Health Council of the Netherlands

Indium and indium compounds

Evaluation of the effects on reproduction, recommendation for classification

Gezondheidsraad
Health Council of the Netherlands

Aan de staatssecretaris van Sociale Zaken en Werkgelegenheid

Onderwerp : aanbieding advies *Indium and indium compounds*
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Geachte staatssecretaris,

Graag bied ik u hierbij het advies aan over de effecten van *Indium en indiumverbindingen* op de vruchtbaarheid en het nageslacht; het betreft ook effecten op de lactatie en via de moedermelk op de zuigeling. Dit advies maakt deel uit van een uitgebreide reeks waarin voor de voortplanting giftige stoffen worden geclassificeerd volgens richtlijnen van de Europese Unie. Het gaat om stoffen waaraan mensen tijdens de beroepsuitoefening kunnen worden blootgesteld.

Dit advies is opgesteld door een vaste commissie van de Gezondheidsraad, de Subcommissie Classificatie Reproductietoxische stoffen. Het is vervolgens getoetst door de Beraadsgroep Gezondheid en omgeving van de raad.

Ik heb dit advies vandaag ter kennisname toegezonden aan de staatssecretaris van Infrastructuur en Milieu en aan de minister van Volksgezondheid, Welzijn en Sport.

Met vriendelijke groet,

prof. dr. W.A. van Gool,
voorzitter

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Indium and indium compounds

Evaluation of the effects on reproduction, recommendation for classification

Subcommittee on the Classification of Reproduction Toxic Compounds
A Committee of the Health Council of the Netherlands

to:

the State Secretary of Social Affairs and Employment

No. 2012/17, The Hague, October 30, 2012

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INAHTA

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Contents

Samenvatting

In het voorliggende advies heeft de Gezondheidsraad indium en indiumverbindingen onder de loep genomen. Indium wordt gebruikt in lagers voor auto's en vliegtuigen, in soldeer en legeringen en in kernreactoren. Indium en indiumverbindingen, inclusief indiumantimonide (InSb), indiumarsenide (InAs) en indiumfosfide (InP), worden ook gebruikt in halfgeleiders, transistoren en transistor materialen. Indiumoxide wordt gebruikt om glas te kleuren. Indiumsulfaat wordt gebruikt voor het galvaniseren van materiaal en radioisotopen van indium en indiumverbindingen (inclusief indiumtrichloride) worden gebruikt in de behandeling van kanker en in diagnostische beeldvorming van organen. Dit advies past in een reeks adviezen waarin de Gezondheidsraad op verzoek van de minister van Sociale Zaken en Werkgelegenheid de effecten van stoffen op de voortplanting beoordeelt. Het gaat vooral om stoffen waaraan mensen tijdens de beroepsuitoefening kunnen worden blootgesteld. De Subcommissie Classificatie reproductietoxische stoffen van de Commissie Gezondheid en beroepsmatige blootstelling aan stoffen van de raad, hierna aangeduid als de commissie, kijkt zowel naar effecten op de vruchtbaarheid van mannen en vrouwen als naar effecten op de ontwikkeling van het nageslacht. Daarnaast worden effecten op de lactatie en via de moedermelk op de zuigeling beoordeeld.

Op basis van Verordening (EG) 1272/2008 van de Europese Unie doet de commissie een voorstel voor classificatie. De commissie komt tot de volgende aanbevelingen:

- indium(3^+)zouten (mits goed oplosbaar):
  - voor effecten op de fertiliteit adviseert de commissie om indium(3+)zouten (mits goed oplosbaar) niet te kenmerken wegens onvoldoende geschikte gegevens
  - voor effecten op de ontwikkeling adviseert de commissie indium(3+)zouten (mits goed oplosbaar) in categorie 1B (*stoffen waarvan verondersteld wordt dat zij toxisch zijn voor de menselijke voortplanting*) te classificeren en met H360D (*kan het ongeboren kind schaden*) te kenmerken
  - voor effecten op of via lactatie, adviseert de commissie om indium(3+)zouten (mits goed oplosbaar) niet te kenmerken wegens onvoldoende geschikte gegevens.
- indiumphosphide en indiumarsenide:
  - voor effecten op de fertiliteit adviseert de commissie om indiumphosphide en indiumarsenide in categorie 2 (*stoffen die ervan verdacht worden dat zij toxisch zijn voor de menselijke voortplanting*) te classificeren en met H361f (*wordt ervan verdacht de vruchtbaarheid te schaden*) te kenmerken
  - voor effecten op de ontwikkeling adviseert de commissie indiumphosphide en indiumarsenide niet te kenmerken wegens onvoldoende geschikte gegevens
  - voor effecten tijdens of via lactatie, adviseert de commissie om indiumphosphide en indiumarsenide niet te kenmerken wegens onvoldoende geschikte gegevens.
- onoplosbare indiumzouten en slecht oplosbare indiumzouten anders dan indiumphosphide en indiumarsenide:
  - wegens onvoldoende geschikte gegevens adviseert de commissie om deze indiumzouten niet te kenmerken voor effecten op fertiliteit en ontwikkeling en effecten op of via lactatie.

Executive summary

In the present report, the Health Council of the Netherlands reviewed indium and indium compounds. Indium is used in bearings for cars and aircrafts, in solders and low-melting alloys, and in nuclear reactor control rods. Indium and its compounds, including indium antimonide (InSb), indium arsenide (InAs), and indium phosphide (InP), find application in semiconductor devices, transistors, and transistor materials. Indium oxide is used for colouring glass. Indium sulphate is used in electroplating, and radioisotopes of indium and indium compounds (including indium trichloride) are employed in the treatment of cancer and in diagnostic imaging of body organs. This report is part of a series in which the Health Council evaluates the effects of substances on reproduction at the request of the Minister of Social Affairs and Employment. It mainly concerns substances to which man can be occupationally exposed. The Subcommittee on the Classification of Reproduction Toxic Substances of the Dutch Expert Committee on Occupational Safety of the Health Council, hereafter called the Committee, evaluates the effects on male and female fertility and on the development of the progeny. Furthermore, the Committee considers the effects of a substance on lactation and on the progeny via lactation.

The Committee recommends classification according to Regulation (EC) 1272/2008 of the European Union. These recommendations are:

- indium (3^+) salts (if well soluble):

    - for effects on fertility, the Committee recommends not classifying indium (3^+) salts (provided they are well soluble) due to a lack of appropriate data
    - for effects on development, the Committee recommends classifying indium (3^+) salts (provided they are well soluble) in category 1B (*presumed human reproductive toxicant*) and labelling with H360D (*may damage the unborn child*)
    - for effects on or via lactation, the Committee recommends not labelling indium (3^+) salts (provided they are well soluble) due to a lack of appropriate data.
- indium phosphide and indium arsenide:
    - for effects on fertility, the Committee recommends classifying indium phosphide and indium arsenide in category 2 (*suspected human reproductive toxicant*) and labelling with H361f (*suspected of damaging fertility*)
    - for effects on development, the Committee recommends not classifying indium phosphide and indium arsenide due to a lack of appropriate data
    - for effects on or via lactation, the Committee recommends not labelling indium phosphide and indium arsenide due to a lack of appropriate data.
- insoluble indium salts and poorly soluble indium salts other than indium phosphide and indium arsenide:
    - for effects on fertility and development and for effects on or via lactation, the Committee recommends not classifying insoluble indium salts and poorly soluble indium salts other than indium phosphide and indium arsenide due to a lack of appropriate data.

Chapter 1

Scope

1.1 Background

As a result of the Dutch regulation on registration of compounds toxic to reproduction that came into force on 1 April 1995, the Minister of Social Affairs and Employment requested the Health Council of the Netherlands to classify compounds toxic to reproduction. This classification is performed by the Health Council's Subcommittee on the Classification of Reproduction Toxic Substances of the Dutch Expert Committee on Occupational Safety (DECOS). The classification is performed according to European Union Regulation (EC) 1272/ 2008 on classification, labelling and packaging (CLP) of substances and mixtures. The CLP guideline is based on the Globally Harmonised System of Classification and Labelling of Chemicals (GHS). The Subcommittee's advice on the classification will be applied by the Ministry of Social Affairs and Employment to extend the existing list of compounds classified as reproductive toxicant (category 1A and B and 2) or compound with effects on or via lactation.

1.2 Committee and procedure

This document contains the classification of indium and indium compounds by the Health Council's Subcommittee on the Classification of Reproduction Toxic Substances, hereafter called the Committee. The members of the Committee are

listed in Annex A. The submission letter (in English) to the State Secretary can be found in Annex B.

In 2012, the President of the Health Council released a draft of the report for public review. The individuals and organizations that commented on the draft report are listed in Annex C. The Committee has taken these comments into account in deciding on the final version of the report.

The classification is based on the evaluation of published human and animal studies concerning adverse effects with respect to fertility and development as well as lactation of the above mentioned compound.

Classification for reproduction (fertility (F) and development (D)):	
Category 1	Known or presumed human reproductive toxicant (H360(F/D))
Category 1A	Known human reproductive toxicant
Category 1B	Presumed human reproductive toxicant
Category 2	Suspected human reproductive toxicant (H361(f/d))
No classification for effects on fertility or development	
Classification for lactation:	
	Effects on or via lactation (H362)
	No labelling for lactation

The classification and labelling of substances is performed according to the guidelines of the European Union (Regulation (EC) 1272/2008) presented in Annex D. The classification of compounds is ultimately dependent on an integrated assessment of the nature of all parental and developmental effects observed, their specificity and adversity, and the dosages at which the various effects occur. The guideline necessarily leaves room for interpretation, dependent on the specific data set under consideration. In the process of using the regulation, the Committee has agreed upon a number of additional considerations (see Annex E).

1.3 Effects on or via lactation

The recommendation for classifying substances for effects on or via lactation is also based on Regulation (EC) 1272/2008. The guideline defines that substances which are absorbed by women and have been shown to interfere with lactation or which may be present (including metabolites) in breast milk in amounts sufficient to cause concern for the health of a breastfed child, shall be classified and labelled. Unlike the classification of substances for fertility and

developmental effects, which is based on hazard identification only (largely independent of dosage), the labelling for effects on or via lactation is based on risk characterization and therefore, it also includes consideration of the level of exposure of the breastfed child.

Consequently, a substance should be labelled for effects on or via lactation when it is likely that the substance would be present in breast milk at potentially toxic levels. The Committee considers a concentration of a compound as potentially toxic to the breastfed child when this concentration leads to exceeding the exposure limit for the general population, e.g. the acceptable daily intake (ADI).

1.4 Data

Literature searches were conducted in the on-line databases Toxline, Toxcenter, and Medline starting from 1950 up to 2008, and an update in PubMed in October 2011. Literature was selected primarily on the basis of the text of the abstracts. Publications cited in the selected articles, but not selected during the primary search, were reviewed if considered appropriate. In addition, handbooks and a collection of most recent reviews were consulted. References are divided in literature cited and literature consulted but not cited.

The Committee describes both the human and animal studies in the text. The animal data are described in more detail in Annex F as well. Of each study, the quality of the study design (performed according to internationally acknowledged guidelines) and the quality of documentation are considered.

1.5 Presentation of conclusions

The classification is given with key effects, species and references specified. In case a substance is not classified as toxic to reproduction, one of two reasons is given:

- lack of appropriate data precludes assessment of the compound for reproductive toxicity
- sufficient data show that no classification for toxic to reproduction is indicated.

1.6 Final remark

The classification of compounds is based on hazard evaluation only (Niesink et al., 1995[11]), which is one of a series of elements guiding the risk evaluation process. The Committee emphasizes that for derivation of health-based occupational exposure limits these classifications should be placed in a wider context. For a comprehensive risk evaluation, hazard evaluation should be combined with dose-response assessment, human risk characterization, human exposure assessment, and recommendations of other organizations.

Chapter 2

Indium and insoluble indium compounds

2.1 Introduction

name	:	indium
CAS number	:	7440-74-6
EINECS-number	:	231-180-0
synonyms	:	-
appearance	:	soft, white metal with bluish tinge
use	:	in bearing alloys for cars and aircrafts; as a thin film on moving surfaces made from other metals; in dental alloys; in semiconductor research; in nuclear reactor control rods (in the form of a Ag-In-Cd alloys)
chemical formula	:	In
molecular weight	:	114.82
boiling point	:	2072 °C
melting point	:	156.60 °C
solubility	:	soluble in acids, insoluble in alkalis

name	:	indium phosphide
CAS-no	:	22398-80-7
EINECS-number	:	244-959-5
synonyms	:	indium monophosphide
appearance	:	brittle mass with metallic appearance
use	:	semiconductors such as indium phosphide for laser diodes used in fiber optic communication systems.
chemical formula	:	InP
molecular weight	:	145.79

melting point	:	1070 °C
solubility	:	insoluble in hot or cold water; soluble in acids; very slightly soluble in sodium hydroxide
EU classification	:	H350, H371, H361f*

* proposal of the EC Committee for Risk Assessment[2]

name	:	indium arsenide
CAS number	:	1303-11-3
EINECS-number	:	215-115-3
synonyms	:	indium monoarsenide
appearance	:	grey cubic crystals
use	:	application in semiconductor devices, transistors, transistor materials.
chemical formula	:	InAs
molecular weight	:	189.740
melting point	:	942 °C
solubility	:	low solubility in water
EU classification		H331; H301*

* concerns arsenic compounds with the exception of those specified elsewhere in Annex VI to Regulation (EC) No 1272/2008

name	:	indium oxide
CAS number	:	1312-43-2
EINECS-number	:	215-193-9
synonyms	:	indium sesquioxide, indium trioxide, indium (III) oxide, diindium trioxide
appearance	:	white to pale-yellow powder
use	:	used for colouring glass
chemical formula	:	In_2O_3
molecular weight	:	277.6
solubility	:	insoluble in water; soluble in hot mineral acids

Data from ECB[3], HSDB[10], and Merck[16]

The toxicity of indium compounds is dependent on the form (solubility) of the compound administered, the dose, and the route of administration. Ionic indium compounds, such as $InCl_3$, are bound to plasma proteins, such as transferrin and to a lesser extent albumin. Although they may cause focal liver necrosis at high doses, they primarily affect the proximal tubules of the kidney. Indium compounds target the endoplasmic reticulum of the liver and kidney, affecting both haem- and non-haem-dependent biochemical functions.[12]

2.2 Human studies

Fertility

No data are available regarding the effects of exposure to indium or insoluble indium compounds on human fertility.

Development

No data are available regarding the effects of exposure to indium or insoluble indium compounds on development in humans.

Lactation

No data are available regarding the excretion of 'indium' in breast milk or the effects of exposure to indium or insoluble indium compounds on infants during the lactation period.

2.3 Animal studies

Fertility and developmental toxicity studies with indium or indium compounds in laboratory animals are summarized in Annex F.

Fertility studies

Inhalation

The US National Toxicology Program (NTP) conducted toxicity and carcinogenicity inhalation studies in which rats and mice were exposed to particulate aerosols of indium phosphide with a mass median aerodynamic diameter of approximately 1.2 µm at concentrations of 0, 1, 3, 10, 30 or 100 mg/m^3, six hours/day, five days/week (week 1-4 and week 10-14) or seven days/week (week 5-9), for fourteen weeks, or at concentrations of 0, 0.03, 0.1 or 0.3 mg/m^3, six hours/day, five days/week, for 22 (0.1, 0.3 mg/m^3) or 105 weeks (0, 0.03 mg/m^3). Animals in the two higher concentration groups were maintained on filtered air from exposure termination at week 22 until the end of the studies. The two-year studies included an interim kill/examination at three months. In the fourteen-week studies, apart from the standard organ weight

recordings and histopathology, sperm motility and vaginal cytology parameters were evaluated in eight to ten animals exposed to 0, 3, 10 and 30 mg/m^3. In addition, indium testis concentrations were determined in rats in three animals of all experimental groups at five time points during exposure and at four time points during a sixteen-week post-exposure period.

In rats exposed to 100 mg/m^3, ovarian and uterine atrophy occurred in all (9/9) females. The ovaries were small with small follicles and corpora lutea and condensed stroma. Uterine horn diameters were decreased, and there were shrunken glands and stromal condensation. Large degenerating cells of testicular germinal epithelial origin were present within seminiferous tubules of the testes (5/10 males) and within the epididymides of all (10/10) males. The glandular epithelium was flattened and there was reduced secretory material (atrophy) within the prostate (10/10) and seminal vesicles (9/10 males). Relative testis weights were increased at concentrations ≥3 mg/ m^3 ($p<0.05$), while absolute testis weights were reduced at 100 mg/m^3 ($p<0.01$). No significant differences were noted in sperm morphology or vaginal cytology parameters. Indium was detected in the testes at much higher concentrations than in blood or serum, although still several orders of magnitude less than in the lung. In all groups, testicular indium concentrations increased with increasing exposure concentration throughout the exposure period, and, unlike blood and serum concentrations, continued to increase post-exposure, indicating that indium was accumulating in the testes over time.

Treatment caused statistically significant decreases in mean final body weights and body weight changes in all male groups and in females exposed to 100 mg/m^3. Apart from one male exposed to 100 mg/m^3, all animals survived. Besides the reproductive organs, several other organs were affected, especially the lungs.

In female mice exposed to 30 and 100 mg/ m^3, atrophy of the uterus (30 mg/m^3: 4/10; 100 mg/m^3: 8/10; controls: 0/10) and ovary (30 mg/m^3: 9/10; 100 mg/m^3: 9/10; controls: 0/9) was observed. Uterine atrophy consisted of a decreased uterine horn diameter, stromal condensation, and shrunken glands. Atrophic ovaries contained follicles but either entirely lacking or having only very few, poorly developed corpora lutea. In addition, testis weights were altered at 10 mg/m^3 (relative testis weight increased, $p<0.05$) and 30 mg/m^3 (absolute testis weight decreased, relative testis weight increased, both $p<0.01$). No significant differences were noted in sperm morphology or vaginal cytology parameters.

All mice exposed to 100 mg/m^3 were removed moribund during week 7 through 11. Also one male and four females exposed to 30 mg/m^3 died before the

end of the study. Final mean body weights and mean body weight gains were statistically significantly decreased in males exposed to concentrations ≥3 mg/m^3 and in females exposed to 10 or 30 mg/m^3; males exposed to 30 mg/m^3 lost weight during the study. Effects observed on other than the reproductive organs were generally similar but more severe than those seen in rats at similar exposures.

In the two-year study, there were no remarkable findings upon histological three-month interim and two-year evaluation of the genital systems of male and female rats and mice exposed to 0.003, 0.01 and 0.3 mg/m^3.[12]

The Committee notes that the animals of the latter groups were exposed for only 22 weeks and examined after a 83-week exposure-free period.

Intratracheal instillation

Omura et al. (1996) exposed male rats (n=8) by intratracheal instillation to doses of indium arsenide of 7.7 mg/kg bw, twice/week for eight weeks. Twenty-four hours after the final instillation, animals were sacrificed and testes and epididymides were removed, weighted and examined for sperm characteristics. Treatment did not affect absolute or relative weights of testes and epididymides and absolute and relative spermatid counts. Concerning the epididymal sperm counts, there were no changes in the sperm counts of the whole epididymis and of the head, but in the epididymal body plus tail a 16% reduction ($p<0.05$) was found. Morphological examination did not reveal increased incidences of sperm abnormalities.[14]

In a similar study, Omura et al. (1996) exposed male Syrian golden hamsters (n=8) to indium arsenide according to the same protocol. However, treatment was discontinued after the 14th instillation since three hamsters died or were euthanized due to emaciation while the remaining five animals exhibited a significant body weight loss. Treatment did not affect absolute weights of testes and epididymides but relative weights were increased ($p<0.05$). No changes were found in epididymidal sperm counts or upon histological evaluation of the testes. Serum concentrations for indium and arsenic, measured at study termination, were 19.5 and 0.3 µmol/L, respectively.[13]

Omura et al. (2000) exposed male Syrian hamsters to indium phosphide or indium arsenide (3 and 4 mg/kg bw, respectively, twice/week) by intratracheal instillation for eight weeks. Animals were analysed serially over a two-year period (weeks 0-88 after the last instillation). Indium phosphide significantly

decreased body weight (80-90% of controls during post-exposure weeks 16-64), testis weight, and epididymis weight (60-70% of control weight between post-exposure weeks 16 and 64) and caudal sperm count (already immediately after last instillation, going down to 40-50% of control value between post- exposure weeks 16-64). Reproductive organ weights and sperm counts returned to control levels 88 weeks after exposure. In addition, severe histopathological changes in the testes were observed. From post-exposure weeks 16 to 64, histopathological alterations were observed in 30-50% of seminiferous tubuli (vacuolization), compared to 14% in the control group. Exposure to indium arsenide resulted in similar, but more severe effects, probably due to the fact that serum indium concentrations in the arsenide group were more than twice as high as those in the phosphide group. There were statistically significant decreases in body weight from post-exposure week 0 to the end of the follow up period (70% of controls). Reproductive organ weights were also statistically significantly reduced from directly after the last instillation until the end of the follow-up period (30-50% of control values from post-exposure weeks 16-88). In addition, caudal sperm counts were already statistically significantly decreased at post-exposure week 0, and decreased even further between post-exposure weeks 16 and 88 (10-30% of control values). Furthermore, the frequencies of seminiferous tubuli with histopathological changes were increased from post-exposure weeks 0 to 88 (statistically significant from post-exposure weeks 16-88; 70-90% vs. 14% in controls). Effects on organs other than reproductive organs were not analysed.[15]

Oral

No data are available regarding the effects of oral exposure to indium or insoluble indium compounds on fertility in laboratory animals.

Developmental toxicity studies

Inhalation

The NTP (2001) conducted developmental toxicity studies as part of the overall toxicity assessment of inhalation exposure to indium phosphide. Rats and mice were exposed to concentrations of indium phosphide of 0, 1, 10 or 100 mg/m^3 on gestational days 4-19.

In rats, exposure to indium phosphide did not induce maternal toxicity other than concentration-related increases in lung weights. Foetal toxicity,

malformations, or effects on any developmental parameters were not observed either.

In mice, exposure to 100 mg/m^3 resulted in early deaths, reduced body weight gain (although not statistically significant), listless appearance and laboured breathing. Lung weights were statistically significantly increased in all exposed mice. In some foetuses of the high-concentration group, renal haemorrhage was observed, but no foetal toxicity, malformations or developmental effects could be attributed to exposure.[12]

Oral

No data are available regarding the effects of oral exposure to indium or insoluble indium compounds on development in laboratory animals.

Lactation

No animal data are available on the excretion of 'indium' in breast milk or on effects of indium of insoluble indium compounds in pups during the lactation period.

2.4 Conclusion

Fertility

No data are available regarding the potential effects of indium or insoluble indium compounds on human fertility.

Inhalation studies with indium phosphide in rats and mice[12], and intratracheal instillation studies with indium phosphide in hamsters[15] and with indium arsenide in rats[14] and hamsters[13,15] resulted in decreased reproductive organ weight in males and atrophy of the reproductive organs in males as well as in females. In addition, caudal epididymal sperm count was decreased and severe histopathological changes in the testes were observed. Although general toxicity was also observed at doses that affect the reproductive organs, the accumulation of indium phosphide in the testes indicates a direct effect on reproductive organs. Although the study results indicate that indium is at least partly responsible for the toxic effects observed in the reproductive organs, it cannot be excluded that phosphide and arsenide also play a role in the reproductive toxicity.

Therefore, the Committee is of the opinion that for indium phosphide and indium arsenide classification in category 2 is justified. Due to a lack of data, other poorly soluble indium salts could not be assessed for effects on fertility.

Development

No data are available regarding the potential effects of indium or insoluble indium compounds on development in humans.

Inhalation exposure to up to 100 mg/m^3 indium phosphide did not result in developmental effects in rats and mice.[12] Although plasma indium levels were not mentioned in this study, it is possible that the lack of effects is caused by a low systemic exposure to indium following inhalation. In addition, indium phosphide has a low solubility in synthetic simulated body fluids.[5] If free indium ions are needed to elicit toxic effects, this can also explain the absence of developmental effects after administration of indium phosphide. Both theories are strengthened by the fact that, besides an increased lung weight, no maternal toxicity was observed in rats, and only after exposure to the highest dose tested in mice. Nevertheless, fertility effects were observed in an inhalation study with similar doses.[12]

In conclusion, there are no human data available to draw a conclusion regarding effects of indium or insoluble indium compounds on development. Since the background of the absence of developmental effects after exposure to indium phosphide is not clear, and no data are available concerning the developmental effects of indium arsenide, the Committee is of the opinion that a lack of appropriate data precludes assessment of indium phosphide and indium arsenide for effects on development. Due to a lack of data, other poorly soluble indium salts could not be assessed for effects on development either.

Lactation

No human or animal data are available regarding the secretion of indium or insoluble indium compounds in milk. Therefore, the Committee concluded that a lack of appropriate data precludes assessment of indium or insoluble indium compounds for effects on or via lactation.

Proposed classification for fertility

For indium phosphide and indium arsenide: category 2; H361f.

Lack of appropriate data precludes the assessment of other poorly soluble or insoluble indium salts on fertility.

Proposed classification for developmental toxicity

Lack of appropriate data precludes the assessment of indium phosphide and indium arsenide, or other poorly soluble or insoluble indium salts for effects on development.

Proposed labelling for effect on or via lactation

Lack of appropriate data precludes the assessment of indium or poorly soluble or insoluble indium compounds for effects on or via lactation.

Chapter 3

Soluble indium compounds

3.1 Introduction

name	:	indium trichloride
CAS-no	:	10025-82-8
EINECS-number	:	233-043-0
synonyms	:	indium chloride
appearance	:	yellowish, deliquescent crystals
use	:	in electroplating using a solution of the salt with dextrose and NaCN; radioisotopes in indium trichloride are used in the treatment of tumours and in organ scanning.
chemical formula	:	$InCl_3$
molecular weight	:	221.18
boiling point		800 °C
melting point	:	586 °C
solubility	:	soluble in water

name	:	indium nitrate
CAS-no	:	13465-14-0
EINECS-number	:	237-393-5
synonyms	:	indium trinitrate, indium(III) nitrate
appearance	:	colourless crystalline solid, powder no odour
chemical formula	:	$In(NO_3)_3$
molecular weight	:	300.82
melting point	:	100 °C
solubility	:	very soluble, hydrolyzes in water

name	:	indium sulfate
CAS-no	:	13464-82-9
EINECS-number	:	236-689-1
synonyms	:	indium trisulfate, diindium trisulfate, indium sequisulfate, indium(III) sulfate
appearance	:	white, hygroscopic powder
use	:	used in electroplating
chemical formula	:	$In_2(SO_4)_3$
molecular weight	:	517.8
melting point	:	600 °C
solubility	:	soluble in water

Data from ECB[3], HSDB[10], and Merck[16]

Indium is used in bearings for automobiles and aircrafts, in solders and low-melting alloys and in nuclear reactor control rods. Indium and its compounds find application in semiconductor devices, transistors and transistor materials. Indium sulfate is used in electroplating, and radioisotopes of indium and indium compounds (including indium trichloride) are employed in the treatment of cancer and in diagnostic imaging of body organs.[10]

The toxicity of indium compounds is dependent upon the form (solubility) of the compound administered, the dose and the route of administration. Ionic indium compounds, such as $InCl_3$, are bound to plasma proteins, such as transferrin and to a lesser extent albumin. Although they may cause focal liver necrosis at high doses, they primarily affect the proximal tubules of the kidney. Indium compounds target the endoplasmic reticulum of the liver and kidney, affecting both haem- and non-haem-dependent biochemical functions.[12]

3.2 Human studies

Fertility

No data are available regarding the effects of exposure to soluble indium compounds on human fertility.

Development

No data are available regarding the effects of exposure to soluble indium compounds on development in humans.

Lactation

No data are available regarding the excretion of 'indium' in breast milk or the effects of exposure to soluble indium compounds on infants during the lactation period.

3.3 Animal studies

Fertility studies

Gavage

Chapin et al. (1995) administered doses of indium trichloride of 0, 50, 150 or 250 mg/kg bw/day to mice (n=10/sex/group) from experimental days 1 to 20 (females) or 3 to 20 (males). Mice were mated during experimental day 7-11. Treatment did not cause effects on ovulation, fertilization or implantation sites or changes in male reproductive organ weights, sperm parameters or microscopic structure of testes and epididymides. Two females of the high-dose group died. Decreased body weight gains ($p<0.05$) were recorded in all treated female groups and mid- and high-dose males. The latter animals also had decreased absolute liver weights ($p<0.05$), but relative liver weights were not affected. In addition, high-dose males showed reduced lymphocyte and haemoglobin values.[1]

Developmental toxicity studies

Gavage

In the high-dose group in the experiment described above, Chapin et al. (1995) reported an approximately 50% decrease in the number of live implants and a trend toward more dead implants/dam.

In a concomitant study, pregnant mice (n=10/group) were given indium trichloride doses of 0, 50, 150 or 250 mg/kg bw/day on gestational days 8-14 or gestational days 6-15. When given during gestational days 8-14, reduced body weights were observed in the dams of the mid- and high-dose groups ($p<0.05$), but no further maternal toxicity was reported. At 250 mg/kg bw/day, the body weight of the pups on postnatal day 1 was reduced ($p<0.05$).

When administered during gestational days 6-15, body weight gains of the dams were not affected, but absolute and relative liver weights were reduced in the high-dose dams ($p<0.05$). In the two high-dose groups, there were dose-

related increases in early (not statistically significant) and late resorptions ($p<0.05$). In addition, at 250 mg/kg bw/day, there were changes in the number of live foetuses/litter (decrease), the number of dead foetuses/litter (increase) and the body weight of live foetuses (decrease) (all $p<0.05$). No statistically significant increases in skeletal or soft tissue abnormalities were found.[1]

Nakajima et al. (1998) treated pregnant rats with single doses of indium trichloride (0, 75, 150, 300 mg indium/kg bw) on gestational day 9. Foetuses were examined for growth and malformation on gestational day 20. In the pregnant rats, there were no toxicological signs including changes in body weight, food consumption and necropsy findings. In the high dose group, not statistically significant increases in foetal mortality (16% vs. 8.3% in controls) and in the number of foetuses with malformations of the tail (11.7% vs. 1.3%) and with skeletal malformations (10.3% vs. 0%) were observed. Indium concentrations in the serum of pregnant rats (approx. 1.6 µg/mL, for one to six hours after administration) showed low bioavailability of indium by oral administration, probably explaining the lack of developmental effects observed after oral exposure to indium.[8]

Ungváry et al. (2000) administered doses of indium trichloride of 0, 50, 100, 200 or 400 mg/kg bw/day to rats on gestational days 6-15. In a second study, single doses of 0 or 400 mg indium trichloride/kg bw/day were given on one of gestational days 8, 9, 10, 11, 12, 13, 14 and 15. Pups were examined on gestational day 21. A dose-dependent decrease in food intake and body weight gain was observed in the dams, being significant at doses ≥100 mg/kg bw/day ($p<0.05$). At 400 mg/kg bw/day, maternal toxicity was reported, including increased relative liver, brain and pancreas weights, statistically significantly decreased bilirubin concentrations and AST and ALT serum activities, and effects on kidneys (congestion; cortico-medullar haemorrhage). At doses ≥100 mg/kg bw/day, statistically significant increases were observed in the number of malformed foetuses (0.8%, 0.8%, 4.7%, 38.6%, 100% in control, 50, 100, 200, 400 mg/kg bw groups, respectively); the defects included tail and limb, neurocranial, viscerocranial and visceral anomalies. In addition, doses ≥200 mg/kg bw/day caused increased post-implantation loss (controls: 2.9%; 200 mg/kg bw: 23.6%; 400 mg/kg bw: 72.1%) and reduced foetal weight (both $p<0.05$). The NOAEL for developmental toxicity was 50 mg/kg bw/day.

After single oral doses of 400 mg/kg/day, reduced foetal body weight and retarded growth of the skeleton and internal organs of surviving foetuses was

observed regardless of the day of exposure, but effects were highest when given on gestational day 11 and 12.[17]

The developmental effects observed after single oral doses of 400 mg indium trichloride/kg bw reached statistical significance with less animals/group than used in the Nakajima *et al.* (1998) study and at a lower dose (expressed as mg indium/kg bw). The Committee could not find an obvious explanation for the difference in results between the study of Nakajima et al. (1998) and Ungváry et al. (2000).

In a similar study by Ungváry et al. (2000), indium trichloride (0, 50, 100 or 200 mg/kg bw/day) was administered to New Zealand rabbits on gestational days 6-20. Animals were examined on gestational day 30. At 200 mg/kg bw/day, maternal toxicity was observed. Food intake and body weight gain were significantly reduced ($p<0.05$), 4 out of 17 dams died, and autopsy and histological examination showed similar results as in highest dose rats. In addition, in the 200 mg/kg bw dose group, there were increases in the number of post-implantation losses (13.9%; controls: 1.1%) and in the frequencies of foetuses with skeletal retardation (7x; controls: 1 x) (both <0.05). Moreover, at doses of ≥100 mg/kg bw/day, gross renal anomalies (renal agenesia and ectopia renis; controls: 0 x; 100 mg/kg bw: 1+1; 200 mg/kg bw: 1+3) were reported, although this increase was not statistically significant. The NOAEL for developmental toxicity was 50 mg/kg bw/day.[17]

Intravenous

Single intravenous injections of doses of indium trichloride of 0.1-0.4 mg/kg bw into Wistar or Sprague Dawley rats on gestational days 9, 10 or 11 caused decreased foetal weights, increased foetal mortality and increased incidences of malformations and variations. Effects were dependent on time of administration, dose and strain. There were no signs of toxicity in the dams.[6-9]

Single intravenous injections of indium trichloride of 0.8 or 1.6 mg/kg bw into mice on gestational days 7, 8 or 9 induced reduced foetal weights at doses ≥0.8 mg/kg bw and foetal death at 1.6 mg/kg bw, but no gross malformations.[9]

When golden hamsters were injected with doses of indium nitrate of 0.5-20 mg/kg bw on gestational day 8 and their embryos recovered 4, 5 or 6 days later, a high incidence of skeletal malformations (at doses of 0,5 and 1.0 mg/kg bw) and mortality of all embryos (at ≥2 mg/kg bw) were observed.[4]

Lactation

No animal data are available on the excretion of 'indium' in breast milk or on effects of soluble indium compounds in pups during the lactation period.

3.4 Conclusion

Fertility

No data are available regarding the potential effects of soluble indium compounds on human fertility.

In an oral study in mice with indium trichloride (doses up to 250 mg/kg bw/day), no effects on ovulation, fertilization or implantation were observed in either of the dose groups, and no effects were found on microscopic structure of selected male tissues or reproductive parameters, whereas at doses ≥50 mg/kg general toxicity was observed in the parents (males as well as females).[1] Other fertility studies in mice or in other animal species with soluble indium (3^+) salts were not available.

Therefore, the Committee is of the opinion that a lack of appropriate data precludes assessment of soluble indium (3^+) compounds for effects on fertility.

Developmental toxicity

No data are available regarding the potential effects of soluble indium compounds on development in humans.

In animals, developmental toxicity was observed in rats, mice and rabbits after oral administration of indium trichloride. Increased resorptions were observed in mice at doses without maternal toxicity.[1] In addition, at oral doses of indium trichloride that induced slight maternal toxicity (restricted to reduced food intake and body weight gain), external malformations, visceral anomalies, skeletal malformations and skeletal variations were observed in rats.[17] At oral doses that induced reduced liver weights but no further toxicity in pregnant mice, the number of live foetuses/litter was decreased, while the number of dead foetuses/litter was increased.[1]

These findings were supported by intravenous studies in which injection of indium trichloride or nitrate induced similar effects in rats, mice or hamsters.[4,6-9]

The Committee is of the opinion that the developmental effects occurred independently from maternal toxicity. Therefore, based on the data from animal

studies the Committee recommends classification of soluble indium (3^+) salts in category 1B.

Lactation

No human or animal data are available regarding the secretion of soluble indium compounds in milk.

Therefore, the Committee concluded that a lack of appropriate data precludes assessment of soluble indium compounds for effects on or via lactation.

Proposed classification for fertility

Lack of appropriate data precludes the assessment of soluble indium (3^+) salts for effects on fertility.

Proposed classification for developmental toxicity

For soluble indium (3^+) salts: category 1B; H360D.

Proposed labelling for effect on or via lactation

Lack of appropriate data precludes the assessment of soluble indium compounds for effects on or via lactation.

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A	The Committee
B	The submission letter (in English)
C	Comments on the public draft
D	Regulation (EC) 1272/2008 of the European Community
E	Additional considerations to Regulation (EC) 1272/2008
F	Fertility and developmental toxicity studies

Annexes

Annex **A**

The Committee

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The first draft of the present document was prepared by dr. B. Tiesjema, of the National Institute for Public Health and the Environment (RIVM), Bilthoven, the Netherlands, by contract with the Ministry of Social Affairs and Employment.

The Health Council and interests

Members of Health Council Committees are appointed in a personal capacity because of their special expertise in the matters to be addressed. Nonetheless, it is precisely because of this expertise that they may also have interests. This in itself does not necessarily present an obstacle for membership of a Health Council Committee. Transparency regarding possible conflicts of interest is nonetheless important, both for the chairperson and members of a Committee and for the President of the Health Council. On being invited to join a Committee, members are asked to submit a form detailing the functions they hold and any other material and immaterial interests which could be relevant for the Committee's work. It is the responsibility of the President of the Health Council to assess whether the interests indicated constitute grounds for non-appointment. An advisorship will then sometimes make it possible to exploit the expertise of the specialist involved. During the inaugural meeting the declarations issued are discussed, so that all members of the Committee are aware of each other's possible interests.

Annex **B**

The submission letter (in English)

Subject	: Submission of the advisory report *Indium and indium compounds*
Your reference	: DGV/MBO/U-932342
Our reference	: U 7401 /HS/fs/543-C13
Enclosed	: 1
Date	: October 30, 2012

Dear State Secretary,

I hereby submit the advisory report on the effects of *Indium and indium compounds* on fertility and on the development of the progeny; it also concerns effects on lactation and on the progeny via lactation. This advisory report is part of an extensive series in which reproduction toxic substances are classified in accordance with European guidelines. This involves substances to which people may be exposed occupationally.

The advisory report was prepared by a permanent committee of the Health Council of the Netherlands, the Subcommittee on the Classification of Reproduction Toxic Compounds. The advisory report was consequently reviewed by the Health Council's Standing Committee on Health and the Environment.

Today I sent copies of this advisory report to the State Secretary of Infrastructure and the Environment and to the Minister of Health, Welfare and Sport, for their information.

Yours sincerely,

(signed)
Prof. dr. W.A. van Gool,
President

Annex C

Comments on the public draft

- T.J. Lenz, S.S. Leonard. National Institute for Occupational Safety and Health, Cincinnati OH, USA.

Annex **D**

Regulation (EC) 1272/2008 of the European Community

3.7 Reproductive toxicity

3.7.1 Definitions and general considerations

3.7.1.1 Reproductive toxicity includes adverse effects on sexual function and fertility in adult males and females, as well as developmental toxicity in the offspring. The definitions presented below are adapted from those agreed as working definitions in IPCS/EHC Document No 225, Principles for Evaluating Health Risks to Reproduction Associated with Exposure to Chemicals. For classification purposes, the known induction of genetically based heritable effects in the offspring is addressed in Germ Cell Mutagenicity (section 3.5), since in the present classification system it is considered more appropriate to address such effects under the separate hazard class of germ cell mutagenicity.

In this classification system, reproductive toxicity is subdivided under two main headings:

(a) adverse effects on sexual function and fertility;

(b) adverse effects on development of the offspring.

Some reproductive toxic effects cannot be clearly assigned to either impairment of sexual function and fertility or to developmental toxicity. Nonetheless, substances with these effects, or mixtures containing them, shall be classified as reproductive toxicants.

3.7.1.2 For the purpose of classification the hazard class Reproductive Toxicity is differentiated into:

- adverse effects
  - on sexual function and fertility, or
  - on development;
- effects on or via lactation.

3.7.1.3 Adverse effects on sexual function and fertility

Any effect of substances that has the potential to interfere with sexual function and fertility. This includes, but is not limited to, alterations to the female and male reproductive system, adverse effects on onset of puberty, gamete production and transport, reproductive cycle normality, sexual behaviour, fertility, parturition, pregnancy outcomes, premature reproductive senescence, or modifications in other functions that are dependent on the integrity of the reproductive systems.

3.7.1.4 Adverse effects on development of the offspring

Developmental toxicity includes, in its widest sense, any effect which interferes with normal development of the conceptus, either before or after birth, and resulting from exposure of either parent prior to conception, or exposure of the developing offspring during prenatal development, or postnatally, to the time of sexual maturation. However, it is considered that classification under the heading of developmental toxicity is primarily intended to provide a hazard warning for pregnant women, and for men and women of reproductive capacity. Therefore, for pragmatic purposes of classification, developmental toxicity essentially means adverse effects induced during pregnancy, or as a result of parental exposure. These effects can be manifested at any point in the life span of the organism. The major manifestations of developmental toxicity include (1) death of the developing organism, (2) structural abnormality, (3) altered growth, and (4) functional deficiency.

3.7.1.5 Adverse effects on or via lactation are also included in reproductive toxicity, but for classification purposes, such effects are treated separately (see Table 3.7.1 (b)). This is because it is desirable to be able to classify substances specifically for an adverse effect on lactation so that a specific hazard warning about this effect can be provided for lactating mothers.

3.7.2 Classification criteria for substances

3.7.2.1 Hazard categories

3.7.2.1.1 For the purpose of classification for reproductive toxicity, substances are allocated to one of two categories. Within each category, effects on sexual function and fertility, and on development, are considered separately. In addition, effects on lactation are allocated to a separate hazard category.

Table 3.7.1(a) Hazard categories for reproductive toxicants.

Categories		Criteria
CATEGORY 1		Known or presumed human reproductive toxicant Substances are classified in Category 1 for reproductive toxicity when they are known to have produced an adverse effect on sexual function and fertility, or on development in humans or when there is evidence from animal studies, possibly supplemented with other information, to provide a strong presumption that the substance has the capacity to interfere with reproduction in humans. The classification of a substance is further distinguished on the basis of whether the evidence for classification is primarily from human data (Category 1A) or from animal data (Category 1B).
	Category 1A	Known human reproductive toxicant The classification of a substance in Category 1A is largely based on evidence from humans.
	Category 1B	Presumed human reproductive toxicant The classification of a substance in Category 1B is largely based on data from animal studies. Such data shall provide clear evidence of an adverse effect on sexual function and fertility or on development in the absence of other toxic effects, or if occurring together with other toxic effects the adverse effect on reproduction is considered not to be a secondary non-specific consequence of other toxic effects. However, when there is mechanistic information that raises doubt about the relevance of the effect for humans, classification in Category 2 may be more appropriate.
CATEGORY 2		Suspected human reproductive toxicant Substances are classified in Category 2 for reproductive toxicity when there is some evidence from humans or experimental animals, possibly supplemented with other information, of an adverse effect on sexual function and fertility, or on development, and where the evidence is not sufficiently convincing to place the substance in Category 1. If deficiencies in the study make the quality of evidence less convincing, Category 2 could be the more appropriate classification. Such effects shall have been observed in the absence of other toxic effects, or if occurring together with other toxic effects the adverse effect on reproduction is considered not to be a secondary non-specific consequence of the other toxic effects.

Table 3.7.1(b) Hazard category for lactation effects.

EFFECTS ON OR VIA LACTATION
Effects on or via lactation are allocated to a separate single category. It is recognised that for many substances there is no information on the potential to cause adverse effects on the offspring via lactation. However, substances which are absorbed by women and have been shown to interfere with lactation, or which may be present (including metabolites) in breast milk in amounts sufficient to cause concern for the health of a breastfed child, shall be classified and labelled to indicate this property hazardous to breastfed babies. This classification can be assigned on the: (a) human evidence indicating a hazard to babies during the lactation period; and/or (b) results of one or two generation studies in animals which provide clear evidence of adverse effect in the offspring due to transfer in the milk or adverse effect on the quality of the milk; and/or (c) absorption, metabolism, distribution and excretion studies that indicate the likelihood that the substance is present in potentially toxic levels in breast milk.

3.7.2.2 Basis of classification

3.7.2.2.1 Classification is made on the basis of the appropriate criteria, outlined above, and an assessment of the total weight of evidence (see 1.1.1). Classification as a reproductive toxicant is intended to be used for substances which have an intrinsic, specific property to produce an adverse effect on reproduction and substances shall not be so classified if such an effect is produced solely as a non-specific secondary consequence of other toxic effects.

The classification of a substance is derived from the hazard categories in the following order of precedence: Category 1A, Category 1B, Category 2 and the additional Category for effects on or via lactation. If a substance meets the criteria for classification into both of the main categories (for example Category 1B for effects on sexual function and fertility and also Category 2 for development) then both hazard differentiations shall be communicated by the respective hazard statements. Classification in the additional category for effects on or via lactation will be considered irrespective of a classification into Category 1A, Category 1B or Category 2.

3.7.2.2.2 In the evaluation of toxic effects on the developing offspring, it is important to consider the possible influence of maternal toxicity (see section 3.7.2.4).

3.7.2.2.3 For human evidence to provide the primary basis for a Category 1A classification there must be reliable evidence of an adverse effect on reproduction in humans. Evidence used for classification shall ideally be from well conducted epidemiological studies which include the use of appropriate controls, balanced assessment, and due consideration of bias or confounding factors. Less rigorous data from studies in humans shall be supplemented with adequate data from studies in experimental animals and classification in Category 1B shall be considered.

3.7.2.3 Weight of evidence

3.7.2.3.1 Classification as a reproductive toxicant is made on the basis of an assessment of the total weight of evidence, see section 1.1.1. This means that all available information that bears on the determination of reproductive toxicity is considered together, such as epidemiological studies and case reports in humans and specific reproduction studies along with sub-chronic, chronic and special study results in animals that provide relevant information regarding toxicity to reproductive and related endocrine organs. Evaluation of substances chemically related to the substance under study may also be included, particularly when information on the substance is scarce. The weight given to the available evidence will be influenced by factors such as the quality of the studies, consistency of results, nature and severity of effects, the presence of maternal toxicity in experimental animal studies, level of statistical significance for inter-group differences, number of endpoints affected, relevance of route of administration to humans and freedom from bias. Both positive and negative results are assembled together into a weight of evidence determination. A single, positive study performed according to good scientific principles and with statistically or biologically significant positive results may justify classification (see also 3.7.2.2.3).

3.7.2.3.2 Toxicokinetic studies in animals and humans, site of action and mechanism or mode of action study results may provide relevant information which reduces or increases concerns about the hazard to human health. If it is conclusively demonstrated that the clearly identified mechanism or mode of action has no relevance for humans or when the toxicokinetic differences are so marked that it is certain that the hazardous property will not be expressed in humans then a substance which produces an adverse effect on reproduction in experimental animals should not be classified.

3.7.2.3.3 If, in some reproductive toxicity studies in experimental animals the only effects recorded are considered to be of low or minimal toxicological significance, classification may not necessarily be the outcome. These effects include small changes in semen parameters or in the incidence of spontaneous defects in the foetus, small changes in the proportions of common foetal variants such as are observed in skeletal examinations, or in foetal weights, or small differences in postnatal developmental assessments.

3.7.2.3.4 Data from animal studies ideally shall provide clear evidence of specific reproductive toxicity in the absence of other systemic toxic effects. However, if developmental toxicity occurs together with other toxic effects in the dam, the potential influence of the generalised adverse effects shall be assessed to the extent possible. The preferred approach is to consider adverse effects in the embryo/foetus first, and then evaluate maternal toxicity, along with any other factors which are likely to have influenced these effects, as part of the weight of evidence. In general, developmental effects that are observed at maternally toxic doses shall not be automatically discounted. Discounting devel-

opmental effects that are observed at maternally toxic doses can only be done on a case-by-case basis when a causal relationship is established or refuted.

3.7.2.3.5 If appropriate information is available it is important to try to determine whether developmental toxicity is due to a specific maternally mediated mechanism or to a non-specific secondary mechanism, like maternal stress and the disruption of homeostasis. Generally, the presence of maternal toxicity shall not be used to negate findings of embryo/foetal effects, unless it can be clearly demonstrated that the effects are secondary non-specific effects. This is especially the case when the effects in the offspring are significant, e.g. irreversible effects such as structural malformations. In some situations it can be assumed that reproductive toxicity is due to a secondary consequence of maternal toxicity and discount the effects, if the substance is so toxic that dams fail to thrive and there is severe inanition, they are incapable of nursing pups; or they are prostrate or dying.

3.7.2.4 Maternal toxicity

3.7.2.4.1 Development of the offspring throughout gestation and during the early postnatal stages can be influenced by toxic effects in the mother either through non-specific mechanisms related to stress and the disruption of maternal homeostasis, or by specific maternally-mediated mechanisms. In the interpretation of the developmental outcome to decide classification for developmental effects it is important to consider the possible influence of maternal toxicity. This is a complex issue because of uncertainties surrounding the relationship between maternal toxicity and developmental outcome. Expert judgement and a weight of evidence approach, using all available studies, shall be used to determine the degree of influence that shall be attributed to maternal toxicity when interpreting the criteria for classification for developmental effects. The adverse effects in the embryo/foetus shall be first considered, and then maternal toxicity, along with any other factors which are likely to have influenced these effects, as weight of evidence, to help reach a conclusion about classification.

3.7.2.4.2 Based on pragmatic observation, maternal toxicity may, depending on severity, influence development via non-specific secondary mechanisms, producing effects such as depressed foetal weight, retarded ossification, and possibly resorptions and certain malformations in some strains of certain species. However, the limited number of studies which have investigated the relationship between developmental effects and general maternal toxicity have failed to demonstrate a consistent, reproducible relationship across species. Developmental effects which occur even in the presence of maternal toxicity are considered to be evidence of developmental toxicity, unless it can be unequivocally demonstrated on a case-by-case basis that the developmental effects are secondary to maternal toxicity. Moreover, classification shall be considered where there is a significant toxic effect in the offspring, e.g. irreversible effects such as structural malformations, embryo/foetal lethality, significant post-natal functional deficiencies.

3.7.2.4.3 Classification shall not automatically be discounted for substances that produce developmental toxicity only in association with maternal toxicity, even if a specific maternally-mediated mechanism has been demonstrated. In such a case, classification in Category 2 may be considered more appropriate than Category 1. However, when a substance is so toxic that maternal death or severe inanition results, or the dams are prostrate and incapable of nursing the pups, it is reasonable to assume that developmental toxicity is produced solely as a secondary consequence of maternal toxicity and discount the developmental effects. Classification is not necessarily the outcome in the case of minor developmental changes, when there is only a small reduction in foetal/pup body weight or retardation of ossification when seen in association with maternal toxicity.

3.7.2.4.4 Some of the end points used to assess maternal effects are provided below. Data on these end points, if available, need to be evaluated in light of their statistical or biological significance and dose response relationship.

Maternal mortality:

an increased incidence of mortality among the treated dams over the controls shall be considered evidence of maternal toxicity if the increase occurs in a dose-related manner and can be attributed to the systemic toxicity of the test material. Maternal mortality greater than 10 % is considered excessive and the data for that dose level shall not normally be considered for further evaluation.

Mating index

(no. animals with seminal plugs or sperm/no. mated × 100) (*)

Fertility index

(no. animals with implants/no. of matings × 100)

Gestation length

(if allowed to deliver)

Body weight and body weight change:

Consideration of the maternal body weight change and/or adjusted (corrected) maternal body weight shall be included in the evaluation of maternal toxicity whenever such data are available. The calcula-

* () It is recognised that the Mating index and the Fertility index can also be affected by the male.

tion of an adjusted (corrected) mean maternal body weight change, which is the difference between the initial and terminal body weight minus the gravid uterine weight (or alternatively, the sum of the weights of the foetuses), may indicate whether the effect is maternal or intrauterine. In rabbits, the body weight gain may not be useful indicators of maternal toxicity because of normal fluctuations in body weight during pregnancy.

Food and water consumption (if relevant):

The observation of a significant decrease in the average food or water consumption in treated dams compared to the control group is useful in evaluating maternal toxicity, particularly when the test material is administered in the diet or drinking water. Changes in food or water consumption need to be evaluated in conjunction with maternal body weights when determining if the effects noted are reflective of maternal toxicity or more simply, unpalatability of the test material in feed or water.

Clinical evaluations (including clinical signs, markers, haematology and clinical chemistry studies):

The observation of increased incidence of significant clinical signs of toxicity in treated dams relative to the control group is useful in evaluating maternal toxicity. If this is to be used as the basis for the assessment of maternal toxicity, the types, incidence, degree and duration of clinical signs shall be reported in the study. Clinical signs of maternal intoxication include: coma, prostration, hyperactivity, loss of righting reflex, ataxia, or laboured breathing.

Post-mortem data:

Increased incidence and/or severity of post-mortem findings may be indicative of maternal toxicity. This can include gross or microscopic pathological findings or organ weight data, including absolute organ weight, organ-to-body weight ratio, or organ-to-brain weight ratio. When supported by findings of adverse histopathological effects in the affected organ(s), the observation of a significant change in the average weight of suspected target organ(s) of treated dams, compared to those in the control group, may be considered evidence of maternal toxicity.

3.7.2.5 Animal and experimental data

3.7.2.5.1 A number of internationally accepted test methods are available; these include methods for developmental toxicity testing (e.g. OECD Test Guideline 414), and methods for one or two-generation toxicity testing (e.g. OECD Test Guidelines 415, 416).

3.7.2.5.2 Results obtained from Screening Tests (e.g. OECD Guidelines 421 — Reproduction/ Developmental Toxicity Screening Test, and 422 — Combined Repeated Dose Toxicity Study with

Reproduction/Development Toxicity Screening Test) can also be used to justify classification, although it is recognised that the quality of this evidence is less reliable than that obtained through full studies.

3.7.2.5.3 Adverse effects or changes, seen in short- or long-term repeated dose toxicity studies, which are judged likely to impair reproductive function and which occur in the absence of significant generalised toxicity, may be used as a basis for classification, e.g. histopathological changes in the gonads.

3.7.2.5.4 Evidence from in vitro assays, or non-mammalian tests, and from analogous substances using structure-activity relationship (SAR), can contribute to the procedure for classification. In all cases of this nature, expert judgement must be used to assess the adequacy of the data. Inadequate data shall not be used as a primary support for classification.

3.7.2.5.5 It is preferable that animal studies are conducted using appropriate routes of administration which relate to the potential route of human exposure. However, in practice, reproductive toxicity studies are commonly conducted using the oral route, and such studies will normally be suitable for evaluating the hazardous properties of the substance with respect to reproductive toxicity. However, if it can be conclusively demonstrated that the clearly identified mechanism or mode of action has no relevance for humans or when the toxicokinetic differences are so marked that it is certain that the hazardous property will not be expressed in humans then a substance which produces an adverse effect on reproduction in experimental animals shall not be classified.

3.7.2.5.6 Studies involving routes of administration such as intravenous or intraperitoneal injection, which result in exposure of the reproductive organs to unrealistically high levels of the test substance, or elicit local damage to the reproductive organs, including irritation, must be interpreted with extreme caution and on their own are not normally the basis for classification.

3.7.2.5.7 There is general agreement about the concept of a limit dose, above which the production of an adverse effect is considered to be outside the criteria which lead to classification, but not regarding the inclusion within the criteria of a specific dose as a limit dose. However, some guidelines for test methods, specify a limit dose, others qualify the limit dose with a statement that higher doses may be necessary if anticipated human exposure is sufficiently high that an adequate margin of exposure is not achieved. Also, due to species differences in toxicokinetics, establishing a specific limit dose may not be adequate for situations where humans are more sensitive than the animal model.

3.7.2.5.8 In principle, adverse effects on reproduction seen only at very high dose levels in animal studies (for example doses that induce prostration, severe inappetence, excessive mortality) would

not normally lead to classification, unless other information is available, e.g. toxicokinetics information indicating that humans may be more susceptible than animals, to suggest that classification is appropriate. Please also refer to the section on maternal toxicity (3.7.2.4) for further guidance in this area.

3.7.2.5.9 However, specification of the actual 'limit dose' will depend upon the test method that has been employed to provide the test results, e.g. in the OECD Test Guideline for repeated dose toxicity studies by the oral route, an upper dose of 1 000 mg/kg has been recommended as a limit dose, unless expected human response indicates the need for a higher dose level.

3.7.3 Classification criteria for mixtures

3.7.3.1 Classification of mixtures when data are available for all ingredients or only for some ingredients of the mixture

3.7.3.1.1 The mixture shall be classified as a reproductive toxicant when at least one ingredient has been classified as a Category 1A, Category 1B or Category 2 reproductive toxicant and is present at or above the appropriate generic concentration limit as shown in Table 3.7.2 for Category 1A, Category 1B and Category 2 respectively.

3.7.3.1.2 The mixture shall be classified for effects on or via lactation when at least one ingredient has been classified for effects on or via lactation and is present at or above the appropriate generic concentration limit as shown in Table 3.7.2 for the additional category for effects on or via lactation.

Table 3.7.2 Generic concentration limits of ingredients of a mixture classified as reproduction toxicants or foreffects on or via lactation that trigger classification of the mixture.

Ingredient classified as:	Generic concentration limits triggering classification of a mixture as:			
	Category 1A reproductive toxicant	Category 1B reproductive toxicant	Category 2 reproductive toxicant	Additional category for effects on or via l actation
Category 1A reproductive toxicant	≥ 0,3 % [Note 1]			
Category 1B reproductive toxicant		≥ 0,3 % [Note 1]		
Category 2 reproductive toxicant			≥ 3,0 % [Note 1]	
Additional category for effects on or via lactation				≥ 0,3 % [Note 1]

Note The concentration limits in the table above apply to solids and liquids (w/w units) as well as gases (v/v units).
Note 1 If a Category 1 or Category 2 reproductive toxicant or a substance classified for effects on or via lactation is present in the mixture as an ingredient at a concentration above 0,1 %, a SDS shall be available for the mixture upon request.

3.7.3.2 Classification of mixtures when data are available for the complete mixture

3.7.3.2.1 Classification of mixtures will be based on the available test data for the individual ingredients of the mixture using concentration limits for the ingredients of the mixture. On a case-by-case basis, test data on mixtures may be used for classification when demonstrating effects that have not been established from the evaluation based on the individual components. In such cases, the test results for the mixture as a whole must be shown to be conclusive taking into account dose and other factors such as duration, observations, sensitivity and statistical analysis of reproduction test systems. Adequate documentation supporting the classification shall be retained and made available for review upon request.

3.7.3.3 Classification of mixtures when data are not available for the complete mixture: bridging principles

3.7.3.3.1 Subject to paragraph 3.7.3.2.1, where the mixture itself has not been tested to determine its reproductive toxicity, but there are sufficient data on the individual ingredients and similar tested mixtures to adequately characterise the hazards of the mixture, these data shall be used in accordance with the applicable bridging rules set out in section 1.1.3.

3.7.4 Hazard Communication

3.7.4.1 Label elements shall be used for substances or mixtures meeting the criteria for classification in this hazard class in accordance with Table 3.7.3

Table 3.7.3 Label elements for reproductive toxicity.

Classification	Category 1A or Category 1B	Category 2	Additional category for effects on or via lactation
GHS Pictograms			No pictogram
Signal Word	Danger	Warning	No signal word
Hazard Statement	H360: May damage fertility or the unborn child (state specific effect if known)(state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard)	H361: Suspected of damaging fertility or the unborn child (state specific effect if known) (state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard)	H362: May cause harm to breast-fed children.
Precautionary Statement Prevention	P201 P202 P281	P201 P202 P281	P201 P260 P263 P264 P270
Precautionary Statement Response	P308 + P313	P308 + P313	P308 + P313
Precautionary Statement Storage	P405	P405	
Precautionary Statement Disposal	P501	P501	

Annex **E**

Additional considerations to Regulation (EC) 1272/2008

The classification and labelling of substances is performed according to the guidelines of the European Union (Regulation (EC)1272/2008) presented in Annex B. The classification of compounds is ultimately dependent on an integrated assessment of the nature of all parental and developmental effects observed, their specificity and adversity, and the dosages at which the various effects occur. The guideline necessarily leaves room for interpretation, dependent on the specific data set under consideration. In the process of using the regulation, the Committee has agreed upon a number of additional considerations:

- If there is sufficient evidence to establish a causal relationship between human exposure to the substance and impaired fertility or subsequent developmental toxic effects in the offspring, the compound will be classified in category 1A, irrespective of the general toxic effects (see Annex B, 3.7.2.2.1.).
- Adverse effects in a reproductive study, reported without information on the parental or maternal toxicity, may lead to a classification other than category 1B, when the effects occur at dose levels which cause severe toxicity in *general* toxicity studies.
- Clear adverse reproductive effects will not be disregarded on the basis of reversibility per se.

- The Committee does not only use guideline studies (studies performed according to OECD* standard protocols) for the classification of compounds, but non-guideline studies are taken into consideration as well.

* Organisation for Economic Cooperation and Development

Annex **F**

Fertility and developmental toxicity studies

Table 1.1 Fertility studies in laboratory animals with indium compounds: inhalation.

authors	species	compound	experimental period/ design	dose	general toxicity	effects on reproductive organs/ effects on reproduction
NTP (2001)	F344/N rats (n=10/sex/ group)	indium phosphide	6 h/d, 5 d/ wk, wk 1-4 and wk 10-14; 6 h/d, 7 d/wk, wk 5-9	0, 1, 3, 10, 30, 100 mg/m^3	decreased mean final bw and bw changes in all exposed male groups and in females exposed to 100 mg/m^3; lung, liver, haematological effects in all exposed groups	100 mg/m^3: atrophy of uterus (decreased uterine horn diameter, stromal condensation, shrunken glands) and ovaries (small with small follicles, corpora lutea, condensed stroma); epididymidal, seminiferous tubular degeneration; flattened glandular epithelium; prostate, seminal vesicle atrophy; reduced absolute testis weight; ≥3 mg/ m^3: increased relative testis weight
NTP (2001)	B6C3F$_1$ mice (n=10/ sex/ group)	indium phosphide	6 h/d, 5 d/ wk, wk 1-4 and wk 10-14; 6 h/d, 7 d/wk, wk 5-9	0, 1, 3, 10, 30, 100 mg/m^3	all 100 mg/m^3 group mice removed moribund; at 30 mg/m^3 mortality in 5/20; decreased bw and bw gains in males at ≥3 mg/m^3, in females at 10 and 30 mg/ m^3; haematological changes; lung lesions	30, 100 mg/ m^3: atrophy of uterus (decreased uterine horn diameter, stromal condensation, shrunken glands) and ovary (no or only few, poorly developed corpora lutea) 10 mg/ m^3: increased relative testis weight 30 mg/m^3: increased absolute, decreased relative testis weight

d=day(s); h=hour(s); n=number; wk=week(s)

Table 1.2 Fertility studies in laboratory animals with indium compounds: intratracheal instillation.

authors	species	compound	experimental period/design	dose	general toxicity	effects on reproductive organs/ effects on reproduction
Omura et al. (1996)	male Wistar rats (n=8/group)	indium arsenide	2x/wk; 8 wk; sacrifice 24 h after final instillation	7.7 mg/kg bw	not reported	no effect on absolute, relative testis, epididymis weight; on absolute, relative spermatid count; on whole and head epididymidal sperm count; 16% decrease in epididymidal body+tail sperm count ($p<0.05$)
Omura et al. (1996)	male Syrian golden hamsters (n= 4-8/ group)	indium arsenide	2x/wk; 7 wk; treatment discontinued after 14th instillation	7.7 mg/kg bw	mortality in 3/8 (emaciation); significant bw loss in remaining 5/8 (leading to treatment termination)	no effect on absolute testis, epididymis weight; increased relative weights ($p<0.05$); no effect on epididymidal sperm count; no histological testicular changes
Omura et al. (2000)	male Syrian golden hamsters (n= 4-8/ group)	indium arsenide	2x/wk for 8 wk; analysis up to 2 y following treatment (wk 0-88)	4 mg/kg bw	decreased bw gain (70% of controls, wk 0-64)	decreased testis, epididymis weight, caudal sperm count; severe histopathological changes in the testes: vacuolization of seminiferous tubuli
Omura et al. (2000)	male Syrian golden hamsters (n= 4-8/ group)	indium phosphide	2x/wk for 8 wk; analysis up to 2 y following treatment (wk 0-88)	3 mg/kg bw	decreased bw gain (80-90% of controls, wk 16-64)	decreased testis, epididymis weight, caudal sperm count; severe histopathological changes in testes (vacuolization of seminiferous tubuli)

bw=body weight; n=number; wk=week(s); y=year(s)

Table 1.3 Fertility studies in animals with indium compounds: gavage.

authors	species	compound	experimental period/design	dose	general toxicity	effects on reproductive organs/ effects on reproduction
Chapin et al. (1995)	Swiss mice (n=10/sex/ group)	indium trichloride	males: d 3-20, females: d 1-20 (mating on d 7-11)	0, 50, 150, 250 mg/kg bw/d	males: 250, 150 mg/kg: bw loss; decreased liver weight 250 mg: reduction lymphocytes, haemoglobin females: all groups: decreased bw gain; 250 mg/kg: mortality in 2/10	250 mg: decreased number of implants, trend towards increased number of dead implants/dam; no effects on ovulation, fertilization, total number of implantations

bw=body weight; d=day(s); n=number; wk=week(s)

Table 2.1 Developmental toxicity studies in laboratory animals with indium compounds: inhalation.

authors	species	compound	experimental period/design	concentration	general toxicity	developmental toxicity
NTP (2001)	Sprague-Dawley rats (n=unknown)	indium phosphide	gd 4-19[a]; analysis after birth	0, 1, 10, 100 mg/m^3	concentration-related increase in lung weights	no significant observed
NTP (2001)	Swiss CD-1 mice (n=unknown)	indium phosphide	gd 4-17[a]; analysis after birth	0, 1, 10, 100 mg/m^3	at all concentrations: increased lung weight; 100 mg/m^3: early deaths, listless appearance, laboured breathing	no significant foetal toxicity observed

[a] exposure schedule (hours/day, days/week) not reported
gd=gestational day(s); n=number

Table 2.2 Developmental toxicity studies in animals with indium compounds: gavage.

authors	species	compound	experi-mental period/ design	dose	general toxicity	developmental toxicity	remarks
Chapin et al. (1995)	Crl:CD-1 (ICR) BR mice (n=10/ group)	indium trichloride	gd 8-14; necropsy pnd 4	0, 50, 150, 250 mg/kg bw/d	150, 250 mg/kg: decreased bw	250 mg/kg: increased number of dead pups, decreased foetal bw	
Chapin et al. (1995)	Crl:CD-1 (ICR) BR mice (n=11-15/ group)	indium trichloride	gd 6-15, necropsy gd 16	0, 50, 150, 250 mg/kg bw/d	250 mg/kg: decreased absolute, relative liver weight	no increases in skeletal or soft tissue abnormalities 250 mg/kg: increased number of late resorptions, of dead foetuses/ litter; reduced number of live foetuses/litter; reduced bw live foetuses 150 mg/kg: increased number of late resorptions	maternal NOAEL: 150 mg/kg bw; foetal NOAEL: 50 mg/kg bw
Nakajima et al. (1998)	Wistar rats (n=7-10/ group)	indium trichloride	gd 9: necropsy gd 20	0, 75, 150, 300 mg/kg bw	no effect on maternal bw, food consumption; no necropsy findings	no statistically significant effects on foetal mortality, foetal weight, number of tail or skeletal malformations [300 mg/kg: decreased foetal weight (of 5%; ns); increased incidence (10-12%) of tail malformations (kinked tail, brachyury; ns)]	foetal NOAEL: ≥ 300 mg/kg bw

Ungváry et al. (2000)	Sprague-Dawley rats (n=21-33/ group)	indium trichloride	gd 6-15, necropsy gd 21	0, 50, 100, 200, 400 mg/kg bw/d	400 mg/kg: increased relative liver, pancreas, brain weight; decreased bilirubin concentration, serum AST and ALAT activities; kidney lesions (congestion, cortico-medullar haemorrhage) ≥100 mg/kg: decreased food intake, bw gain	≥100 mg/kg: increased number of foetuses with external malformations (≥100 mg/kg: cleft palate; rudimentary, missing tail; ≥200 mg/kg: club foot; 400 mg/kg: exencephalia, rudimentary mandible, syndactilia) ≥200 mg/kg: increased post-implantation loss; decreased foetal weight; increased number of foetuses with visceral anomalies (≥200 mg/kg: ectopia renis, ectopia testis, dilated pelvis renalis, dilated ureter; 400 mg/kg: ectopia ovaries), with major skeletal anomalies (cranium, sternum, ribs, vertebrae) 400 mg/kg: decreased placental weight	maternal and foetal NOAEL: 50 mg/kg bw/d
Ungváry et al. (2000)	Sprague-Dawley rats (n=3-5 dams/ group)	indium trichloride	gd 8, 9, 10, 11, 12, 13, 14 or 15; necropsy gd 21	0, 400 mg/ kg bw (single dose)	maternal toxicity not discussed	all exposure days: decreased foetal bw, retarded skeleton and internal organ growth in surviving foetuses; gd 9, 10, 11, 12, 15: mortality in 10-20% gd 11, 12: gross (external) anomalies gd 10, 11, 14: increased frequency of skeletal malformations gd 14, 15: internal organ anomalies.	
Ungváry et al. (2000)	New Zealand rabbits (n=12-17/ group)	indium trichloride	gd 6-20; necropsy gd 30	0, 50, 100, 200 mg/kg bw/d	200 mg/kg: mortality (4/17), reduced food intake, bw gain; autopsy results to those found in highest dosed rats (see above)	200 mg/kg: increased number of abortions and full resorptions; increased frequency of foetuses with skeletal retardation (sternum hypoplasia, double vertebral ossification centers, shortened rib 13, dilated cranial sutures) ≥100 mg/kg: gross renal anomalies (unilateral renal agenesis, dystopia renis)	maternal NOAEL: 100 mg/kg bw; foetal NOAEL: 50 mg/kg bw

gd=gestational day(s); n=number; ns=not statistically significant

Table 2.3 Developmental toxicity studies in animals with indium compounds: intravenous injection

authors	species	compound	experimental period/ design	dose	general toxicity	developmental toxicity	remarks
Ferm/ Carpenter (1970)	golden hamsters (n= 1-23/ group)	indium nitrate	gd 8, recovery of embryos at gd 12, 13 or 14	0.5, 1, 2, 5, 10, 20 mg/ kg bw	maternal toxicity not extensively investigated; 20 mg/kg: mortality with 48 h	≥2 mg/kg: mortality in all embryos 0.5,1 mg/kg: high incidence of malformations of the digits of the extremities (fusion, stunting, polydactyly)	maternal NOAEL: 10 mg/kg bw; foetal LOAEL: 0.5 mg/kg bw
Nakajima et al. (1998)	Crj:Wistar rats (n=8-10/group)	indium trichloride	gd 9, necropsy gd 20	0, 0.1, 0.2, 0.4 mg/kg bw	no maternal toxicity observed	0.4 mg/kg: decreased foetal, placental weigth; increased incidence of gross (kinked tail, brachyury, cleft palate), visceral (undescended testis, dilatation of renal pelvis), skeletal (fused sternebrae, ribs) malformations, or skeletal variations (number of ossified sternebrae)	maternal NOAEL: 0.4 mg/kg bw; foetal NOAEL: 0.2 mg/kg bw
Nakajima et al. (2000)	ICR Crj:CD-1 mice (n= 6-7/group)	indium trichloride	gd 7, 8 or 9; necropsy gd 18	0, 0.8, 1.6 mg/kg bw	decreased bw in all 1.6 mg treatment groups and in 0.8 mg gd 8 group; no further maternal toxicity observed	all treatment groups gd 8 and 1.6 mg gd 7: decreased foetal weight; 0.8 mg gd 8 and 1.6 mg gd 7: decreased placental weight; 1.6 mg: increased mortality, most severe at gd 8	1.6 mg gd 8 and 9: number of live foetuses insufficient for statistical inference maternal NOAEL: 0.8 mg/kg bw; foetal LOAEL: 0.8 mg/kg bw
Nakajima et al. (2000)	Crj:Wistar rats (n= 5-8/ group)	indium trichloride	gd 9, 10 or 11; necropsy gd 20	0, 0.4 mg/ kg bw	no maternal toxicity observed	in all exposure groups: decreased foetal weight; increased incidence of gross malformations (brachyury, kinked tail, cleft palate, oligodactyly, abnormal abdomen), all effects most severely in the group treated on gd 10; in gd 9 and 10 groups: decreased placental weight	maternal NOAEL: 0.4 mg/kg bw; fetal LOAEL: 0.4 mg/kg bw

Nakajima et al. (2007)	Sprague-Dawley rats (n=8-10/ group)	indium trichloride	gd 10; necropsy gd 21	0, 0.1, 0.2, 0.3 mg/kg bw	no obvious maternal toxicity observed	0.3 mg/kg: increased mortality of implants, decreased foetal, placental weight, increased incidence of external (anal atresia, anury, brachyury, small limb, oligodactyly), skeletal (deformed vertebrae, ribs, forepaw phalanx, sternebrae, scapulae, femur, absent ulna or femur) malformations 0.2 mg/kg: external (kinked tail), skeletal (deformed vertebrae) malformations	maternal NOAEL: 0.3 mg/kg bw; fetal NOAEL: 0.1 mg/kg bw
Nakajima et al. (2008)	Sprague-Dawley rats (n=3-5/ group)	indium trichloride	gd 10; embryos examined on gd 11, 12 or 13	0, 0.4 mg/ kg bw	not mentioned	gd 11, 12, 13: caudal hypoplasia, reduced number of somite pairs gd 11, 12: reduced crown-rump length gd 11: increased tailbud apoptosis	

ALAT=alanine aminotransferase; AST=aspartate aminotransferase; gd=gestational day(s); n=number; pnd=postnatal day(s)