# Committee for Risk Assessment

# RAC

# Annex 3

# to the RAC Opinion on gallium arsenide

# in relation to toxicity to reproduction

ECHA/RAC/xxxxxxx

# Response to comments document (RCOM)

Compilation of comments and RAC response to comments related to toxicity to reproduction submitted during the public consultation on carcinogenicity of

**gallium arsenide**

**10 January 2012**

**Extracted from Annex 1 -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**

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

| Date | Country/ Person/ Organisation/ MSCA | Comment | RAC response |
|---|---|---|---|
| 13/04/2011 | France / Thomas Pearsall / European Photonics Industry Consortium / Industry or trade association | 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. ….<br><br>…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.<br>…<br>Thomas P. Pearsall<br>Secretary General | **…**<br>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 were 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." |

| Date | Country/ Person/ Organisation/ MSCA | Comment | RAC response |
|---|---|---|---|
| 18/04/2011 | Germany / Christian Eckert / ZVEI / Industry or trade association | Gallium Arsenide<br>Position of ZVEI – German Electrical and Electronic Manufacturers' Association<br>On "Opinion of the Committee for Risk Assessment (RAC) proposing harmonized classification and labelling at Community level of Gallium Arsenide, adopted 25th May 2010" …<br><br>**Please find below our serious concerns described in detail:**<br>…<br>**2) Content of RAC opinion:**<br>…<br>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<br>…<br>3 Dr. Ernst M. Bomhard, *Classification of Gallium Arsenide regarding Reprotoxicity (Fertility)*<br>19 November 2010 | **…** 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.<br>**…** |
| 21/04/2011 | Germany /<br>Dietmar Schmitz / AIXTRON SE / Company-Manufacturer | …<br>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.<br><br>Sincerely,<br><br>Dietmar A. Schmitz<br>AIXTRON SE<br>Vice President Corporate Technology Transfer | **…**<br>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 | Germany / European Technology Platform Photonics21 / Industry | **…**<br>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. | **…**<br>Regarding your comment on toxicity to |

| Date | Country/ Person/ Organisation/ MSCA | Comment | RAC response |
|---|---|---|---|
| | or trade association | Sincerely,<br><br>Bernd Schulte<br>Vice President, Photonics21 European Technology Platform<br>Executive Vice President and Chief Operating Officer, AIXTRON | 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 | Germany / AZURSPACE SOLAR POWER GmbH / Company-Downstream user | **…**<br>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.<br>**…**<br><br>References:<br>**…**<br>/4/ E.M.Bomhard, REACH ChemConsult GmbH, Gallium Arsenide, On the Subject of Carcinogenicity and Fertility effects, March 11, 2011<br>**…**<br>/13/ E.M.Bomhard, REACH ChemConsult GmbH, Gallium Arsenide, On the Subject of Carcinogenicity and Fertility effects, April 21, 2011<br>**…** | **…**<br>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.<br>…<br><br>Regarding your comment on toxicity to reproduction, please see response to France / Thomas Pearsall / European Photonics |

| Date | Country/ Person/ Organisation/ MSCA | Comment | RAC response |
|---|---|---|---|
| | | | Industry Consortium / Industry or trade association in the beginning of this document.<br>… |
| 21/04/2011 | Germany /<br>Gerhard Hirschle /<br>United Monolithic Semiconductors /<br>Company-Downstream user | 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.<br><br>**Comments on the RAC Opinion on Gallium Arsenide by Dr. Ernst M. Bomhard**<br>**REACH ChemConsult GmbH**<br>**…**<br>In the following, we would like to comment on the RAC opinion, focusing on the two following issues: reproduction toxicity/fertility and carcinogenicity.<br><br>**1. Reproduction toxicity/fertility**<br>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.<br>This opinion was justified by:<br>***"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"***<br>*1.1 Ad "clear evidence of effects on fertility at low doses in the absence of other toxic effects"*<br>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).<br><br>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. | **…**<br>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.<br>**…** |

| Date | Country/ Person/ Organisation/ MSCA | Comment | RAC response |
|---|---|---|---|
| | | 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 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).<br><br>*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).<br><br>However, RAC ignored this conclusion from the rat study (4).<br>**…**<br>**3. Concluding remarks**<br>**…**<br>□ The fertility effects secondary to inflammatory effects are not GaAs specific and do not justify classification into Reprotoxic 1B – H360F.<br>**…**<br>**4. References**<br>**…**<br>5. Goering et al.Toxicol Appl Pharmacol. 92, 1988, 179-193.<br>6. Tanaka et al. Fukuoka Igaku Zasshi 91, 2000, 21-33.<br>7. Webb et al. Toxicol Appl Pharmacol 76, 1984, 96-104.<br>8. Webb et al. Toxicol Appl Pharmacol 82, 1986, 405-416.<br>9. Webb et al.. Am Ind Hyg Assoc J. 48, 1987, 660-667.<br>**…**<br>**Gallium Arsenide On the Subject of Carcinogenicity and Fertility Effects ;** (*08 April 2011)*<br>Author:<br>**Dr. Ernst M. Bomhard**<br>REACh ChemConsult GmbH<br>Upon request by **Freiberger Compound Materials GmbH** | |

| Date | Country/ Person/ Organisation/ MSCA | Comment | RAC response |
|---|---|---|---|
| | | **TABLE OF CONTENTS**<br>**…**<br>4 SUMMARY OF THE EXPERIMENTAL DATA ON THE POSSIBLE EFFECTS OF GALLIUM ARSENIDE ON FERTILITY ..... 5<br>**…**<br>**4 SUMMARY OF THE EXPERIMENTAL DATA ON THE POSSIBLE EFFECTS OF GALLIUM ARSENIDE ON FERTILITY**<br><br>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).<br><br>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).<br><br>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.<br>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.<br><br>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.<br>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!<br><br>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.<br>**…** | |

| Date | Country/ Person/ Organisation/ MSCA | Comment | RAC response |
|---|---|---|---|
| | | **8 EVALUATION OF FERTILITY STUDIES WITH GALLIUM ARSENIDE**<br><br>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).<br><br>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.<br><br>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!<br><br>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).<br><br>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.<br><br>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.<br><br>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 .<br><br>One of the two reasons for RAC's decision to classify gallium arsenide into reprotoxicity Cat. 1B was „..clear effects | |

| Date | Country/ Person/ Organisation/ MSCA | Comment | RAC response |
|---|---|---|---|
| | | on fertility at low doses in the absence of other toxic effects…“ is thus not substantiated by the available data.<br><br>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.<br>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).<br><br>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).<br><br>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).<br><br>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.<br><br>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.<br><br>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 .<br><br>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 mg/m3 (still causing irritation to the lung) there were no traces of gallium detectable in the testes at any time and the | |

| Date | Country/ Person/ Organisation/ MSCA | Comment | RAC response |
|---|---|---|---|
| | | concentration of arsenic was at the level of the controls.<br><br>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.<br><br>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.<br><br>In summary there is no effect of gallium arsenide on fertility relevant to classification and labeling.<br>**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).<br>**…**<br><br>**10 REFERENCES**<br>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.<br>…<br>Donayre et al. Endocrine studies at high altitude. IV. Changes in the semen of men. J Reprod Fertil 16, 1968, 55-58.<br>**…**<br>Farias et al. Oxidative stress in rat testis and epididymis under intermittent hypobaric hypoxia: protective role of ascorbate supplementation. J Androl 31, 2010, 314-321.<br>Farias et al. Effects of chronic hypobaric hypoxia on testis histology and round spermatid oxidative metabolism. Andrologia 37, 2005, 47-52.<br>**…**<br>Gasco et al. Effect of high altitude exposure on spermatogenesis and epididymal sperm count in male rats. Andrologia 35, 2003, 368-374.<br>**…**<br>Goering et al. Effect of intratracheal gallium arsenide administration on delta-aminolevulinic acid dehydratase in rats: | |

| Date | Country/ Person/ Organisation/ MSCA | Comment | RAC response |
|---|---|---|---|
| | | relationship to urinary excretion of aminolevulinic acid. Toxicol Appl Pharmacol 92, 1988, 179-193.<br>**…**<br>Gosney. Atrophy of Leydig cells in the testes of men with longstanding chronic bronchitis and emphysema. Thorax 42, 1987, 615-619.<br>Gosney. Effects of hypobaric hypoxia on the Leydig cell population of the testis of the rat. J Endocrinol 103, 1984, 59-62.<br>…<br>Liao et al. Hypobaric hypoxia causes deleterious effects on spermatogenesis in rats. Reproduction 139, 2010, 1031-1038.<br>…<br>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.<br>…<br>Omura et al. Toxic effects of gallium arsenide on sperm in rats by repeated intratracheal instillations. Sangyo Eiseigaku Zasshi (J Occup Health) 37, 1995, 165-166.<br>Omura et al. Testicular toxicity of gallium arsenide, indium arsenide, and arsenic oxide in rats by repetitive intratracheal instillation. Fundam Appl Toxicol 32, 1996a, 72-78.<br>Omura et al. Testicular toxicity evaluation of arsenic-containing binary compound semiconductors, gallium arsenide and indium arsenide, in hamsters. Toxicol Lett 16, 1996b, 123-129.<br>Osaki et al. Association of adrenal pheochromocytoma and lung pathology in inhalation studies with particulate compounds in the male F344 rat--the National Toxicology Program experience. Toxicol Pathol 30, 2002, 263-270.<br>…<br>Semple et al. Sex hormone suppression and sexual impotence in hypoxic pulmonary fibrosis. Thorax 39, 1984, 46-51.<br>Shevantaeva and Kosyuga. Effect of acute hypobaric hypoxia on spermatogenesis and lactate concentration in testicular tissue of male albino rats. Bull Exp Biol Med 141, 2006, 20-22.<br>…<br>Tanaka et al. Comparative study of the toxic effects of gallium arsenide, indium arsenide and arsenic trioxide following intratracheal instillations to the lung of Syrian golden hamsters. Fukuoka Acta Med 91, 2000, 21-33.<br>…<br>Verratti et al. Evidence that chronic hypoxia causes reversible impairment on male fertility. Asian J Androl 10, 2008, 602-606.<br>…<br>Webb et al. In vitro solubility and in vivo toxicity of gallium arsenide. Toxicol Appl Pharmacol 76, 1984, 96-104. | |

| Date | Country/ Person/ Organisation/ MSCA | Comment | RAC response |
|---|---|---|---|
| | | Webb et al. Comparative pulmonary toxicity of gallium arsenide, gallium(III) oxide, or arsenic(III) oxide intratracheally instilled into rats. Toxicol Appl Pharmacol 82, 1986, 405-416.<br>Webb et al. Pulmonary clearance and toxicity of respirable gallium arsenide particulates intratracheally instilled into rats. Am Ind Hyg Assoc J 48, 1987, 660-667.<br>…<br>**Gallium Arsenide**<br>**Position of United Monolithic Semiconductors GmbH on the**<br>**Opinion of the Committee for Risk Assessment**<br>**proposing harmonized classification and labelling**<br>**at the EU level for GaAs adopted May 25, 2010**<br>G. Hirschle, FE Quality-/Environmental Manager April 21, 2011<br>…<br>**Please find below our serious concerns described in detail:**<br>…<br>**2) Content of RAC opinion:**<br>…<br>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.<br>…<br>**Conclusion:**<br>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<br>- Carc. 1A - H350 and ignoring a threshold and<br>- Repr. 1B – H360F.<br><br>References:<br>- Dr. Ernst M. Bomhard: *Comments on the RAC Opinion on Gallium Arsenide*, Jan. 2011<br>- Dr. Ernst M. Bomhard, G*allium Arsenide*: On the Subject of Carcinogenicity and Fertility Effects, 08. April 2011<br><br>… | |

| Date | Country/ Person/ Organisation/ MSCA | Comment | RAC response |
|---|---|---|---|
| 21/04/2011 | Germany / Sylvi Claussnitzer / WirtschaftsVereinigung Metalle / Industry or trade association | **…**<br>**Comments on second public consultation for a harmonised classification & labelling for Gallium arsenide (*2011-04-21)***<br>**Substance name: Gallium arsenide**<br>**CAS Number: 1303-00-0**<br>**EC Number: 215-114-8**<br>**…**<br>3) Reprotox analysis should be reopened<br>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.<br><br>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. | …<br>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 | Germany / Birgit Müller / Freiberger Compound Materials GmbH / Company-Manufacturer | **…**<br>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.<br><br>…<br>**Gallium Arsenide**<br>**Position ot Freiberger Compounds Materials GmbH on the**<br>**Opinion of the Committee for Risk Assessment proposing harmonized classitication and labeling at the EU level for GaAs adopted 25 May 2010** | **…**<br>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 |

| Date | Country/ Person/ Organisation/ MSCA | Comment | RAC response |
|---|---|---|---|
| | | April 21.2011<br>…<br>b) Data regarding reprotoxicity<br>(i) Omission of findings<br>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, 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.<br><br>(ii) lncorrec interpretation – alleged primary reprotoxic effects<br><br>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."<br><br>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.<br><br>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<br>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 | document.<br>… |

| Date | Country/ Person/ Organisation/ MSCA | Comment | RAC response |
|---|---|---|---|
| | | supported by the potential of gallium to accumulate in rat testis following inhalation exposure (see toxicokinetics section in the Background Document)''<br><br>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<br>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<br>the effect is not primary either.<br><br>(iii) Incomplete<br>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.<br>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.<br>With best regards,<br>Birgit Müller<br>REACh Coordinator<br>…<br>**Expert Report Gallium Arsenide**<br>**On the Subject of Carcinogenicity and Fertility Effects by Dr. Ernst M. Bomhard**<br>REACh ChemConsult GmbH, Dresden (*2011-04-21)*<br>**Prof. Dr. Michael Iatropoulos**<br>Dept of Pathology, New York Medical College<br>Valhalla, NY 10595, USA<br>**Prof. Dr. Gary Williams** | |

| Date | Country/ Person/ Organisation/ MSCA | Comment | RAC response |
|---|---|---|---|
| | | Dept of Pathology, New York Medical College<br>Valhalla, NY 10595, USA<br>…<br>**2. NEW RELEVANT SCIENTIFIC EVIDENCE NOT INCLUDED IN THE IARC AND RAC BACKGROUND DOCUMENT 5**<br>**3. IDENTIFIED OMISSIONS IN THE PRESENT BACKGROUND DOCUMENT 6**<br>…<br>**8. EVALUATION OF FERTILITY STUDIES WITH GALLIUM ARSENIDE 14**<br>…<br>**2 "NEW RELEVANT SCIENTIFIC EVIDENCE" NOT INCLUDED IN THE IARC/ATSDR AND RAC BACKGROUND DOCUMENT**<br><br>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.<br>…<br>_ on the interpretation of the effects on male fertility parameters<br>• 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.<br>…<br>**3. IDENTIFIED "OMISSIONS" IN THE PRESENT BACKGROUND DOCUMENT**<br>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.<br>• for example:<br>…<br>• the results on male fertility parameters (as well as haematological parameters) have not been put into a perspective with the chronic lung toxicity.<br>• 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.<br>• 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.<br>…<br>**8. EVALUATION OF FERTILITY STUDIES WITH GALLIUM ARSENIDE** | |

| Date | Country/ Person/ Organisation/ MSCA | Comment | RAC response |
|---|---|---|---|
| | | Four studies reveal effects on spermatozoa and testes: two studies in rats and hamsters with 16 i.t. instillations 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).<br><br>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.<br><br>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 .<br><br>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<br>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 | |

| Date | Country/ Person/ Organisation/ MSCA | Comment | RAC response |
|---|---|---|---|
| | | 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<br>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.<br><br>In summary there is no effect of gallium arsenide on male fertility relevant to classification and labeling.<br><br>**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).<br><br>**9. REFERENCES**<br>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.<br>…<br>Chitambar. Medical applications and toxicities of gallium compounds. Int J Environ Res Public Health 7, 2010, 2337-2361.<br>**…**<br>Donayre et al. Endocrine studies at high altitude. IV. Changes in the semen of men. J Reprod Fertil 16, 1968, 55-58.<br>**…**<br>Farias et al. Oxidative stress in rat testis and epididymis under intermittent hypobaric hypoxia: protective role of ascorbate supplementation. J Androl 31, 2010, 314-321.<br>Farias et al. Effects of chronic hypobaric hypoxia on testis histology and round spermatid oxidative metabolism. Andrologia 37, 2005, 47-52.<br>**…**<br>Gasco et al. Effect of high altitude exposure on spermatogenesis and epididymal sperm count in male rats. Andrologia 35, 2003, 368-374.<br>**…** | |

| Date | Country/ Person/ Organisation/ MSCA | Comment | RAC response |
|---|---|---|---|
| | | Gosney. Atrophy of Leydig cells in the testes of men with longstanding chronic bronchitis and emphysema. Thorax 42, 1987, 615-619.<br>Gosney. Effects of hypobaric hypoxia on the Leydig cell population of the testis of the rat. J Endocrinol 103, 1984, 59-62.<br>…<br>Liao et al. Hypobaric hypoxia causes deleterious effects on spermatogenesis in rats. Reproduction 139, 2010, 1031-1038.<br>…<br>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.<br>…<br>Omura et al. Toxic effects of gallium arsenide on sperm in rats by repeated intratracheal instillations. Sangyo Eiseigaku Zasshi (J Occup Health) 37, 1995, 165-166.<br>Omura et al. Testicular toxicity of gallium arsenide, indium arsenide, and arsenic oxide in rats by repetitive intratracheal instillation. Fundam Appl Toxicol 32, 1996a, 72-78.<br>Omura et al. Testicular toxicity evaluation of arsenic-containing binary compound semiconductors, gallium arsenide and indium arsenide, in hamsters. Toxicol Lett 16, 1996b, 123-129.<br>Osaki et al. Association of adrenal pheochromocytoma and lung pathology in inhalation studies with particulate compounds in the male F344 rat--the National Toxicology Program experience. Toxicol Pathol 30, 2002, 263-270.<br>…<br>Semple et al. Sex hormone suppression and sexual impotence in hypoxic pulmonary fibrosis. Thorax 39, 1984, 46-51.<br>Shevantaeva and Kosyuga. Effect of acute hypobaric hypoxia on spermatogenesis and lactate concentration in testicular tissue of male albino rats. Bull Exp Biol Med 141, 2006, 20-22.<br>…<br>Verratti et al. Evidence that chronic hypoxia causes reversible impairment on male fertility. Asian J Androl 10, 2008, 602-606.<br>… | |