine: a toxicochemical review. *Toxicol and Applied Pharmacol*, *193*, 309-334. Darnton et al. A further study of cancer among the current and former employees of National Semiconductor (UK) Ltd., Greenock. Health and Safety Executive, UK 2010. ECHA Committee for Risk Assessment. 2010.Background document to the Opinion proposing harmonised classification and labelling at Community level of gallium arsenide ECHA/RAC/CLH-0000000792-73-03/A1 Hunter F.T., A.F. Kip, and J.W. Irvine. 1942. Radioactive tracer studies on arsenic injected as potassium arsenite. J. Pharmacol. Exp. Ther. 76:207220 Klaassen, C.D. 1974. Biliary excretion of arsenic in rats, rabbits and dogs. Toxicol. Appl. Pharmacol. 29: 447-457. Lerman, S., and T.W. Clarkson. 1983. The metabolism of arsenite and arsenate by the rat. Fundam. Appl. Toxicol. 3:309-314. Nichols und Sorahan. Cancer incidence and cancer mortality in a cohort of UK among semiconductor workers. Occup Med 55, 2005, 625-630. Odanaka, Y., O. Matano, and S. Goto. 1980. Biomethylation of inorganic arsenic by the rat and some laboratory animals. Bull. Environ. Contam. Toxicol. 24: 452-459. Vahter, M. 1983. Metabolism of Inorganic Arsenic in Relation to Chemical Form and Animal Species. Doctoral Thesis. Karolinska Institutet, Stockholm. Vahter, M., E. Marafante, and L. Dencker. 1984. Tissue distribution and retention of 74As-dimethylarsinic acid in mice and rats. Arch. Environ. Contam. Toxicol. 13:259-264 Vahter, M. 1994. Species differences in the metabolism of arsenic compounds. Appl. Organomet. Chem. 8: 175-182.	
26/04/2011	United States / John Sharp / TriQuint Semiconductor Inc. / Company-Manufacturer	In Article 5 of the CLP Regulation regarding the Identification and examination of available information on substances, it is stated: "The information shall relate to the forms or physical states in which the substance is placed on the market and in which it can reasonably be expected to be used." The animal testing that was used in the studies cited - NTP, (2000) - used Fine Particulate Matter with an MMAD of 0.8 micron. Other studies - Yamauchi (1986), Webb (1984), Webb (1987) - also used Fine Particulate forms of gallium arsenide. This form of gallium arsenide is clearly not representative of the form that that is placed on the	Thank you for your comment. For all dossiers being considered in the harmonised classification and labelling process, any

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		market, and in which it can reasonably be expected to be used. Therefore, the NTP (2000) study is not applicable to any carcinogenicity and reproductive toxicity risk assessment, as pointed out by TriQuint and others in comments already submitted to ECHA. Thank you for your time and consideration. John Sharp	relevant information from registration dossiers and other available information may be used (Regulation No.1272/2008; Annex VI, Part 2).
27/04/2011	Germany / Birgit Müller / Freiberger Compound Materials GmbH / Company-Manufacturer	*ECHA comment: The same information as in the attachment 2011_04_27 Dr Bomhard and Dr Williams - On GaAs Toxicology.pdf was submitted already on 21/4/2011 in a document: 2011_04_21 Dr Bomhard et al – On GaAs Toxicology.pdf)*	Please see response to your comments submitted on 21/04/2011.
27/04/2011	Germany / Birgit Müller / Freiberger Compound Materials GmbH / Company-Manufacturer	*ECHA comment: The attached document (2011_04_26 Dr Cohen - Evaluation of the potential carcinogenicity of gallium arsenide.pdf) is copied below.* Expert Opinion Evaluation of the Potential Carcinogenicity of Gallium Arsenide Samuel M. Cohen, M.D., Ph.D. Department of Pathology and Microbiology University of Nebraska Medical Center 983135 Nebraska Medical Center Omaha, NE 68198-3135 **INTRODUCTION** In the review by the RAC of the Gallium Arsenide Harmonized Classification, a conclusion was reached to classify it as Class Ia carcinogen. I have been asked to comment on the scientific basis for such a classification based on my knowledge and experience in arsenic toxicology and carcinogenesis research over the past 15 years, and also based on my experience in general in carcinogenesis, toxicology and pathology research over the past more than 40 years. I have also been trained as a pathologist in human medicine, and continue practicing as an active basic researcher and also as a surgical pathologist. Thus, I am aware of the pathologic entities involved in the discussion of gallium arsenide as well as arsenical toxicity and carcinogenicity in general. It appears that the RAC based much of its interpretation on its classification on the International Agency for Research on Cancer (IARC) assessment that gallium arsenide is carcinogenic to humans (Group I) (IARC, 2006). The IARC based its conclusions primarily on the results of an inhalation two-year bioassay in rats and mice utilizing gallium arsenide by the National Toxicology Program (NTP, 2000) and also on the consideration of gallium arsenide representing an arsenical, in general, and therefore can be classified on the basis of known human carcinogenicity of inorganic arsenic. There are significant limitations to the NTP study, but there are extensive scientific reasons why the information known about inorganic arsenic in general should not be applied to gallium arsenide. This report is an attempt to provide a rational basis for interpretation of gallium arsenide not only in the NTP study, but in its	Thank you for your comments. Assessment of the hazard properties of GaAs as a substance and risk assessment from exposure related to usage of GaAs in the microelectronic industry are different things. RAC agrees with IND who claims that the spontaneous incidence of mononuclear-cell leukemia (MCL)8 in Fischer F344 rats is so high that this effect should be disregarded. Please see the opinion (of 1 December 2011). We also agree with IND that due to irrelevance to humans the findings of

[8] synonyme LGLL (Large Granular Lymphocyte Leukemia)

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		relationship to inorganic arsenic in general. **NTP INHALATION STUDY** Gallium arsenide was tested by the NTP in a two year inhalation study for possible carcinogenicity (NTP, 2000). The study was performed in B6C3F1 mice and in F344 rats, with exposures at 0, 0.01, 0.1, and 1.0 mg/m3 (rats) as well as 0.1, 0.5 and 1.0 mg/m3 (mice). In both sexes of both species there were inflammatory changes in the lung. The animals were exposed to gallium arsenide by inhalation, but neither the male or female mice showed any evidence of an increase incidence of tumors in any organ. Similarly, the male rat showed no increased incidence of tumors, but the female rat showed an increased incidence of certain tumors. Statistically significant increases were seen in lung adenomas, adrenal pheochromocytomas, and in splenic mononuclear cell leukemia. The incidences of the lung adenomas were 0, 0, 2, and 7 of 50 female rats administered 0, 0.01, 0.1, and 1.0 mg/m3, respectively. Incidences of lung adenocarcinomas in these same groups were 0, 0, 2, and 3, respectively. For adrenal pheochromocytomas, the incidences were 4, 5, 6, and 13, respectively, and for the mononuclear cell leukemia the incidences were 22, 21, 18, and 33, respectively. For each of these target sites, statistical significance was only found at the highest dose. Based on the results of this study, the NTP concluded that there was evidence of carcinogenicity in female rats, but no evidence of carcinogenicity in male rats or in male or female mice. A closer look at these results indicate that the only tumor finding that is of potential concern is the lung adenomas and adenocarcinomas. Mononuclear cell leukemia in the F344 rat appears to be a species and even a strain specific lesion. It occurs at extremely high incidences, with historical 3 controls occasionally being higher than 50 percent (Caldwell, 1999; Dinse et al., 2010). It is actually one of the major reasons why the NTP has recently discontinued use of the F344 rat as its test model strain, since it has a significant effect on survival of the rats, also. The incidence at the highest dose in the female rats exposed to gallium arsenide was statistically significant at $p < 0.05$. However, Dr. Joe Haseman (1990) of the National Toxicology Program has written extensively about the statistical evaluation of commonly occurring tumors in these bioassays. He concluded that for common tumors, and certainly mononuclear cell leukemia is a very common tumor in the F344 rat, statistical significance should be at a level of $p < 0.01$ rather than 0.05 to avoid false positive interpretations. Furthermore, many scientists do not regard this lesion of significance with respect to humans (Caldwell, 1999). For an interpretation of gallium arsenide carcinogenesis the results for this tumor should not be further considered. Adrenal pheochromocytomas are also a common tumor in the F344 rat (Greim et al., 2009). These are nearly always benign, and there is considerable evidence that these do not have any predicative value for potential human carcinogenesis, either for the adrenal specifically or for carcinogenic risk in general. Therefore, these lesions also should not be further considered in the risk assessment of gallium arsenide carcinogenicity. The tumors in the lung need to be placed in proper perspective in assessing a potential risk to humans. This is particularly important because inorganic arsenic is known to increase tumors in humans at specific target sites, including the lung. To begin with, it should be noted that the only statistically increased incidence was at the highest dose, and only for benign tumors, adenomas. Furthermore, nearly all of the animals had inflammatory changes in the lungs. It should be noted that gallium arsenide by inhalation in these studies led to deposition of gallium arsenide particles in the lungs of these animals, and apparently it is these particles that gave rise to the inflammatory response (Watson and Valberg, 1996; NTP, 2000). This is similar to a number of other substances related to particulate matter, such as asbestos and silicon (Watson and Valberg, 1996). For both of these instances with respect to the lung, tumors in animal models as well as in humans only occur at extremely high doses, exposures at which there is not only an inflammatory response, but there is	benign pheochromocytoma of the adrenal medulla should be disregarded when assessing carcinogenicity, with reference to Greim et al. (2009). Please see the opinion (of 1 December 2011). IND claim that the only statistically increased incidence was at the highest dose and only for benign tumours? This is the case, but it was also seen at 0.1 mg/m3, see NTP (2000): ”Compared to the chamber controls, the incidences of alveolar/bronchiolar adenoma, alveolar/bronchiolar carcinoma, and alveolar/bronchiolar adenoma or carcinoma (combined) were significantly increased in females exposed to 1 mg/m3 and exceeded the historical control ranges for 2-year inhalation studies (Tables 13, B3, and B4a). The incidence of alveolar/bronchiolar adenoma or carcinoma (combined) in 0.1 mg/m3 females was increased and exceeded the historical control range.

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		evidence of fibrosis (Colby et al., 1995). This is in contrast to the types of lung tumors secondary to arsenic exposure, whether from drinking water or by inhalation from mining exposures. There is not an associated inflammatory change, and certainly not fibrosis. In these animal models, whether rats or mice or even hamsters, there is a close association between these inflammatory changes and the ultimate development of tumors. Thus, it is highly unlikely that the tumors that were seen in the female rat lung were related to the gallium arsenide itself, but rather were secondary to the inflammation that was produced by the deposition of particulate matter. Such deposition of particulate matter is not known to occur in humans exposed to environmental levels of gallium arsenide, including in the semiconductor industry (IARC, 2006). A further complication in interpreting rodent lung tumors with respect to potential risk to humans is the rodent lung cancer model itself. In rodents, the pathogenesis of lung tumors involves a sequence of events beginning with increased cell proliferation, as evidenced by an increase in DNA replication measured by various labeling indexes, such as bromodeoxyuridine (BrdU), eventually leading to the development of pulmonary hyperplasia, adenomas, and carcinomas. This sequence of events does not occur in humans (Colby et al., 1995). There is no such entity as a lung adenoma in humans. Furthermore, in the rodent, most tumors arise in the periphery of the lung, presumably from the bronchioles. In contrast, most lung tumors in humans arise from the bronchi, and only infrequently from the peripheral bronchioles. Even when they do arise from the peripheral bronchioles they do not go through the sequence of hyperplasia and adenomas, but go from a histologically appearing normal lung (or with emphysema) directly to adenocarcinomas. There is no hyperplasia or adenoma intermediate. Thus, based on this analysis, there is essentially no evidence of a tumorigenic response in either rats or mice that is directly relevant to human exposure to gallium arsenide. In this analysis, assessment as Class Ia is inappropriate for gallium arsenide based on the animal data. Furthermore, there is extensive epidemiologic evidence regarding the development of tumors in workers exposed to gallium arsenide in the semiconductor industry, not only with respect to lung cancer but also with respect to tumors in general (Beall et al., 2005; Bender et al., 2007; Boice et al., 2010; Darnton et al., 2010; Nichols and Sorahan, 2005). There is no evidence of an increased incidence of lung tumors or other tumors in such workers. In the animal studies and in the human epidemiology, there is no basis for classifying gallium arsenide as a carcinogen. **INORGANIC VS. ORGANIC ARSENICALS** The other issue, therefore, that needs to be considered is the conclusion by IARC and subsequently by the RAC that gallium arsenide should be considered as part of the overall exposure to inorganic arsenic in general, and therefore it should be classified as a human carcinogen based on the known human carcinogenicity of inorganic arsenic. This represented a gross distortion of the IARC criteria for evaluation of substances for potential carcinogenicity, and consequently, it is inappropriate for the RAC to also follow this same rationale. There are several scientific reasons why gallium arsenide should not be considered as part of inorganic arsenic in general. Inorganic arsenic is a known human carcinogen, inducing tumors of the skin, urinary bladder, and lung, and possibly a few other tissues such as kidney and liver (NRC, 2001). The evidence for this is based primarily on exposure to inorganic arsenic in the drinking water, but is also based on occupational mining exposures with respect to lung cancer, and also with respect to exposures to various arsenicals used as pharmaceuticals leading to the development of skin cancer. However, these exposures are related to inorganic arsenic in the form of arsenite and/or arsenate, and	Regarding your comments on carcinogenicity from inflammation caused by fine particulate matter-, please see point 3) of the Annex to RCOM (Additional response to comments). You state that there is no such entity as a lung adenoma in humans. RAC considers that the mechanisms proposed for particle induced lung tumourigenesis in animals are relevant also for humans. Although, there may be differences in the particle induced pulmonary tumour biology, lung tumours in experimental animals should be considered predictive for cancer potential in humans if there are not definitive data showing otherwise. In human studies, workplace exposures to certain poorly soluble particles including quartz have been associated with increased incidences of lung cancer and IARC considers there to be sufficient evidence in humans for the carcinogenicity of inhaled

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		possibly arsenic trioxide. It is inappropriate to include other arsenicals with these. Humans are exposed to arsenic not only as inorganic arsenic in the form of arsenate or arsenite, but also in various organic forms (NRC, 2001). These include the mono-, di-, and trimethylated related forms, certain arsenosugars, and arsenobetaine and arsenocholine. Arsenobetaine and arsenocholine are present at relatively high levels in various seafoods, and arsenosugars are also occasionally present in seafood, not only shellfish and other aquatic animals, but also in seaweed. These forms of arsenic are primarily in the food supply rather than in drinking water, and certainly do not appear in an occupational setting. There is no evidence that these forms are toxic to animals or to humans, and there is no evidence relating food consumption of arsenicals to a carcinogenic effect. These organic forms of arsenic are not metabolized to any great extent. Individuals exposed to high levels of of arsenobeatine, arsenocholine and arsenosugars, however, are known to have increased levels of dimethylarsinic (DMA) in their urine (see below). An assessment of the potential contribution of gallium arsenide to human cancer risk from inorganic arsenic requires examination of the exposure, metabolism, toxicokinetics, and interspecies differences. Although most environmental inorganic arsenic exposure for humans is in the form of arsenate, some environmental exposure to inorganic arsenic is in the form of arsenite. In evaluating arsenic carcinogenicity, whether from inorganic or organic sources, the metabolism of these compounds needs to be considered. Inorganic arsenic is converted to organic, methylated arsenicals in mammalian species involving a sequence of reduction from the pentavalent form to the trivalent form, followed by oxidative methylation (Aposhian, 1997; Healy et al., 1998; Vahter, 1999). This is repeated for the mono- and dimethyl forms with the eventual production of trimethyl arsenic. There are considerable differences quantitatively in this metabolic pathway between mammalian species, but qualitatively it is the same. There are also significant quantitative differences between species with respect to the kinetics following exposure to these compounds, which is due to a combination of bioavailability, metabolism, as well as other influences on kinetics, such as cell transport, binding to various cellular constituents and excretion patterns. Before the last decade, there was no evidence in animal models demonstrating the carcinogenicity of any arsenicals, whether inorganic or organic (Tokar et al., 2010). However, within the last decade, models have been developed which clearly show that the mouse and rat are susceptible to the carcinogenic effects of arsenic. For the mouse, Dr. Michael Waalkes of the National Cancer Institute demonstrated that administration of inorganic arsenic to mice transplacentally followed by oral administration in the pups induces various types of tumors (Tokar et al., 2010). In rats, DMA has been shown to be carcinogenic toward the urinary bladder (Arnold et al., 2006; Wei et al., 2002). There is also some evidence in mouse skin that there is a potentially cocarcinogenic effect of inorganic arsenic (Rossman et al., 2004). Differences in the carcinogenic effects of the various forms of arsenic in the different species can now be clearly demonstrated to be due to differences in kinetics following administration by various routes in the various species. This also is related to the lower susceptibility in rodents compared to humans. The kinetic basis for species differences was also the conclusion of a Science Advisory Board of the United States Environmental Protection Agency, published in 2007. Arsenate is rapidly converted in all mammalian species by reduction to arsenite, either within the gastrointestinal tract or by a variety of enzymes within the organism once it is absorbed from the gastrointestinal tract (Aposhian, 1997; Herbel et al., 2002). Arsenite is then rapidly methylated in the liver to the mono- and dimethyl forms monomethylarsonic acid (MMAV) as well as DMAV (Aposhian, 1997; Radabaugh et al., 2002)). In rats, a significant proportion, approximately 20%, is further methylated to trimethylarsine oxide (TMAO). TMAO is produced at much lower levels in mice. In humans under usual exposures, including high levels in the	silica in the form of quartz. RAC considers that the mechanisms proposed for particle induced lung tumourigenesis in animals are relevant also for humans. Although, there may be differences in the particle induced pulmonary tumour biology, lung tumours in experimental animals should be considered predictive for cancer potential in humans if there are not definitive data showing otherwise. Regarding your comment on occupational epidemiological studies please see response to Germany / Christian Eckert / ZVEI / Industry or trade association in the beginning of this document. Response on comments on page 167 on DMA in urine from individuals exposed to arsenobetaine etc.: DMA(V) levels in urine is known to be elevated due to seafood consumption. High levels of DMA(V) may induce cancer in rodents possibly through the formation of DMA(III). To what extent

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		drinking water, TMAO is not detectable in the urine (Lu et al., 2003; Cohen et al., 2006). It can only be detected in individuals who are exposed to enormous amounts of inorganic arsenic, usually involving acute poisoning episodes or exceedingly high levels in the drinking water (> 1 ppm). Furthermore, in rodents, there appears to be a storage compartment for arsenic that does not occur in humans. In the rat, this is the red blood cell and is due to the trivalent form of DMA (dimethylarsinous acid, DMAIII) binding covalently to hemoglobin (Aposhian, 1997). This binding to hemoglobin does not occur in other species, including humans. The basis for the rat specificity of this phenomenon has been determined to be related to the presence of a free sulfhydryl group in one of the chains of rat hemoglobin which binds the trivalent form of DMA (Lu et al., 2004; 2007). This is stored in the red blood cell until the red blood cell dies several weeks later. Nevertheless, considerable DMA is not bound and is excreted in the urine (Lu et al., 2003; Cohen et al., 2002). In the mouse, the storage compartment appears to be the mitochondria of the urothelium of the lower urinary tract (Suzuki et al., 2008b). This is present as the trivalent form of inorganic arsenic, arsenite. What it is bound to in the cell is not known. This is specific to the mouse and results in the accumulation of intramitochondrial inclusion in the urothelium, especially the superficial, fully differentiated cells. Further complicating the kinetics of arsenic between species are differences in their cellular transport in the different species (Dopp et al., 2010). Overall, the pentavalent forms of arsenic are difficult to transport across cell membranes, whereas the trivalent forms are readily transported. In addition, there are significant differences between species in the particular cell types and their ability to transport the various trivalent forms of arsenic. Biological consequences of arsenic exposure are due to the interaction of the arsenical with sulfhydryl groups of the cell, whether glutathione or sulfhydryl groups of proteins (Aposhian, 1997). At extremely high exposure levels, there can be a depletion of glutathione in cells of certain tissues. More importantly, there are marked variations between species in the availability of free sulfhydryl groups of specific proteins which bind the trivalent arsenicals. This partially explains the different tissue distributions of toxicity and carcinogenicity in the various species. An example is the binding of DMAIII to rat hemoglobin described above. Another example is the binding of arsenite to the mouse estrogen receptor, which has a free sulfhydryl group. It does not bind to rat or human estrogen receptor, which do not have this free sulfhydryl group with which to bind (Kitchin and Wallace, 2008a; 2005). This at least potentially explains the tissue distribution of targets for arsenic carcinogenesis in the mouse, including liver, uterus and adrenal. **GALLIUM ARSENIDE** Gallium arsenide does not appear to be bioavailable to any great extent, whether consumed by oral administration, intraperitoneal administration or by administration through the airways, either by inhalation or by intratracheal administration (Rosner and Carter, 1987; Yamauchi et al., 1986). This most likely explains the lack of carcinogenic effect of gallium arsenide in rodents beyond the administration site, the airways. The fact that the lung tumors in rats develop as a consequence of an inflammatory reaction secondary to the deposition of particles, rather than to the chemical reactivity of gallium arsenide, is also most likely related to this phenomenon. Limited bioavailability in humans to gallium arsenide has also been assessed (Yamauchi et al., 1989; Morton and Mason, 2006; Hwang et al., 2002). There is very limited evidence that any of the arsenic in gallium arsenide is actually absorbed and excreted. There has been some evidence that workers in the semiconductor industry have a slightly increased level of DMA excreted in the urine compared to non-worker controls (Morton and Mason, 2006), although these studies have	this may occur also in humans at relevant exposure levels is unclear. Seafood may contain high levels non-toxic organoarsenics such as arsenobetaine, arsenocholine, and arsenosugar. Only a small percentage of the arsenic in seafood is in the form of inorganic arsenic. High levels of As in urine has been shown to be caused by seafood consumption. The increased amount of total As metabolites by seafood ingestion is considered to be mostly unmetabolised organoarsenicals and DMA(V). Inorganic As, arsenite and arsenate, and MMA(V) are detected only at a limited level. The Tokar paper (Tokar et al., 2010) is discussed in the opinion (of 1 December 2011). You claim that increased level of DMA in the urine in workers could have been confounded by cigarette smoking and/or intake of seafood. The semiconductor workers had been advised to refrain from eating fish

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		confounding factors (see below) and are not reproducible in other studies (Hwang et al., 2002). In humans, most inorganic arsenic is excreted in the urine as DMA, with much lower levels of MMA or inorganic arsenic (Aposhian, 1997; Cohen et al., 2006). However, interpretation of these findings is complicated by significant confounding factors. To begin with, such an elevation was observed in only a few of the exposed workers (Morton and Mason, 2006). Furthermore, in these studies, there has been no control for cigarette smoking, which is known to significantly increase the excretion of various arsenicals, especially DMA, in the urine. Furthermore, individuals who consume large amounts of seafood also excrete increased levels of DMA in the urine compared to when they are not eating seafood (Wei et al., 2003; Farmer and Johnson, 1990; Heinrich-Ramm et al., 2002; Borak and Hosgood, 2007). Although the seafood contains primarily forms of arsenic that appear not to be metabolized, there nevertheless is an increase of the amount of DMA excreted in the urine, suggesting that at least some of the organic arsenicals present in seafood can be converted to DMA. There has not been control of the dietary exposure of the workers in the excretion studies of individuals in the semiconductor industry. Thus, although a few individuals have been found to have increased levels of DMA in the urine in an occupational setting, it is unknown whether it is actually due to the occupational setting or whether it is secondary to cigarette smoking and/or exposure to seafood. In these analyses, it would appear that exposure to gallium arsenide does not increase exposure to potentially carcinogenic forms of arsenic, such as arsenate or arsenite. **MODE OF ACTION OF INORGANIC ARSENIC CARCINOGENESIS** To further evaluate the possibility of gallium arsenide contributing to the carcinogenic inorganic arsenic pool, an understanding of mechanism of action of arsenic carcinogenesis is also required in addition to the consideration of the quantitative aspects of metabolism and kinetics described above. For the various forms of arsenic, whether inorganic or methylated organic forms, the evidence strongly suggests that the mode of action of arsenic-induced cancer is non-genotoxic (Kitchin and Wallace, 2008b; Nesnow et al., 2002; Cohen et al., 2007). Gallium arsenide is nongenotoxic in the Ames assay in vitro and mouse micronucleus test in vivo (NTP, 2000; Zeiger et al., 1992; IARC, 2006) Conclusive evidence demonstrating the lack of DNA reactivity has been demonstrated by Nesnow and his colleagues at the US EPA (Nesnow et al., 2002). This is based on a consideration of the chemistry of the various forms of arsenic as well as experimental evaluations. There have been reports of positive findings in various genotoxicity of assays, but it is unlikely that these actually represent a direct genotoxic effect of the arsenical (Kitchin and Wallace, 2008b; Cohen et al., 2006; 2007). More likely, it is a consequence of the cytotoxicity that is produced in the assays. These positive findings have only been found in vitro, not in vivo, and they occur only at extremely high concentrations which are known to be lethal to the cell type being utilized. Similarly, considerable evidence has evolved over the past decade suggesting that arsenic produces its toxic and carcinogenic effects by oxidative damage (NRC, 2001; Tokar et al., 2010; Vahter, 2002). However, again, these findings are demonstrable only in vitro, and at concentrations that are lethal to the cells. Oxidative damage has not been demonstrable at lower concentrations in vitro which do not kill the cells. Co-administration of various antioxidants in vivo has little or no effect on the biological effects of arsenic administration (Wei et al., 2005; Suzuki et al., 2009). Thus, it is unlikely that oxidative damage is the mode of action by which arsenic induces cancer, at most contributing a small effect. This was also the conclusion of the above-mentioned SAB by the US EPA.	prior to collecting the sample. The semi-conductor workers showed higher levels of DMA in their urine and slightly higher levels of arsenite and arsenate in their urine samples than both the fish eating and the non-fish eating control (unexposed) groups. Inorganic arsenic species were only observed in samples from nine smokers within the non-fish consuming group. No inorganic arsenic species were detected in the urine samples of non-smokers. However, it is not known whether the semi-conductor workers smoked, so it is not possible to say whether the results are directly as a result of occupational exposure. Regarding your comments on genotoxicity and mode of action for carcinogenicity, please see point 2) of the Annex to RCOM (Additional response to comments). This also applies to consideration of a possible threshold for

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		The more likely mode of action for arsenic carcinogenicity appears to be cytotoxicity with consequent regenerate proliferation (Cohen et al., 2001; 2006; 2007). This has been best demonstrated for the urinary bladder, but also in the skin there is considerable evidence for this mode of action and some evidence for it occurring in the lung. DMA induces bladder cancer in rats administered extremely high concentrations in the diet or drinking water (Arnold et al., 2006; Wei et al., 2002). The mode of action has clearly been shown to be due to metabolism of the DMAV to its highly reactive trivalent form, DMAIII, which is excreted in high concentrations in the urine (Cohen et al., 2001; 2006; 2007). The urinary concentrations at the carcinogenic dose are sufficient to induce cytotoxicity with consequent regenerative proliferation, hyperplasia, and eventually a low incidence of urinary bladder tumors (Cohen et al., 2002; 2006; 2007; Nascimento et al., 2008). Cytotoxicity is observed at dietary exposures of 10 ppm, whereas hyperplasia is not detectable until 40 ppm and tumors occur at 100 ppm. A dose of 2 ppm appears to be a no effect level. The urinary concentration of DMAIII, the reactive form of arsenic that is produced by exposure to DMAV, is considerably higher in the urine than concentrations which have been demonstrated to be cytotoxic to urothelial cells in vitro. The concentration is sufficiently high in the rats exposed to DMAV at exposures of 10 ppm and above, which correlates with the observed cytotoxicity. At 2 ppm of the diet, where there is no effect on the urothelium, the level of DMAIII in the urine is not detectable (< .01 μM). There is a clear threshold for this process. A similar mode of action and dose response holds in rodents for inorganic arsenic (Suzuki et al., 2010; Yokohira et al., 2010; Tokar et al., 2010). There are many other examples in the bladder as well as in other tissues where cytotoxicity is a threshold phenomenon. The threshold is related to generation of adequate levels of the trivalent form of arsenic to be excreted in the urine at concentrations sufficient to produce the cytotoxicity. Exposure to levels lower than this will not produce cytotoxicity and will not lead to the development of tumors. There is also evidence in humans that urothelial cytotoxicity is the mode of action for arsenic carcinogenesis. This is based on a recent occupational accident that occurred in China leading to high exposures of inorganic arsenic (Xu et al., 2008). A significant portion of these individuals had detectable levels of TMAO in their urine, indicating that at extremely high exposures humans are capable of methylating arsenic to the level of the trimethyl form, but this does not occur at lower exposure levels since TMAO is undetectable, even utilizing radioactively labelled arsenic. In addition, approximately 1/3 of the individuals exposed to these high levels of arsenic in this accident developed hematuria, definitive evidence of urothelial toxicity. In individuals that did not die from this accident, the hematuria and other toxic effects of this acute exposure were reversible and the individuals returned to normal. For skin, the evidence for cytotoxicity and regenerative proliferation is based on findings in humans. The precursor lesion for cancers in humans induced by arsenic exposure is a lesion that has been referred to as arseniasis or arsenicosis (Wooden, 2002). This skin lesion consists of hyperplasia and hyperkeratosis of the epidermis with a chronic inflammatory infiltrate in the dermis. The lesion evolves, cellular nuclear atypia gradually develops, eventually in some individuals becoming carcinoma in situ and eventually invasive squamous cell carcinoma. Since no arsenical by itself has been shown to induce skin cancer in mice or rats, there is no adequate animal model yet available to evaluate this. It should be noted that there is a clear basis for urothelium and skin to be target tissues for arsenic. The urothelium is a target based on the excretion and concentration of arsenic in the urine following oral or inhalation exposures. The skin is most likely a target, not because of direct dermal contact, but rather because of the exceedingly high concentration of sulfhydryl groups present in the epidermis. In the lung, the evidence is not as strong either in animal models or in humans. In animal models, the difficulty is that there has yet to be much evidence that arsenic induces lung tumors, and in addition, the limited evidence available is	carcinogenicity.

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		based on a sequence of events that does not exist in humans, as described above. In humans, recent epidemiologic evidence indicates that exposure to high concentrations of inorganic arsenic in the drinking water actually increases the risk of pulmonary toxicity (Parvez et al., 2010). Furthermore, in vitro studies utilizing human bronchial epithelial cells demonstrate that these epithelial cells are as susceptible to the cytotoxic concentrations of trivalent arsenicals as are urothelial cells or keratinocytes (Arnold et al., 2011; Styblo et al., 2000; 2006). For all three epithelial cell types, cytotoxicity occurs for arsenite at concentrations of approximately 1-5 μM and to arsenate at concentrations of 10-50 μM. Toxicity produced by arsenate has been thought to be due to its rapid conversion to arsenite, but the evidence for this is not strong. The trivalent methylated arsenicals are somewhat more toxic than arsenite to the urothelial cells, bronchial epithelial cells, or keratinocytes in vitro. MMAIII and DMAIII are cytotoxic at concentrations of approximately 0.1-0.5 μM. In contrast, the pentavalent methylated arsenicals have little cytotoxic potential, generally producing cytotoxicity only at millimolar concentrations, concentrations which are unattainable in vivo. **HUMAN RISK ASSESSMENT** Consideration of the mode of action for arsenic-induced carcinogenesis is critical for risk assessment that is to be performed on gallium arsenide. Linear extrapolation implies a greater risk at low concentrations than a non-linear, especially threshold type of mode of action. The only basis for linear extrapolation to low dose for carcinogenesis would involve DNA reactivity. This has clearly been excluded for all arsenicals. Thus, the dose response for arsenic carcinogenesis is non-linear. Evidence from the animal models clearly demonstrates this. Interestingly, regardless of the model, mice or rats, or even based on in vitro evaluations and extensions to the in vivo situation, the no effect level (NOEL) in rodents appears to be 1 ppm of arsenic in either the diet or drinking water (Cohen et al., 2006; 2007; Tokar et al., 2010; Gentry et al., 2010). This translates to approximately 1.7 ppm of inorganic arsenic and 2 ppm of organic arsenicals. Evidence for a threshold effect in humans has been controversial. Based on the initial review of the southwest Taiwanese data, the population most extensively evaluated for carcinogenesis, it was thought that the extrapolation could be linear down to low doses (NRC, 2001). This has been the basis for the risk assessment by the US EPA for utilizing 10 ppb as a safe level in drinking water. However, reanalysis of the Taiwanese data taking into consideration the effect of township as well as other factors, clearly demonstrates that there is an apparent no effect level in humans with respect to bladder cancer (Lamm et al., 2006). That level appears to be 150 ppb in the drinking water, considerably higher than drinking water supplies in the United States, and much higher than those that are present in Europe (where drinking water supplies are well below 10 ppb). Furthermore, other epidemiologic investigations have demonstrated a carcinogenic effect not only of the urinary bladder but in the skin and lung at levels that are extremely high compared to usual exposures in most of the world, especially in the United States and in Europe. These include epidemiologic studies in various populations in the United States, where there is no evidence of any increase in any type of cancer secondary to exposure to arsenic (Lamm et al., 2004; Mink et al., 2008; Schoen et al., 2004; Tapio and Grosche, 2006; Brown and Ross, 2002). Levels of inorganic arsenic in the drinking water in the United States, generally are below the 10 ppb, nearly always below 50 ppb, and even in locales where the levels have been as high as 100 ppb there is no evidence of an increased risk of bladder cancer. The results of epidemiologic investigations of populations exposed to low levels of arsenic in the drinking water have uniformly shown no increased cancer risk. A meta-analysis also supports a lack of a cancer	

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		effect at low exposures (Mink et al., 2008). **SUMMARY** In summary, it is inappropriate to classify gallium arsenide as a Class 1a carcinogen for several reasons: 1. Gallium arsenide is not soluable in aqueous solution and has low bioavailability. 2. Gallium arsenide shows little evidence of toxicity except at extremely high concentrations in rodent experiments. 3. Gallium arsenide was negative for carcinogenicity in male and female mice and in male rats, and the tumor findings in the female rat are not relevant to human risk. 4. Gallium arsenide is non-genotoxic in vitro and in vivo. 5. Mode of action for inorganic arsenic carcinogenesis involves a non-linear dose response, most likely involving a threshold. 6. It is inappropriate to include gallium arsenide in a consideration of inorganic arsenic carcinogenesis because of the significant differences of bioavailability, metabolism and kinetics between various forms of arsenic. 7. Epidemiology studies in workers in the semiconductor industry show no evidence of an increased risk of cancer of any tissue, even those that are known target sites for inorganic carcinogenesis in humans. REFERENCES Aposhian, H. V. (1997). Enzymatic methylation of arsenic species and other new approaches to arsenic toxicity. Annu. Rev. Pharmacol. Toxicol. 37: 397-419. Arnold, L.L., Nyska, A., Eldan, M., van Gemert, M. and Cohen, S.M. Dimethylarsinic acid: Results of chronic toxicity/oncogenicity studies in F344 rats and B6C3F1 mice. Toxicol. 223: 82-100, 2006. Arnold, L., Kakiuchi-Kiyota, S., Pennington, K.L., and Cohen, S.M. Cytotoxicity of arsenicals on human bronchial epithelial cells in vitro. The Toxicologist, Abstract #2655, 2011. Bates MN, Rey OA, Biggs ML, Hopenhayn C, Moore LE, Kalman D, Steinmaus C, Smith AH. Casecontrol study of bladder cancer and exposure to arsenic in Argentina. Am. J. Epidemiol. 159(4):381-9, 2004. Beall C, Bender TJ, Cheng H, Herrick R, Kahn A, Matthews R, Sathiakumar N, Schymura M, Stewart J, Delzell E. Mortality among semiconductor and storage device-manufacturing workers. J. Occup. Environ. Med. 47(10):996-1014, 2005. Bender TJ, Beall C, Cheng H, Herrick RF, Kahn AR, Matthews R, Sathiakumar N, Schymura MJ, Stewart JH, Delzell E. Cancer incidence among semiconductor and electronic storage device workers. Occup. Environ. Med. 64(1):30-6, 2007. Boice JD Jr, Marano DE, Munro HM, Chadda BK, Signorello LB, Tarone RE, Blot WJ, McLaughlin JK. Cancer mortality among US workers employed in semiconductor wafer fabrication. J. Occup. Environ. Med. 52(11):1082-97, 2010. Borak, J. and H. D. Hosgood (2007). Seafood arsenic: implications for human risk assessment. Reg. Toxicol. Pharmacol 47(2): 204-12. Brown, K. G. and G. L. Ross. Arsenic, drinking water, and health: A position paper of the American Council on Science and Health. Reg. Toxicol. Pharmacol. 36: 162-174, 2002. Caldwell, D. J. (1999). Review of mononuclear cell leukemia in f-344 rat bioassays and its significance to human cancer risk: A case study using alkyl phthalates. Reg. Toxicol. Pharmacol. 30: 45-53.	

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Date	Country/ Person/ Organisation/ MSCA	Comment	RAC response
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Date	Country/ Person/ Organisation/ MSCA	Comment	RAC response
		knockout mice. A preliminary report. Toxicol. Appl. Pharm., 246:1-7, 2010. Zeiger E, Anderson B, Haworth S, Lawlor T, Mortelmans K. Salmonella mutagenicity tests: V. Results from the testing of 311 chemicals. Environ. Mol. Mutagen. 1992; 19 Suppl 21:2-141. Omaha, April 26, 2011 (signed) (Samuel M. Cohen M.D., Ph.D.)	
27/04/2011	Unites States / AXT, Inc. / Company-Manufacturer	**Position of AXT, Inc.** **On "Opinion of the Committee for Risk Assessment (RAC) proposing harmonized classification and labeling at EU level of Gallium Arsenide adopted 25th May 2010"** **April 21, 2011** As a Gallium Arsenide (GaAs) substrate supplier, AXT, Inc. has been involved in growing single□crystal GaAs ingots and substrates to the Compound Semiconductor since 1986. In all of its diverse operations, AXT, Inc. has been aware of the epidemiological and toxicological studies associated with the GaAs material, and, during that time, AXT, Inc. has observed all the necessary precautions and implemented all the recommended measures for monitoring the exposure levels of its employees. A thorough search into the scientific work and research associated with the toxicity of GaAs in general and its carcinogenicity in particular revealed that major discrepancies in the results and conclusions suggest that more work is needed before the appropriate classification is released. For example, a comprehensive analysis, supported by scientific references, of the work on Gallium and Semiconductor Compounds is covered in Chapter 27, of the Handbook on the Toxicology of Metals (2007 Academy Press). In particular, in section 7.2.1 the classification of the International Agency for Research on Cancer (IARC) is stated as a Group 1 carcinogen to humans and that no data on human cancer were available. We have also reviewed the CAS Registry Number: 1303□00□0 Toxicity Effects as outlined in the National Toxicology Program (NTP) website: http://ntp.niehs.nih.gov/index.cfm?objectid=E87D387C□BDB5□82F8□F3517BEDC60248E8# and, under the section "Human Toxicity Values", the notation: "None found" was entered. Toxicity testing conditions and results on "non□human" (mice and rats) are outlined in the report, but these have no direct relevance to the "human toxicity" effects. A review of the published Material Safety Data Sheets (MSDS) for GaAs (see for example: http://www.utdallas.edu/research/cleanroom/safety/msds/documents/Gallium_Arsenide.pdf) show that the chemical, physical and toxicological properties of gallium arsenide have not been thoroughly investigated and reported. On the other hand, in some MSDS documents on GaAs it is not uncommon to read: "This product contains a known human carcinogen" and general guidelines on "safe" exposure limits are given but with no background evidence presented. With the above information, AXT, Inc. proposes that, in the absence of any compelling scientific evidence of the carcinogenicity of GaAs, its classification as a carcinogen must be carefully reviewed before it is released.	

Date	Country/ Person/ Organisation/ MSCA	Comment	RAC response
		Dr. Hani Badawi Vice President Applications Engineering and Intellectual Property	
27/04/2011	United Kingdom / Member State	We welcome this second consultation and expect the dossier submitter and RAC to ensure any new information is fully integrated into the background documentation as well as the opinion. We recognise that the mandate from the Commission indicates that any relevant new information should be considered against the criteria for carcinogenicity classification. Could the final documentation accordingly reflect all of the available data and take account of any remaining uncertainties.	

COMMENTS RECEIVED:

Position papers and letters:

AIXTRON SE , Risk Assessment Committee concerning Gallium Arsenide: Opinion proposing harmonised classification and labelling at Community level of gallium arsenide (*document AIXTRON GaAs.pdf is included in the table under Carcinogenicity*)

Avago Technologies Wireless, Reactions to and recommendations for modifying The Background document to the Opinion proposing harmonised classification and labelling at Community level of gallium arsenide *(document Dr_HV_Aposhian_Critique_of_ECHA_Background_Document.pdf is included in the table under Carcinogenicity)*

Avago Technologies Wireless (U.S.A.), Avago Technologies comments regarding the proposed classification of gallium arsenide *(document* Avago_comments_letterhead.pdf *is included in the table under Carcinogenicity)*

AXT, Inc. Position of AXT, Inc. On "Opinion of the Committee for Risk Assessment (RAC) proposing harmonized classification and labeling at EU level of Gallium Arsenide adopted 25th May 2010" April 21, 2011 (*documentReach (AXT) .pdf is included in the table under Carcinogenicity*)

European Photonics Industry Consortium, Risk Assessment Committee concerning Gallium Arsenide:
Opinion proposing harmonised classification and labelling at Community level of gallium arsenide *(document EPIC_Comments on GaAs_ECHA.pdf is included in the table under Carcinogenicity)*

European Technology Platform Photonics21, Opinion proposing harmonised classification and labelling at Community level of gallium arsenide (*document REACh_Photonics21.docx is included in the table under Carcinogenicity*)

European Trade Union Institute, GALLIUM ARSENIDE CARCINOGENICITY (*document GALLIUM ARSENIDE CARCINOGENICITY.doc is included in the table under Carcinogenicity*)

Freiberger Compound Materials GmbH, Position ot Freiberger Compounds Materials GmbH on the Opinion of the Committee for Risk Assessment proposing harmonized classitication and labeling at the EU level for GaAs adopted 25 May 2010 ECHA *(document 2011_04_21 Briefing paper is included in the table under Carcinogenicity)*

Freiberger Compound Materials GmbH, Expert Report Gallium Arsenide On the Subject of Carcinogenicity and Fertility Effects by Dr. Ernst M. Bomhard *(document 2011_04_21 Dr Bomhard et al - On GaAs Toxicology is included in the table under Carcinogenicity)*

Freiberger Compound Materials GmbH, Expert Opinion Evaluation of the Potential Carcinogenicity of Gallium Arsenide Samuel M. Cohen, M.D., Ph.D *(document 2011_04_26 Dr Cohen - Evaluation of the potential carcinogenicity of gallium arsenide.pdf is included in the table under Carcinogenicity)*

GaAs Industry Team, Position of the Gallium Arsenide Industry Team (GAIT) on the Opinion of the Committee for Risk Assessment proposing harmonized classification and labeling at the EU level for GaAs adopted 25 May 2010 *(document GAIT Comments on GaAs Carcinogenicity Classification_25-Apr-2011.pdf is included in the table under Carcinogenicity)*

IQE plc, The Harmonised Classification of Gallium Arsenide at Community level by the European Chemicals Agency (*document 2011 IQE Gallium Arsenide Classification-ReadAcross-LH.pdf is included in the table under Carcinogenicity*)

RF Micro Devices, RFMD letter *(document RFMD ECHA letter.pdf is included in the table under Carcinogenicity)*

Thales Corporate Services, REACH/Gallium Arsenide for Aerospace and military application *(document 11-0863 ECHA - Harmonizing classification and labelling – Answer to the public consultation issued on 25th May 2010.pdf is included in the table under Carcinogenicity)*

TriQuint Semiconductor, Inc. Position of TriQuint Semiconductor, Inc. on the Opinion of the Committee for Risk Assessment proposing harmonized classification and labeling at the EU level for GaAs adopted 25 May 2010 *(document TriQuint Comments on GaAs Carc Classification_20-Apr-2011.pdf is included in the table under Carcinogenicity)*

TriQuint Semiconductor, Inc. Position of TriQuint Semiconductor, Inc. on the Opinion of the Committee for Risk Assessment proposing harmonized classification and labeling at the EU level for GaAs adopted 25 May 2010 *(document TriQuint FPM Comments on GaAs Dossier 25-Apr-2011.pdf is included in the table under Carcinogenicity*

United Monolithic Semiconductors, Comments on the RAC Opinion on Gallium Arsenide by Dr. Ernst M. Bomhard REACH ChemConsult GmbH (*document Bomhard_Scientific coments on RAC Opinion on GaAs is included in the table under Carcinogenicity*)

United Monolithic Semiconductors, Gallium Arsenide On the Subject of Carcinogenicity
and Fertility Effects by Dr. Ernst M. Bomhard (*document GaAs_Carcinogenicity_Fertility_Dr_E_Bomhard_08_April_2011 is included in the table under Carcinogenicity*)

United Monolithic Semiconductors, Gallium Arsenide Position of United Monolithic Semiconductors GmbH on the Opinion of the Committee for Risk Assessment proposing harmonized classification and labelling at the EU level for GaAs adopted May 25, 2010 (*document UMS_comments on_Further_Public_Consultation_Phase_of_ECHA_for_GaAs_classification2011 is included in the table under Carcinogenicity*)

Wafer Technology Ltd, WT letter to ECHA *(document WT letter to ECHA incl RTB.doc is included in the table under Carcinogenicity)*

WIN Semiconductors, Position of WIN Semiconductors 20th April 2011
On "Opinion of the Committee for Risk Assessment (RAC) proposing harmonized classification and labeling at EU level of Gallium Arsenide adopted 25th May 2010" *(document WIN Comments on GaAs Classification.pdf is included in the table under Carcinogenicity)*

WirtschaftsVereinigung Metalle, Comments on second public consultation for a harmonised classification & labelling for Gallium arsenide (*document 2011-04-21_WVM_Comment_Consultation_GaAs.pdf is included in the table under Carcinogenicity*)

ZVEI, Position of ZVEI – German Electrical and Electronic Manufacturers' Association On "Opinion of the Committee for Risk Assessment (RAC) proposing harmonized classification and labelling at Community level of Gallium Arsenide, adopted 25th May 2010" *(document 2011_Jan_28_GaAs_ZVEI-Position.pdf is included in the table under Carcinogenicity)*

Reports and articles:

Tokar, E.J et al, Critical Rewiews in Toxicology, 210; 40 (10):912-927.

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

Annex
Additional response to comments

1) Read-across between arsenic oxides and GaAs

Application of read-across to other arsenic compounds in the RAC opinion of 25 May 2010 was strongly challenged and deemed as flawed by several: European Photonics Industry Consortium, ZVEI – German Electrical and Electronic Manufacturers' Association, European Semiconductor Industry Association (ECCA-ESIA), Wafer Technology Ltd, as well as by GAIT members. Especially physico-chemical properties of GaAs were claimed to be overlooked and the OECD guidance on grouping not applied ("They did not analyze the physicochemical characteristics of the analogues they chose to compare to gallium arsenide. They did not perform any of the subsequent steps to properly use the read-across method that are recommended in the OECD (2007) guidance document on the grouping of chemical substances."). TriQuint and IQE carried out an exercise according to the OECD guidance concluding that only arsenic compounds or solution species in the same oxidation state should be compared, and that this plus the low solubility of gallium arsenide called for deeming the read-across as inappropriate. Read-across was also deemed unnecessary by comments received in the public consultation because animal data on GaAs exists. In RAC's opinion the NTP study was valid and supports a classification as carcinogenic, however we could not disregard the available epidemiological data of arsenicals causing cancer in humans due to the low sensitivity to arsenic in standard animal carcinogenicity tests. Thus, an assessment of the transformation products of gallium arsenide was included in the overall evaluation of carcinogenesis of gallium arsenide.

RAC did not apply the OECD guidance (OECD, 2007) per se because a more direct comparison could be applied due to the formation of similar transformation products from gallium arsenide and other arsenic compounds already classified and listed as carcinogens in CLP Annex VI. See also CLP section .3.6.2.2.7.

Comments received claimed that the genotoxic effects of GaAs do not seem totally comparable with other arsenicals, limiting the validity of the read-across. Please see paragraph on threshold for response to this. It was claimed by industry that methylation did not happen in humans as a study showed arsenic in urine, but no increase in methylated species (Yamauchi et al., 1989). For discussion of bioavailability and this study please see paragraph on metabolism and the adopted opinion.

2) Threshold for carcinogenicity

Several comments were received from Industry (Gallium Arsenide Industry Team (GAIT) , Zvei, TriQuint) calling for an interpretation of the genotoxicity studies to conclude on a non-genotoxic action and hence a threshold for arsenic carcinogenicity. Also comments were received stating that a number of more recent epidemiological studies based on quite accurate exposure assessments (essentially studies on drinking water) indicates the existence of a threshold for the carcinogenic effects of (other) arsenicals well above the known exposure experienced during the production and processing of gallium arsenide (Bates et al. 2004; Brown and Ross, 2002; Lamm et al. 2004, 2006, 2007; Meliker et al. 2010; Mink et al. 2008; Schoen et al. 2004; Snow et al. 2005; Tapio and Grosche 2006).
A shift in risk assessment approach in U.S. EPA from linear extrapolation to a non-linear (Margin of Exposure (MOE)) approach was submitted to support this view (Cohen et al., 2006). Also a thorough analysis of the genotoxicity data, commissioned by Freiburger and compiled by Dr. M. Kirsch-Volders (Kirsch-Volders 2011), was received giving reference to (Mateuca et al., 2006; Kirsch-Volders et al., 2000, 2009; Speit et al., 2000; Lutz (1998); Elhajouji et al., 1995, 1997; Kirsch-Volders et al., 2003: Kirsch-Volders et al., 2000; Jenkins et al., 2005; Zeiger et al., 1992 (cited in NTP, 2000); Gibson et al., 1997; NTP, 2000; Stone V., 2010 (unpublished results); Hoyes et al., 1992; Riaz et al., 1995; Yang and Chen, 2003; Basu et al., 2002; Kligerman and Tennant, 2007; Klein et al., 2007; Gebel, 2001; Jomova et al. 2011; Nollen et al. (2011); Gentry *et al., 2010;* Schoen et al, 2004; Snow et al., 2005; Schoen et al., 2004; Rudel et al., 1996, Andrew et al., 2006; Basu et al., 2001; Elhajouji et al., 1995, 1997, 2011; Decordier et al.,2011; Cammerer et al., 2009; Decordier et al., 2009, 2011); (Dertinger et al. 2011; Avlasevich et al. 2011).

In conclusion although inorganic arsenicals and metabolites are considered to act mainly by non-mutagenic mechanisms, a threshold for carcinogenicity has so far not been established.

3) Fine particulate matter-considerations

With reference to CLP section 3.6.2.2.6 one of the important factors to take into consideration, when assessing the overall level of concern, is the possibility of a confounding effect of excessive toxicity at test doses. In the CLP guidance this is further discussed in section 3.6.2.3.1 letter j). Tumours occurring only at sites of contact and/or only at excessive doses need to be carefully evaluated for human relevance for carcinogenic hazard.

In the NTP carcinogenicity study in rats (NTP, 2000), chronic active inflammation of the lungs was observed at all concentrations tested. Gallium arsenide industry team (GAIT) companies like Freiberger Composite Materials, TriQuint and United Monolithic Semiconductors, supported by experts (Dr. Bomhard and others), claim that symptoms in the NTP study would have shown up regardless of the chemical composition of the substance, because of the fine particulate matter effect (<1 micron, poorly soluble) from the concentration of active surface sites on the particles: "The non-neoplastic effects reported were: chronic active inflammation, atypical hyperplasia, alveolar epithelial hyperplasia, proteinosis, alveolar epithelial metaplasia in the lung. All of these changes result from a chronic irritation of the lung tissue. They are qualitatively similar to those effects reported as the typical outcome of the exposure to other particles e.g. talc ($H_2Mg_3(SiO_3)_4$) or quartz (SiO_2) by inhalation (NTP 2000, Wolff et al. 1988)." Talc and quartz give rise to different inflammatory reactions. To state that the effects would have shown up regardless of the chemical composition seems incorrect as GaAs induces lung toxicity and carcinogenicity at doses well below those of more inert particles like titanium dioxide. However we agree that inflammation and cytotoxicity may play a role in lung tumours induced by gallium arsenide in female rats. Comments were also received stressing the occurrence of lung tumours in rats under conditions of chronic inflammation of the lungs as a phenomenon that has been observed with other particulate matters and reported in the literature (Nikula. Inhal Toxicol 12, 2000, 97-119; Federico et al., 2007; Mossman, 2000)." Other concerned parties, like WIN semiconductors also argue that chronic inflammatory effects from particles are probably more responsible for the neoplastic transformations observed in animals than the carcinogenic effects of gallium arsenide. RAC agrees the mechanisms of the carcinogenic seen in the NTP study might involve chronic inflammation. No overload was reported in the study (see the opinion for details on no overload). RAC considers that the pulmonary effects observed in rodents are caused by the specific properties of GaAs and is not a "pure particle effect" as GaAs induces lung toxicity and carcinogenicity at doses well below those of more inert particles such as titanium dioxide.

TriQuint reiterates the IPC comments from the public consultation on gallium arsenide in 2009 that the particle sizes used in the NTP study (NTP, 2000) have zero relevance to the form of gallium arsenide that will be encountered by any consumer. RAC assumes this refers to the state of gallium arsenide as a semiconductor contained within an electronic device, and agrees. However this is not relevant for assessing the intrinsic properties of the substance.

RAC considers that the mechanisms proposed for particle induced lung tumorigenesis in animals are relevant also for humans. Although, as commented by Industry there may be differences in the particle induced pulmonary tumour biology, lung tumours in experimental animals should be considered predictive for cancer potential in humans if there are not definitive data showing otherwise.

4) Bioavailability

From the CLP guidance, 1.3.2 Bioavailability: "In general, bioavailability is not explicitly evaluated in hazard classification – the observation of systemic toxicity implicitly demonstrates a degree of bioavailability." "Information on bioavailability is usually obtained from adequate, reliable, and conclusive toxicokinetic studies for all relevant routes of exposure and all relevant forms or physical states where the substance and/or metabolite(s) of the substance have been quantified in body fluids and/or target organs. It should be noted that concluding that there is lack of or reduced bioavailability has a high burden of evidence and needs to be supported by robust data and expert evaluation. Bioavailability of a substance or a mixture is normally assumed if there are in vitro studies available which show the solubility of a substance or mixture in body fluids or artificial simulated body fluids."

Several of the comments received during the second public consultation (GAIT members supported by experts, e.g. Dr Bomhard) claim that the bioavailability of GaAs has not been convincingly documented and that several reports demonstrate low or no internal exposure in the working atmosphere in the semiconductor industries. RAC acknowledges that the data provided indicate that the workplace exposure to GaAs do not significantly increase the body burden of arsenic. However, the issue of bioavailability was determined based on in vitro solubility data and animal studies with exposure to GaAs particles of varying sizes via inhalation or intratracheal instillation. These studies have been described in the opinion and are shortly mentioned below.

Although the solubility of GaAs in water is very low it has an increased *in vitro* solubility in phosphate buffer and in Gamble solution (Webb et al., 1984; Pierson et al., 1989, Yamauchi et al., 1986). The solubility reported varied between approximately 10% - 70%. The reason for the high in vitro solubility reported in the study by Webb (1984) is unclear, but may be related to a disruption of the crystalline structure of the particles used as discussed in the opinion. The solubility in the Gamble solution which is an artificial lung fluid was performed to extend earlier information (Pierson et al., 1989). GaAs was found to dissolve slowly over a period of several days and more As than Ga was dissolved. The authors report that As was oxidized at the particle surface to a species resembling arsenic trioxide.

In a study by Rosner and Carter (1987) it was estimated that about 5-10% of arsenic form GaAs particles were systemically available following intratracheal instillation. The bioavailability of GaAs was further supported by measurement of gallium and arsenic in blood and testis following inhalation exposure of rodents in the NTP studies (2000). Systemic toxicity (such as microcytic anemia) reflects systemic release of gallium and arsenic ions in the NTP studies. Furthermore, NTP has conducted a series of toxicity studies as part of the overall toxicity assessment of inhalation exposure to gallium arsenide, that includes whole-body inhalation developmental toxicity studies with 0, 10, 37, or 75 mg/m^3 gallium arsenide in Sprague-Dawley rats and Swiss (CD-1) mice (cited as Battelle 1990c in NTP 2000). The results from these studies are briefly described in the NTP (2000) report, but were not included in the 2010 Background Document to the RAC opinion as developmental toxicity was not proposed nor evaluated by the dossier submitter. Analysis of the concentrations of As and Ga in maternal rat blood and in the conceptus showed that maternal blood concentrations of arsenic in the rat increased with increasing exposure concentration and duration, and achieved high levels (170 µg/g) at the highest dose level (75 mg/m^3). Levels in the conceptus increased with advancing gestation, and by day 20 arsenic was detectable in all exposed groups, but not in the controls. In the rat, arsenic is tightly bound to hemoglobin in the erythrocytes, and this is likely to limit placental transfer. Levels of gallium in the maternal blood was low, however, fetal tissue had gallium concentrations greater than those found in maternal blood for all exposed groups. These analyses complement the data from the rat carcinogenicity study and confirm that arsenic and gallium is released following inhalation exposure to crystalline GaAs particles.

Several studies indicate that semiconductor workers are exposed to very low levels of gallium arsenide (Yamauchi et al., 1989; Farmer and Johnson, 1990; Morton and Mason, 2006; Morton and Leese, 2011) and these studies are now included in the Art 77.3(c) opinion. In one of these studies (Yamauchi et al., 1989) arsenic species in different groups of Japanese workers in a GaAs plant was measured. Urine was sampled twice a day (before work and after work) for three consecutive days. A slight, but significant increase in inorganicAs levels was found in postwork urinary samples compared to prework samples from workers involved in GaAs production or processing. This study suggests that GaAs dust in the working atmosphere is bioavailable to a certain extent. No increase in total arsenic or in DMA(V) was observed, a fact that may be due to dietary sources contribution to urinary DMA levels. This point is discussed in the study by Morten and Leese (2011) who suggest that it “may be more accurate to sum up MMA, As3+ and As5+ when trying to assess exposure to inorganic arsenic”.
RAC consider that the bioavailability of GaAs via inhalation is sufficiently demonstrated based on *in vitro* and *in vivo* studies.

5) Toxicokinetic considerations

The comparison with other arsenical compounds relies to a large extent on data showing the release of inorganic arsenic and the formation of As(III), As(V), MMA(V) and DMA(V) in experimental studies following exposure to GaAs. The study by Rosner and Carter (1987) and the review by Carter et al. (2003) are both central for the evaluation performed. The interpretation of these data by RAC has been challenged by IND in the public consultation (European Photonics Industry Consortium, ZVEI – German Electrical and Electronic Manufacturers‘

Association, European Semiconductor Industry Association (ECCA-ESIA), Wafer Technology Ltd, as well as by GAIT members, also supported by experts as Dr Asposhian; Dr. Bomhard; Dr Cohen).

Hamsters are considered a suitable animal model for such studies since its urinary metabolic profile resembles that of humans following inorganic arsenic exposure. The comparative study of Rosner and Carter (1987) as well as the oral hamster study by Yamauchi et al. (1986) show that there is a wide tissue distribution of arsenic species following exposure to GaAs, but the levels of the different species at the target sites are not known. However, the lung is a target site for arsenic-induced carcinogenesis following both oral and inhalation exposure. Importantly, the lung has metabolic capacities (oxidation, reduction, methylation) suggesting that both inorganic As and methylated species will be formed at the target site.

Industry states that gallium arsenide should not be considered as part of the overall exposure to inorganic arsenic in general and that data on carcinogenicity of arsenite and arsenate are not relevant for GaAs. Several of the objections seem to be related to the mode of action of arsenic carcinogenicity and the assumption that a threshold of effects is high compared to the small amounts that are released from GaAs exposures. These considerations are commented elsewhere in this document. However, RAC recognises that there are differences in bioavailability and likely also in tissue levels of the different arsenic species at the target sites. However, these are considered to be quantitative and not qualitative differences.

Furthermore, there is an apparent disagreement on whether the data reviewed by Carter et al. (2003) and the conclusions in this paper is in contrast to the interpretations made by RAC. Several quotes from the review paper are made to support the view that the read-across approach performed in the 2010 opinion was inappropriate. The review by Carter and co-workers relates to the comparison of toxicity (non-cancerous endpoints) between different inorganic arsenicals and provides a thorough discussion also of the toxicokinetic information on several arsenic compounds including GaAs. In RAC's opinion the review paper gives a clear support for the qualitative similarity of the systemically released arsenic ions and metabolites. Carcinogenic endpoint was however, not included in the review.

The *quotations* (from the review paper pp. 309, 326, 323, 310) submitted and underlined by IND in the comments are briefly answered below:

6) Specific comments to the review by Carter et al., 2003, received in the public consultation:

- Abstract on page 309 state that

"*The urinary metabolites after GaAs exposure were the same as excreted by arsenic oxides but the chemical compounds responsible for the toxic effects of GaAs are different from the arsenic oxides. The review concludes that there is insufficient evidence to equate the different arsenic compounds*."

The review discusses the toxicity of several inorganic arsenicals. It is clear that the acute and subacute toxicities of GaAs are not the same as those of arsenic oxides. In RAC's opinion, these statements relates to the lung and testicular toxicities seen following GaAs exposure that are not easily explained by arsenic toxicity alone.

- page 326 states that

"*The toxicity of gallium appears to be limited by its solubility and by the solution composition of materials that could bind or solubilize gallium. The toxicity of arsenic appeared to depend on the species formed during dissolution: arsine, arsenious acid, or arsenic acid. It is clear that highly insoluble arsenide semiconductors were less acutely toxic than equal amounts of arsine or their more soluble arsenious acid products*."

RAC agrees that the systemic toxicity of GaAs is limited by its solubility. The authors further state: "The target organs of GaAs are the lung and the testis but the dissolved compounds that are likely to enter the circulation are inorganic arsenic oxides (AsIII and AsV) and not arsine." In the article by Rosner and Carter (1987) it is stated that "the systemic arsenic released from GaAs appeared to be treated like trivalent arsenic by the body."

- page 323 states that

"…..…arsine and gallium arsenide, [that] are in widespread use in the microelectronics industry. These two arsenic compounds are not found in nature and should not be judged by the same drinking water exposure scenarios that are used for the inorganic oxides."

- page 310 state that

"*There is one major question that should be asked before the standards for industrial exposure are revised. Can the results used for the drinking water standards of environmental arsenic compounds be extrapolated to industrial inhalation exposures for the important arsenic compounds used in industry? The drinking water standard did not analyze individual arsenic compounds separately. We doubt that total arsenic in all environmental arsenic exposures is representative of risk when there appear to be several different "most toxic arsenic compounds*."

We agree to the two above mentioned quotations. The review was said to "attempt to define the dose–response relationships for the different health effects and to define the arsenic chemical species that are important in these effects." Clearly the different oxidation states and metabolic forms of arsenic have different toxicities. In addition, the route of exposure and bioavailability will influence the levels of the different arsenic ions and metabolites at the target sites in the body. These facts however, do not contrast the view that the formation of arsenic species in the body following GaAs exposure is qualitatively similar to those formed following exposure to arsenic oxides, as is also stated in the review.

In conclusion, RAC believes that there is sufficient information showing the release of similar arsenic transformation products following GaAs inhalation exposure as following exposure to classified carcinogenic inorganic arsenicals. However, it is important to stress that the data are used in a qualitative assessment and no quantitative assessment of the carcinogenic potency of GaAs based on the read-across has been performed.

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