Aluminium and aluminium compounds

Evaluation of the effects on reproduction, recommendation for classification

Gezondheidsraad **Voorzitter**
Health Council of the Netherlands

Aan de minister van Sociale Zaken en Werkgelegenheid

Onderwerp : Aanbieding advies *Aluminium and aluminium compounds*
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Geachte minister,

Graag bied ik u hierbij het advies aan over de effecten van aluminium en aluminiumverbindingen op de vruchtbaarheid en het nageslacht, ook via de borstvoeding. 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 beroeps-uitoefening 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 ook ter kennisname toegezonden aan de minister van Volksgezondheid, Welzijn en Sport en de minister van Volkshuisvesting, Ruimtelijke Ordening en Milieu.

Met vriendelijke groet,

prof. dr. J.A. Knottnerus

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Evaluation of the effects on reproduction, recommendation for classification

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

to:

the Minister of Social Affairs and Employment

No. 2009/02OSH, The Hague, May 28, 2009

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Samenvatting

Op verzoek van de Minister van Sociale Zaken en Werkgelegenheid beoordeelt de Gezondheidsraad de effecten op de reproductie van 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, adviseert een classificatie van reproductietoxische stoffen volgens Richtlijn 93/21/EEC van de Europese Unie. In het voorliggende rapport heeft de commissie aluminium onder de loep genomen.

De aanbevelingen van de commissie zijn:

- Metallisch aluminium en aluminiumverbindingen die niet oplosbaar zijn in water:
  - voor effecten op de fertiliteit adviseert de commissie metallisch aluminium en niet-oplosbare aluminiumverbindingen niet te classificeren wegens onvoldoende geschikte gegevens.
  - voor effecten op ontwikkeling adviseert de commissie metallisch aluminium en niet-oplosbare aluminiumverbindingen niet te classificeren wegens onvoldoende geschikte gegevens.
  - voor effecten tijdens de lactatie adviseert de commissie om metallisch aluminium en niet-oplosbare aluminiumverbindingen niet te kenmerken.

- Oplosbare aluminiumverbindingen:
  - voor effecten op de fertiliteit adviseert de commissie oplosbare aluminiumverbindingen niet te classificeren wegens onvoldoende geschikte gegevens.
  - voor effecten op ontwikkeling adviseert de commissie oplosbare aluminiumverbindingen in categorie 2 te classificeren (*stoffen die dienen te worden beschouwd alsof zij bij de mens ontwikkelingsstoornissen veroorzaken)* en met T; R61 (*kan het ongeboren kind schaden*) te kenmerken.
  - voor effecten tijdens de lactatie adviseert de commissie om oplosbare aluminiumverbindingen te kenmerken met R64 (*kan schadelijk zijn via de borstvoeding*).

Executive summary

At the request of the Minister of Social Affairs and Employment, the Health Council of the Netherlands evaluates the effects on the reproduction of substances at the workplace. The evaluation and subsequent classification, according to the Directive 93/21/EEC of the European Union, are performed by 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. In the present report the committee reviewed aluminium and its compounds.

The committee's recommendations are:

- Metallic aluminium and insoluble (i.e., not soluble in water) aluminium compounds:
  - for effects on fertility, the committee recommends not classifying metallic aluminium and insoluble aluminium compounds due to a lack of appropriate data.
  - for developmental toxicity, the committee recommends not classifying metallic aluminium and insoluble aluminium compounds due to a lack of appropriate data.
  - the committee is of the opinion that labelling of metallic aluminium and insoluble aluminium compounds for effects during lactation is not indicated.

- Soluble (i.e., in water) aluminium compounds:
  - for effects on fertility, the committee recommends not classifying soluble aluminium compounds due to a lack of appropriate data.
  - the committee recommends classifying soluble aluminium compounds in category 2 (*substances which could be regarded as if they cause developmental toxicity in humans*) and labelling soluble aluminium compounds with T; R61 (*may cause harm to the unborn child*).
  - for effects during lactation, the committee recommends labelling soluble aluminium compounds with R64 (*may cause harm to breastfed babies*).

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. The classification is performed by the Health Council's Subcommittee on the Classification of Reproduction Toxic Substances, hereafter called the committee, according to the guidelines of the European Union (Directive 93/21/EEC). The committee'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 toxic to reproduction (class 1, 2 or 3) or labelled as 'may cause harm to breastfed babies' (R64).

1.2 Subcommittee and procedure

The present document contains the classification of aluminium and its compounds by the Health Council's Subcommittee on the Classification of Reproduction Toxic Substances. The members of the committee are listed in Annex A. The classification is based on the evaluation of published human and animal studies concerning adverse effects with respect to fertility, development, and lactation of the above mentioned compound.

Classification and labelling was performed according to the guidelines of the European Union listed in Annex B.

Classification for fertility and development:	
Category 1	Substances known to impair fertility in humans (R60)
	Substances known to cause developmental toxicity in humans (R61)
Category 2	Substances which should be regarded as if they impair fertility in humans (R60)
	Substances which should be regarded as if they cause developmental toxicity in humans (R61)
Category 3	Substances which cause concern for human fertility (R62)
	Substances which cause concern for humans owing to possible developmental toxic effects (R63)
No classification for effects on fertility or development	
Labelling for lactation:	
	May cause harm to breastfed babies (R64)
	No labelling for lactation

In July 2008, the President of the Health Council released a draft of the report for public review. The individuals and organisations 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.

1.3 Additional considerations

The classification of compounds toxic to reproduction on the basis of the Directive 93/21/EEC 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 directive necessarily leaves room for interpretation, dependent on the specific data set under consideration. In the process of using the directive, 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 progeny, the compound will be classified in category 1, irrespective the general toxic effects (see Annex B, 4.2.3.1 category 1).
- Adverse effects in a reproductive or developmental study, in the absence of data on parental toxicity, occurring at dose levels which cause severe toxicity in other studies, need not necessarily lead to a category 2 classification.
- If, after prenatal exposure, small reversible changes in foetal growth and in skeletal development (e.g. wavy ribs, short rib XIII, incomplete ossification)

in offspring occur in a higher incidence than in the control group in the absence of maternal effects, the substance will be classified in category 3 for developmental toxicity. If these effects occur in the presence of maternal toxicity, they will be considered as a consequence of this and therefore the substance will not be classified for developmental toxicity (see Annex B, 4.2.3.3 developmental toxicity final paragraph).

- Clear adverse reproductive effects will not be disregarded on the basis of reversibility per se.
- Effects on sex organs in a general toxicity study (e.g. in a subchronic or chronic toxicity study) may warrant classification for fertility.
- The committee not only uses guideline studies (studies performed according to OECD standard protocols*) for the classification of compounds, but non-guideline studies are taken into consideration as well.

1.4 Labelling for lactation

The recommendation for labelling substances for effects during lactation is also based on Directive 93/21/EEC. The Directive defines that substances which are absorbed by women and may 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, should be labelled with R64. Unlike the classification of substances for fertility and developmental effects, which is based on a hazard identification only (largely independent on the dose), the labelling for effects during lactation is based on a risk characterisation and therefore also includes consideration of the level of exposure of the breastfed child.

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

1.5 Data

Literature searches were conducted in the on-line databases Current Contents and Medline, starting from 1966 up to 2005, and by searches on the Internet. An additional search performed in Medline in March 2008 did not result in information that would change the committee's conclusions (see 'References'). Litera-

* Organisation for Economic Cooperation and Development

ture 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 as well as several websites regarding (publications on) toxicology and health. References are divided in literature cited and literature consulted but not cited. Data are described in the text and animal studies with respect to fertility and development are summarised in Annex D. Of each study, the quality of the study (performed according to internationally acknowledged guidelines) and the quality of documentation are considered.

1.6 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.

1.7 Final remark

The classification of compounds is based on hazard evaluation (Niesink *et al.*[1]) only, which is one of a series of elements guiding the risk evaluation process. The committee emphasises 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 characterisation, human exposure assessment, and recommendations of other organisations.

Chapter 2

Introduction

Aluminium is the most abundant metallic element. It is widely distributed and constitutes approximately 8% of the earth's surface layer. Since aluminium is a very reactive element, it is never found as the free metal (i.e., the metallic state) in nature, but exists in only one oxidation state (+3). As such, it is found combined with other elements, most commonly with oxygen, silicon, and fluorine. Generally, these compounds are found in soil, minerals, (igneous) rocks, and clays, and are the natural forms of aluminium rather than the silvery metal. The metal is obtained from aluminium-containing minerals, primarily bauxite.[2,3]

Aluminium is released into the environment both by natural processes and from anthropogenic sources. The general population may be exposed to aluminium via diet and drinking water, through medicinal (such as vaccines, antacids, analgesics, dialysis fluids) and cosmetic products (such as antiperspirants), and by inhalation of ambient air. Infants may also be exposed via breast milk or infant formulae. Occupational exposure to aluminium occurs in the refining of the primary metal, in secondary industries that produce and use aluminium products, and in welding.[2,3]

Aluminium is poorly absorbed following either oral or inhalation exposure and is essentially not absorbed dermally. Under normal circumstances, the absorption of aluminium by the gastrointestinal tract is low (usually, 0.1-1% of ingested aluminium is absorbed), since the gastrointestinal tract represents a barrier to aluminium absorption and aluminium is precipitated in the small intestine and excreted in the faeces. The rate of absorption largely depends on the form of

ingested aluminium and the presence of dietary constituents which can complex with aluminium and thereby enhance or inhibit its absorption by forming absorbable (usually water-soluble) complexes or not-absorbable (usually water-insoluble) compounds. Bioavailability from occupational inhalation exposure is estimated to be about 2%.[4]

Although in general absorption and bioavailability appear to parallel water solubility, insufficient data are available to directly extrapolate from solubility in water to bioavailability and/or toxicity.[2] However, some animal studies described in this report comparing the effects of water-soluble and water-insoluble aluminium compounds on developmental toxicity showed clear differences. The severity of developmental toxicity appeared to be highly dependent on the form of aluminium given to the animals (see, e.g., Gomez *et al.*[5]; Colomina *et al*.[6]).

For this reason, aluminium compounds are categorised into two groups in this report: compounds not soluble in water (including metallic aluminium) and compounds soluble in water, hereafter referred to as insoluble and soluble aluminium compounds, respectively.

Chapter 3

Metallic aluminium and insoluble aluminium compounds

3.1 Properties

name	:	aluminium
CAS number	:	7429-90-5
synonyms	:	alumina fibre; metana; aluminium bronze; aluminium dehydrated
uses	:	Metallic aluminium is soft and lacks strength. By forming alloys, one can increase the strength and hardness and add other useful properties to the metal. The major uses of aluminium and its alloys are in packaging, building and construction, transportation, and electrical applications.
atomic weight	:	26.98
atomic formula	:	Al

name	:	aluminium oxide
CAS number	:	1344-28-1
synonyms	:	activated aluminium oxide; α-aluminium, α-aluminium oxide; alumina; aluminium sesquioxide; aluminium trioxide; β-aluminium oxide; γ-alumina; γ-aluminium oxide
uses	:	Aluminium oxide is mainly (ca. 90%) used in the production of aluminium and further for non-metallurgical uses, including abrasives, chemicals, and refractory materials, and in specialty industries.
molecular weight	:	101.94
molecular formula	:	Al_2O_3
conversion factor	:	1 mg/L $Al(OH)_3$ is equivalent to 0.26 mg/L Al

name	:	aluminium hydroxide
CAS number	:	21645-51-2
synonyms	:	α-alumina trihydrate; alumina hydrate; alumina hydrated; aluminium oxide trihydrate; aluminium oxide hydrate; aluminium(III)hydroxide; hydrated alumina; hydrated aluminium oxide; aluminium hydrate; hydrated alumina
uses	:	Aluminium hydroxide is used in stomach antacids, as a desiccant powder, in antiperspirants and dentrifrices, in packaging materials, as a chemical intermediate, as a filler in plastics, rubber, cosmetics and paper, as a soft abrasive for brass and plastics, as a glass additive to increase mechanical strength and resistance to thermal shock, weathering, and chemicals, and in ceramics. Aluminium hydroxide is also used pharmaceutically to lower the plasma phosphorus levels of patients with renal failure.
molecular weight	:	77.99
molecular formula	:	$Al(OH)_3$
conversion factor	:	1 mg/L $Al(OH)_3$ is equivalent to 0.35 mg/L Al

name	:	aluminium phosphate
CAS number	:	7784-30-7
synonyms	:	aluminium orthophosphate; phosphoric acid, aluminium salt (1:1); aluminium phosphate tribasic
uses	:	used in over-the-counter stomach antacids
molecular weight	:	121.95
molecular formula	:	$AlPO_4$
conversion factor	:	1 mg/L $AlPO_4$ is equivalent to 0.22 mg/L Al

name	:	aluminium borate
CAS number	:	11121-17-7
synonyms	:	mineral: eremeyevite, jeremejevite
uses	:	as a polymerisation catalyst; component of glass
molecular weight	:	variable
molecular formula	:	$Al_2O_3.B_2O_3$
conversion factor	:	-

name	:	aluminium hypophosphite
CAS number	:	7784-22-7
synonyms	:	-
uses	:	as a polymer fibre finishing agent
molecular weight	:	221.95
molecular formula	:	$Al(H_2PO_2)_3$
conversion factor	:	1 mg/L $Al(H_2PO_2)_3$ is equivalent to 0.12 mg/L Al

name	:	aluminium magnesium silicate
CAS number	:	12511-31-8
synonyms	:	magnesium aluminium silicate; magnesium alumino-silicate; colerainite and other mineral forms
uses	:	as a thickening agent
molecular weight	:	262.43
molecular formula	:	$MgAl_2(SiO_4)_2$
conversion factor	:	1 mg/L $MgAl_2(SiO_4)_2$ is equivalent to 0.10 mg/L Al

name	:	aluminium oxalate
CAS number	:	814-87-9
synonyms	:	-
uses	:	as a dyening mordant
molecular weight	:	318.02
molecular formula	:	$Al_2(C_2O_4)_3$
conversion factor	:	1 mg/L $Al_2(C_2O_4)_3$ is equivalent to 0.08 mg/L Al
name	:	aluminium silicate
CAS number	:	12141-46-7
synonyms	:	aluminium silicate n-hydrate
uses	:	in glass; manufacturing of ceramics; semiprecious stones and enamels; paint filler
molecular weight	:	-
molecular formula	:	$Al_2SiO_5.nH_2O$
conversion factor	:	-

Data from ATSDR [3] and Krewski *et al*.[4]

3.2 Human studies

Fertility studies

There are no studies regarding the effects of exposure to metallic aluminium or insoluble aluminium compounds on human fertility.

Hovatta *et al*.[7] studied the effect of aluminium, lead, and cadmium on semen quality in two groups of Finnish men. Group I consisted of 27 employees of a refinery and a polyolefin factory (mean age 34 years). Group II consisted of 45 sperm donor candidates of a sperm bank (mean age 28 years). Concentrations of aluminium, lead, and cadmium (in sperm and seminal plasma) and semen parameters (concentration, motility, and morphology) were measured in the same samples. Furthermore, to check the representativeness of the results of the sperm analyses, the sperm of another 352 donor candidates was also analysed. Except

for the aluminium concentration in seminal plasma, the concentrations of aluminium, lead, and cadmium in sperm cells and seminal plasma in group I were lower than in group II, whereas no differences were observed between the groups in concentration, motility, and morphology of the sperm cells. A statistically significant inverse relation was observed between aluminium concentration in the spermatozoa and sperm motility and sperm morphology but no relation was observed between the concentration of aluminium in seminal plasma and sperm parameters. Hovatta *et al*. did not present data on occupational exposures (compounds, concentrations). They stated that the factories were situated in a rural area, that most of the employees lived in the countryside, and that the sperm bank donor candidates were from the urban Helsinki area.

Developmental toxicity studies

No human studies were found regarding the developmental effects of exposure to metallic aluminium or to insoluble aluminium compounds.

Lactation

See Chapter 5.

3.3 Animal studies

Fertility studies

No studies were found examining the effects of exposure to metallic aluminium on fertility in experimental animals.

Regarding insoluble aluminium compounds, Pettersen *et al*.[8] fed groups of 4 male and 4 female beagle dogs diets containing 0, 3, 10, or 30 g basic sodium aluminium phosphate (KASAL) per kg diet for 26 weeks. Each dog received 400 gram of blended diet containing KASAL over a 3-hour feeding period per day. Mean aluminium doses, in which the aluminium levels contributed by the basal diet were included, were calculated by Pettersen *et al*. to be 4, 10, 27, and 75 mg/kg bw/day, respectively, for males and 3, 10, 22, and 80 mg/kg bw/day, respectively, for females. Food consumption and body weights of the male animals of the high-dose group were decreased. Absolute testis weights were decreased in the males of the high-dose group. In the testes of two males of this

group, histopathological changes (seminiferous tubule germinal epithelial cell degeneration and atrophy) were observed (see Annex D).

Developmental toxicity studies

No experimental animal studies were found regarding the developmental effects following exposure to metallic aluminium.

Developmental studies with insoluble aluminium compounds in experimental animals are summarised in Annex D.

Prenatal development

Mated Swiss mice (n=18-20/group) were given aluminium hydroxide (0, 66.5, 133, 266 mg/kg bw/day; i.e., 0, 23, 46, 92 mg Al/kg bw/day) by gavage on gestational days 6-15 by Domingo *et al*.[43] On gestational day 18, mice were sacrificed and foetuses were examined for external, soft-tissue, and skeletal abnormalities. No statistically significant effects of aluminium hydroxide treatment on food consumption, body weight, organ weights, appearance, and behaviour of the dams were found. Furthermore, no effects were observed on the number of implantation sites, resorptions, number of live and dead foetuses, sex ratio, foetal weights and foetal lengths, and external, soft-tissue, and skeletal abnormalities.

Four groups of pregnant Wistar rats (n=18-19/group) were treated with aluminium hydroxide (0, 192, 384, 768 mg/kg bw/day; i.e., 0, 66, 133, 266 mg Al/kg bw/day) by gavage on gestational days 6-15. On gestational day 20, rats were sacrificed and foetuses were examined for external, soft-tissue, and skeletal abnormalities. No statistically significant effects on body weights were observed whereas food consumption of animals of all groups was slightly and not dose relatedly decreased. No effects were observed on pregnancy rate, implantations sites, resorptions, number of live and dead foetuses, foetal weights, liver and kidney weights, and external, soft-tissue, and skeletal abnormalities. No statistically significant differences were observed among the groups in aluminium concentration of liver, brain, and bone of the dams and placentas. In the foetuses, aluminium concentrations were below the detection limit of 0.05 µg/g wet weight (Gomez *et al*.[9]).

Gomez *et al*.[5] treated Sprague-Dawley rats (n=15-18) with aluminium hydroxide (384 mg/kg bw/day), soluble aluminium citrate (1064 mg/kg bw/day), or aluminium hydroxide concurrent with citric acid from gestational days 6-15 by gavage

(for both aluminium compounds, the amount of aluminium was 133 mg/kg bw/day). Rats were sacrificed on gestational day 20 and foetuses were examined for external, soft-tissue, and skeletal abnormalities. No effects were observed on food consumption, body weights, and liver, kidney, and brain weights. No effects were observed on pregnancy rate, implantations, resorptions, live and dead foetuses, and foetal weights in the groups treated with aluminium hydroxide or aluminium citrate. Foetal weight was slightly decreased in the group treated with aluminium hydroxide and citric acid. In the rats treated with aluminium hydroxide, no effects were observed on external, soft-tissue, and skeletal abnormalities. In the rats treated with aluminium citrate, the incidence of foetuses with absent xiphoides was statistically significantly increased. In the groups treated with aluminium hydroxide and citric acid, the incidence of foetuses showing delayed ossification of the occipitalis and sternebrae and absent xiphoides was statistically significantly increased. Placental aluminium levels were similar in control animals and in animals treated with aluminium hydroxide alone (3.0-3.2 µg/g wet weight) but increased in animals treated with aluminium hydroxide and citric acid or with aluminium citrate (5.1 vs. 9.2 µg/g; $p<0.01$). In the foetuses, aluminium concentrations were below the detection limit of 0.05 µg/g.

In a study of Colomina *et al.*[6], pregnant Swiss mice (n=10-13) were given aluminium hydroxide (166 mg/kg bw/day), soluble aluminium lactate (627 mg/kg bw/day) or aluminium hydroxide concurrent with lactic acid (570 mg/kg bw/day) from gestational days 6-15 by gavage (for both aluminium compounds, the amount of aluminium was 57 mg/kg bw/day). On gestational day 18, mice were sacrificed and foetuses were examined for external, soft-tissue, and skeletal abnormalities. Food consumption was decreased in the mice treated with aluminium lactate, whereas no statistically significant effects were observed in the mice treated with aluminium hydroxide or aluminium hydroxide and lactic acid. Body weight (gain) was decreased in the mice treated with aluminium lactate and aluminium hydroxide and lactic acid. No effect on body weight (gain) was observed in the mice treated with aluminium hydroxide alone. No effects were observed on maternal liver and kidney weights and on pregnancy rate, implantations, resorptions, and live and dead foetuses. Foetal weight was statistically significantly decreased in the aluminium lactate group, whereas no effects on foetal weights were observed in mice treated with aluminium hydroxide with or without lactic acid. In the aluminium lactate group, the incidence of foetuses with cleft palate and delayed ossification of the parietalis was increased, whereas no treatment-related effects were observed in the groups treated with aluminium hydroxide with or without lactic acid. The concentrations of aluminium in the

foetuses treated with aluminium lactate (16.81 µg/g wet weight) were higher than the concentrations in foetuses treated with aluminium hydroxide (0.18 µg/g wet weight) or aluminium hydroxide and lactic acid (1.13 µg/g wet weight), while they were below the limit of detection (i.e., 0.05 µg/g) in the control foetuses (concentrations were measured in whole foetuses).

Colomina *et al*.[10] investigated the effects of concurrent ingestion of high doses of aluminium hydroxide and ascorbic acid on maternal and developmental toxicity in Swiss mice. Pregnant females (number of groups not specified) were given daily doses of aluminium hydroxide (300 mg/kg bw/day; i.e., 104 mg Al/kg bw/day), ascorbic acid (85 mg/kg bw/day) or aluminium hydroxide and ascorbic acid from gestational days 6-15 by gavage. Dams were sacrificed and foetuses were examined for external, soft-tissue, and skeletal abnormalities. Three foetuses per dam were used for whole body analyses of aluminium. Although food consumption of the dams treated with aluminium hydroxide alone was decreased, no maternal toxicity was observed in this group. Furthermore, no effects were observed on number of implantations, resorptions, live foetuses, implantation loss, sex ratio, and foetal body weights. External, soft-tissue, and skeletal examinations did not reveal any developmental effect of aluminium hydroxide treatment. No differences in foetal aluminium concentrations, which ranged between 0.55 and 0.88 µg/g wet weight, were observed among the groups. Ascorbic acid had no effect on toxicity of aluminium hydroxide.

Post-natal development

No experimental animal studies were found on the post-natal developmental effects of metallic aluminium or insoluble aluminium compounds.

Lactation

See Chapter 5.

Conclusion

Hovatta *et al*.[7] showed a statistically significant inverse relation between aluminium concentration in the spermatozoa and sperm motility and sperm morphology, whereas no relation was observed between the concentration of aluminium in seminal plasma and sperm parameters. No studies were available concerning the effects of metallic aluminium on fertility in animals.

For insoluble compounds, no human data were available. In dogs, Pettersen *et al*.[8] found histopathological changes in the testes of males, accompanied by decreased body weights, at daily dietary doses of basic sodium aluminium phosphate of 30 g/kg diet (i.e., ca. 75 mg Al/kg bw/day).

The committee is of the opinion that the data available are inadequate to classify metallic aluminium and insoluble aluminium compounds with respect to effects on fertility.

Five developmental toxicity studies were described with insoluble aluminium compounds (viz., aluminium hydroxide).[5,6,9,10,43] None of these studies showed effects of aluminium hydroxide on prenatal developmental. Furthermore, no[5,9] or only minor amounts[6,10] of aluminium were detected in the foetuses of dams orally treated with aluminium hydroxide, contrary to soluble aluminium compounds.

No post-natal developmental toxicity studies with insoluble aluminium compounds were available.

The committee is of the opinion that the data available are inadequate to classify metallic aluminium and insoluble aluminium compounds with respect to developmental effects.

Proposed classification for fertility

Lack of appropriate data precludes assessment of metallic aluminium and of insoluble aluminium compounds for effects on fertility.

Proposed classification for developmental toxicity

Lack of appropriate data precludes assessment of metallic aluminium and of insoluble aluminium compounds for effects on development.

Proposed labelling for effects during lactation

See Chapter 5.

Chapter **4**

Soluble aluminium compounds

4.1 Properties

name	:	aluminium chloride (anhydrous form or hexahydrate form)
CAS number	:	7446-70-0 (anhydrous) and 10124-27-3 (hexahydrate)
synonyms		aluminium trichloride; trichloroaluminium; pearsall.
uses	:	Aluminium chloride is used as an acid catalyst, as a chemical intermediate for other aluminium compounds, in the cracking of petroleum in the manufacturing of rubbers and lubricants, and as an antiperspirant. The hexahydrate form is used in preserving wood, in disinfecting stables and slaughterhouses, in deodorants and antiperspirants, in cosmetics as a topical astringent, in refining crude oil, in dyeing fabrics, and in manufacturing paper
molecular weight	:	133.34 (anhydrous) and 241.43 (hexahydrate)
molecular formula	:	$AlCl_3$ or $AlCl_3.(6H_2O)$
conversion factor	:	1 mg/L $AlCl_3$ is equivalent to 0.2 mg/L Al 1 mg/L $AlCl_3(6H_2O)$ is equivalent to 0.11 mg/L Al

name	:	aluminium nitrate
CAS number	:	13473-90-0
synonyms		aluminium trinitrate; aluminium (III)nitrate; nitric acid, aluminium salt.
uses	:	Aluminium nitrate is used in antiperspirants, for tanning leather, as a corrosion inhibitor, in the preparation of insulating papers, on transformer laminates, in incandescent filaments, and in cathode ray tube heating elements.
molecular weight	:	213.00
molecular formula	:	$Al(NO_3)_2$
Conversion factor	:	1 mg/L $Al(NO_3)_2$ is equivalent to 0.13 mg/L Al

name	:	aluminium lactate
CAS number	:	18917-91-4
synonyms		Aluctyl; aluminium, tris(2-hydroxypropanoate-O^1,O^2); propanoic acid, 2-hydroxy-aluminium complex; aluminium tris(α-hydroxypropionate).
uses	:	Aluminium lactate is used in antiperspirants and as an astringent. Aluminium lactate is also used as a pH buffer and for the treatment of quartz surfaces to reduce its reactivity.
molecular weight	:	294.18
molecular formula	:	$C_9H_{15}AlO_9$
conversion factor	:	1 mg/L $C_9H_{15}AlO_9$ is equivalent to 0.09 mg/L Al

name	:	aluminium sulphate
CAS number	:	10043-01-3
uses	:	Aluminium sulphate is primarily used for water purification systems and sewage treatment systems as a flocculent, in the paper and pulp industry, in fireproofing and waterproofing cloth, in clarifying oils and fats, in waterproofing concrete, in antiperspirants, in tanning leather, as a mordant in dying, in agricultural pesticides, as an intermediate in the manufacturing of other chemicals, as a soil conditioner to increase acidity for plants, and in cosmetics and soap. A saturated solution of aluminium sulphate is employed as a mild caustic. Solutions containing 5-10% aluminium sulphate have been used as local applications to ulcers and to arrest foul discharges from mucous surfaces.
molecular weight	:	342.14
molecular formula	:	$Al_2(SO_4)_3$
conversion factor	:	1 mg/L $Al_2(SO_4)_3$ is equivalent to 0.08 mg/L Al

Data from ATSDR[2].

4.2 Human studies

Fertility

The committee did not locate studies on the effects of soluble aluminium compounds on human fertility.

Developmental studies

Golding *et al*.[11] studied the effects of high concentrations of aluminium sulphate in drinking water (concentrations not specified), inadvertently dumped in a water supply in North Cornwall (England), on pregnancy outcome. Outcomes of all singleton pregnancies in the affected area (n=92) were compared with those in two control groups: pregnancies completed before the incident (n=68) and pregnancies in a neighbouring area (n=193). Except for a statistically significant

increased prevalence of children showing talipes (4 cases vs. one control from the same area; p=0.014), no exposure-related effects of aluminium were found on perinatal deaths, low birth weight, preterm delivery, and severe congenital malformations. The four infants with talipes had been exposed at different times during gestation (one during the first, two during the second, and one during the third trimester).

The Golding study was one of a number of studies investigating the potential health effects of chemical exposure, viz., aluminium, sulphate, copper, zinc, lead, manganese, and iron, resulting from the water pollution incident. A specially convened subgroup of the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) of the English Department of Health was, amongst others, asked to advise on whether the exposure to chemicals from this incident had caused, or was expected to cause, delayed or persistent harm to human health.[12]

Morton *et al*. determined the concentrations of 20 trace elements by atomic absorption spectrophotometry on representative samples of tap-water collected from 48 local authority areas in South Wales, and examined the associations between 12 of the elements and central nervous system malformation rates for the 48 areas. They found statistically significant relations for 4 elements: negative associations for calcium, barium, and copper, and a positive association for aluminium. Regression analysis of the data suggested that the relationships between barium and copper and central nervous system malformation rates were more important than those of aluminium and barium.

The committee questions the relevance of these findings and notes that the mean concentrations of aluminium in morning (n=48) and evening (n=48) samples were 0.061 and 0.049 mg/L, respectively, i.e., below the drinking water guideline value of 0.2 mg/L. Assuming a daily water consumption of 1.5 litres, daily intake of aluminium from these sources would amount to 0.09 mg, which is far below the daily dietary exposure (3.2 mg; from the UK Total Diet Study 1976 to 1997)[13] and the daily amount that would be tolerable according to WHO (9 mg/day, calculated from a provisional tolerable weekly intake (PTWI) of 1 mg/kg bw).[14]

Lactation

See Chapter 5.

4.3 Animal studies

Fertility and prenatal and post-natal developmental studies with water-soluble aluminium compounds in experimental animals are summerised in Annex D.

Fertility studies

Drinking water

The chronic toxicity of aluminium in Dobra Voda mice (n=10) was studied in a poorly reported reproduction study by Ondreicka *et al*.[15] F0-generation mice were mated three times to produce three F1 litters and subsequently, animals of the first F1 litters were mated two times to produce two F2 litters. Both parental mice and their offspring received aluminium chloride in their drinking water (average 19.3 mg Al/kg bw/day) from 4 weeks of age. The experiment lasted 180-390 days during which body weights, number of litters, and number of offspring were recorded. There were no effects on red blood cell count and no histological lesions in the liver, spleen, and kidneys. Body weight gain in the F0 generation and in the first F1 litter was not affected, but in the second and third F1 litters and in the F2 litters growth was clearly retarded. No statistically significant effects were observed on reproduction.

Male Sprague-Dawley rats (n=31/group) were given drinking water containing aluminium chloride (0, 44.8, 447.6, and 4476.0 mg/L of drinking water; i.e., 0, 5, 50, 500 mg Al/L) for up to 90 days (Dixon *et al*.[16]). Seven animals per group were sacrificed on days 30, 60, and 90. From day 90 onwards, the remaining males were given drinking water without aluminium and used for serial matings with untreated females (10 consecutive mating periods of one week). At sacrifice, blood was sampled for determination of plasma levels of luteinizing hormone (LH) and follicle stimulating hormone (FSH). Liver, lungs, spleen, kidneys, brain, heart, and testes were microscopically examined. In the untreated females used in the serial mating experiments, no effects were observed on the number of implantation sites and average litter size. Microscopic examinations revealed no effects of aluminium treatment and plasma LH and FSH levels were similar among the groups.

Effects of long-term ingestion (12 weeks) of aluminium chloride hexahydrate (1000 mg/L in drinking water; i.e., 9 mg Al/kg bw/day calculated from a bw of

309 g, presented in the study, and a water intake of 25 mL/day, assumed) was investigated on aggression, sexual behaviour, and fertility in male Sprague-Dawley rats (n=10-13).[17] Body weights were statistically significantly decreased. Male sexual and aggressive behaviour was suppressed by aluminium chloride. Mating experiments with untreated females showed no effects of aluminium chloride on reproductive parameters (number of pregnant females, number of implantations, number of viable foetuses, and the number of resorptions). Absolute testis and seminal vesicle weights of the males treated with aluminium chloride were statistically significantly decreased, whereas no statistically significant effects were observed on relative weights.

Intraperitoneal

In a study of Llobet *et al.*[18], adult male Swiss mice (n=18/group) were treated intraperitoneally with aluminium nitrate nonahydrate (0, 50, 100, and 200 mg/kg bw/day; i.e,. 0, 3.6, 7.2, 14.4 mg Al/kg bw/day) for 4 weeks. After the treatment period, 8 males per group were mated with untreated females (1 male with 2 females) for 4 days. Ten days after the end of the mating period, females were sacrificed and examined for implantations, resorptions, and dead and live foetuses. The other males were sacrificed after the end of the treatment period and examined for testicular and epididymal weight, epididymal sperm motility and sperm morphology, and testicular sperm production, for histopathological examinations of the testes, and for determination of the aluminium concentration in the testes. Body weights were statistically significantly decreased in mice of all aluminium-treated groups. The number of pregnant females was statistically significantly decreased in the mid- and high-dose groups. No effects were observed on the number of implantations, resorptions, and live and dead foetuses. Although effects were observed on absolute testicular and epididymal weights, no effects of aluminium treatment were observed on relative weights. The concentration of sperm cells was statistically significantly decreased in the testis (at 100 and 200 mg/kg bw) and epididymis (at 200 mg/kg bw). No effects were observed on sperm motility and sperm morphology. Histological changes (necrosis of spermatids and spermatocytes) were observed in the testis of males at doses of 100 and 200 mg/kg bw. Aluminium concentrations in the testis of males treated with 0, 50, 100, and 200 mg/kg bw were 0.10, 0.92, 1.19, and 1.47 µg/g tissue, respectively.

Developmental toxicity studies

Prenatal development

Diet

McCormack *et al.*[19] fed pregnant Sprague Dawley rats (n=6-8) with diets containing 119 (control), 500, or 1000 mg/kg aluminium chloride from gestational days 6-19. On gestational day 19, dams were sacrificed and foetuses were examined for external, soft-tissue and skeletal examination. Furthermore, one subgroup was used for whole carcass aluminium determination. Maternal toxic effects were not described. No statistically significant effects were observed on number of live foetuses, resorptions, foetal weight, foetal crown rump length, whole carcass aluminium concentration, and external, soft-tissue, and skeletal abnormalities.

Gavage

Sprague-Dawley rats (n=7-10) were treated with aluminium nitrate nonahydrate (0, 180, 360, or 720 mg/kg bw/day; i.e., 0, 13, 26, 52 mg Al/kg bw/day) from gestational days 6-14 (Paternain *et al.*[20]). Rats were sacrificed on gestational day 20 and foetuses were examined for external, soft-tissue, and skeletal abnormalities. Maternal body weight gain during gestation was statistically significantly decreased in all treatment groups. No effects were observed on implantations, resorptions, and live and dead foetuses. Foetal body weights were decreased in all treatment groups. Foetal examinations revealed effects on skull (decreased ossifications of supraoccipital bone), ribs (hypoplastic deformations; vertebral alterations), and sternebrae (partial ossification; bilobed appearance; other variations) in all treatment groups. In the high-dose group, the incidence of foetuses showing haematomas in the abdomen, thorax, and limbs was statistically significantly increased.

In a study of Bellés *et al.*[21], CD1 mice (n=10-32) were treated with doses of aluminium nitrate nonahydrate of 398 mg/kg bw/day (i.e., 29 mg Al/kg bw/day) from gestational days 6-15. On gestational day 18, dams were sacrificed and foetuses were examined for external, soft-tissue, and skeletal abnormalities. Body weight gain and food consumption during gestation was statistically significantly decreased. The incidence of dead females in the aluminium-treated group was

56%. In the remaining dams, no effects were observed on number of early and late resorptions, live and dead foetuses, and sex ratio. Foetal weights were decreased. External and soft-tissue examinations showed no differences among the groups. Skeletal examinations revealed retarded ossification in various bones.

CD1 mice (n=10-14/group) were given single doses of aluminium nitrate nonahydrate (995 mg/kg bw/day; i.e., 72 mg Al/kg bw/day) on gestational days 8, 9, 10, 11, or 12 (Albina *et al*.[22]). On gestational day 18, mice were sacrificed and foetuses were examined for external, soft-tissue, and skeletal abnormalities. Maternal body weight gain through gestation was statistically significantly decreased. Except for the females treated on gestational day 11, the number of females with live foetuses was decreased due to death of the female, abortions, and completely resorbed litters. In the remaining dams, no effects were observed on number of early and late resorptions, live and dead foetuses, and sex ratio. Foetal weights were decreased. External and soft-tissue examinations showed no differences among the groups. Skeletal examinations revealed retarded ossification in various bones.

Intravenous

Wide[23] intravenously injected aluminium chloride hexahydrate into NMRI mice (n=8-28) on gestational day 3 (0, 50, 100 mM = 0, 4.5, 9 mg Al/kg bw/day, assuming a bw of 30 g) and gestational day 8 (0, 50 mM = 0, 4.5 mg Al/kg bw/day). On gestational day 17, mice were sacrificed and foetuses were examined for external, soft-tissue, and skeletal abnormalities. No effects were observed on pregnancy rate, resorptions, number of foetuses per litter, weight of the foetuses, and external abnormalities. In the foetuses injected with 100 mM, the incidence of foetuses with abdominal haemorrhages was increased. In the foetuses treated on gestational day 8 with 50 mM, skeletal ossification of supraoccipital bone, sternum, metatarsal, and caudal vertebrae was retarded, and the incidence of abdominal haemorrhages was increased. Maternal toxic effects were not described. However, Wide reported that concentrations were chosen so that they apparently did not affect the animals (i.e., half the dose that caused signs of discomfort such as increased immobility and raised hairs of the fur) and that injection of 100 mM at gestational day 8 had resulted in animals appearing sick.

Subcutaneous

Golub *et al*.[24] subcutaneously injected Swiss Webster mice (n=10/group) with aluminium lactate (0, 10, 20, 40 mg Al/kg bw) on gestational days 3, 5, 7, 9, 11, 13, and 15. On gestational day 18, dams were sacrificed and foetuses were examined for external, soft-tissue, and skeletal abnormalities. No effects on maternal body weight at sacrifice, food consumption, and mortalities were observed. Necrotic skin lesions were observed near the injection sites. A dose-related decrease in pregnancy rate was observed (80, 71, 57, and 25% at 0, 10, 20, and 40 mg/kg, respectively). Due to the severe, necrotic skin lesions near the injection site and the low pregnancy rate at 40 mg/kg, treatment of this group was discontinued, and data were not presented. Absolute and relative spleen weights and relative liver weights were increased in the dams of the 20 mg/kg group, while absolute and relative weights of other organs (brain, heart, kidneys, adrenals, thymus) were comparable among groups. No effects were observed on foetal resorptions, number of foetuses, uterine weight, foetal weights, and external, soft-tissue, and skeletal examinations. Crown-rump length was decreased in the 20 mg/kg group.

On gestational day 16, pregnant Wistar rats (n=3) were subcutaneously injected with $^{26}AlCl_3$ (705 pg) and $^{27}AlCl_3$ (0.28 mg) (Yumoto *et al*.[25]). On gestational day 21, rats were sacrificed and foetuses and maternal organs were sampled for determination of aluminium incorporation. No maternal or foetal toxicity was observed. Approximately 0.23% of the aluminium injected into the pregnant rat was transferred to the foetuses by placental transfer.

Intraperitoneal

Colomina *et al*.[26] administered aluminium chloride (0, 37.5, 75 mg/kg bw/day; i.e., 0, 7.6, 15 mg Al/kg bw/day) intraperitoneally to pregnant Swiss mice (n=10-14) from gestational days 6-15. On gestational day 18, mice were sacrificed and foetuses were examined for external, soft-tissue, and skeletal abnormalities. No statistically significant effects were observed on food consumption and body weight change, but 1 and 2 mice died in the low- and high-dose groups, respectively (day of death was not specified). No effects were observed on liver and kidney weights. Gravid uterine weight was statistically significantly decreased in both treatment groups. No effects were observed on pregnancy rate, implantations, resorptions, and live and dead foetuses. Foetal weight was statistically significantly decreased in both treatment groups. No statistically significant

treatment-related effects were observed on the incidences of external, soft-tissue, and skeletal abnormalities.

Post-natal development

Diet

Wistar rats (n=12-14) were given aluminium chloride (0, 160, 200 mg Al/kg bw/day) in the diet from gestational days 8-21. Pups were subjected to a series of neuromotor developmental tests (surface righting reflex, grasping reflex, negative geotaxis test, suspension test, locomotor coordination test). No maternal toxic effects were observed. Litter size at birth was not affected but pup mortality during post-natal days 1-18 was statistically significantly increased in both treated groups when compared to the control group. In the first week post-partum, pup body weights of the treated dams were decreased. Treated pups performed less well in the righting reflex and the negative geotaxis test than the control pups, whereas no effects were observed in the grasping reflex test, suspension test, and locomotor coordination test (Bernuzzi *et al*.[27]).

Swiss Webster mice (n=6-14) were fed diets containing 100 (control), 500, or 1000 mg aluminium lactate/kg diet (i.e., 15-60, 95-275, 170-390 mg Al/kg bw/day) calculated from data presented by Golub *et al*.) during gestation and lactation. Animals in an additional control group received 100 g aluminium/kg diet and were pair-fed to the 1000 mg/kg group as a control for effects of decreased food consumption in the 1000 mg/kg group. Neurobehavioural testing was performed in 10-12 pups/group. Remaining pups (n=14-22) were sacrificed on post-natal day 20 for measurement of organ weights. Maternal weights at parturition were similar among the groups, but during the lactation period, food consumption and body weight gain of the dams of the 500 and 1000 mg/kg groups were statistically significantly decreased. Furthermore, neurotoxic effects (ataxia) were observed in these groups and 1 dam of the 500 mg/kg group and 4 dams of the 1000 mg/kg group died before the end of the lactation period. Litter size was similar in all groups. Dose-dependently reduced body weighs and crown-rump lengths were observed. Absolute and relative weights of liver and spleen were decreased in pups of the 1000 mg/kg group. Neurobehavioural performance was slightly decreased in the aluminium-treated groups (Golub *et al*.[24]).

Bernuzzi *et al*.[28] studied the effects of aluminium chloride and aluminium lactate in pregnant rats on mortality, weight gain, and neuromotor development of their

offspring. Pregnant Wistar rats (n=5-12) were given diets containing 0, 100, 300, or 400 mg Al/kg bw/day as aluminium chloride or as aluminium lactate throughout gestation. Pups were subjected to a series of neuromotor developmental tests (surface righting, grasping reflex, negative geotaxis, suspension test, locomotor coordination test) within 2 weeks after birth. On gestational day 18, dam body weights were decreased in the groups given 300 and 400 mg/kg aluminium chloride and 400 mg/kg aluminium lactate. No effect was observed on litter size, but pup mortality was statistically significantly increased and pup weights were statistically significantly decreased in the groups given 300 and 400 mg/kg aluminium chloride and 400 mg/kg aluminium lactate group. Neuromotor development of the pups assessed was delayed by prenatal exposure to both aluminium salts.

Swiss Webster mice were fed diets containing 25 (control), 500, or 1000 mg aluminium lactate/kg diet (according to Donald *et al*. 5-10, 100-210, 200-420 mg Al/kg bw/day) during gestation and lactation. After weaning, all pups were fed control diets. Pups were assessed for neurobehavioural development pre-weaning and immediately and two weeks after weaning. No maternal toxic effects were observed. No differences in pregnancy rate, litter size, sex ratio, and birth rate were observed among the groups. Except for poor performance in a climbing test in the high-dose group, no pre-weaning effects of aluminium were observed on pup mortality, pup growth, and neurobehavioural development. Post-weaning neurobehavioural tests showed effects on foot splay, forelimb and hind limb grip strengths, and thermal sensitivity in both treatment groups, whereas the startle response was not affected (Donald *et al*.[29]).

Wistar rats (n=6-9) were fed diets containing 400 mg aluminium/kg diet (as aluminium lactate) from gestational days 1-7 (group 1) and 1-14 (group 2) and throughout gestation (group 3) in order to determine the effects of aluminium on mortality, weight gain, neuromotor maturation (righting reflex, grasping reflex, negative geotaxis test, suspension test, locomotor coordination test) and learning ability (operant conditioning test) of the offspring. In the dams of group 3, food consumption and body weights were decreased at the end of the gestational period. No effects were observed on litter size, mortality rate, and pup weights. Pups of treated dams performed less well, compared to controls, in the negative geotaxis test (group 2 and 3), the locomotor coordination test, and the operant conditioning test (group 1-3). In addition, there was a statistically non-significant trend for delay in righting reflex in all treated groups (Muller *et al*.[30]).

Swiss Webster mice (n=9-14) were fed diets containing 25 mg Al/kg diet (background concentration in control diet) or 1000 mg aluminium lactate/kg diet (according to Golub *et al*. ca. 250 mg Al/kg bw/day) during pregnancy and lactation in order to determine the sensitive periods for the induction of neurodevelopmental effects of aluminium. At birth, pups were cross-fostered either within or between groups and used for neurobehavioural testing. At sacrifice on post-natal day 21, liver and brain were sampled for analysis of aluminium concentration. During gestation, there were no effects on body weights. Food intake and body weights of the dams of the aluminium-treated group were decreased during lactation. One treated dam showed neurotoxic effects and died 4 days after weaning. From post-natal day 10 onwards, retarded growth was observed in pups of dams treated during gestation and lactation. Neurobehavioural effects were observed in pups of dams treated during gestation (forelimb grasp strength) or lactation (negative geotaxis test), but especially during gestation and lactation (hind limb grasp and temperature sensitivity). Aluminium concentrations in pup liver and brain were similar among the groups but manganese and liver iron concentrations were decreased (Golub *et al*.[31]).

In a study of Golub *et al*.[32], Swiss Webster mice were fed diets containing 7 mg Al/kg diet (background concentration in control diet) or 1000 mg aluminium lactate/kg diet during gestation and lactation (according to Golub *et al*. ca. 200-420 mg Al/kg bw/day). At weaning, half of the litters of the treated group were fed the same diet as the dams (accoring to Golub *et al*. resulting in doses in offspring of ca. 130 mg Al/kg bw/day) and the other half was fed a control diet. One male and one female from each litter were studied in an automated auditory startle response test on post-natal days 22 and 52 (n=6-7/sex/group). In the dams, no effect on body weight was observed. On both days, the auditory startle response was reduced in treated pups. However, on post-natal day 52, the effects were more pronounced in the pups continuously exposed to aluminium compared to pups that were fed control diets after weaning.

Swiss Webster mice (n=40 group) were exposed to dietary doses of 7 mg Al/kg diet (background concentration in control diet; i.e., 1.4-2.9 mg Al/kg bw/day, according to Golub *et al*.) and 500, or 1000 mg aluminium lactate/kg diet ((according to Golub *et al*. ca. 100-210, 200-420 mg Al/kg bw/day) from gestational day 1 until weaning. At weaning, each litter was assigned to either continue with the diet of its dam or was transferred to the control diet. At 50 days of age, mice were used for behavioural testing (operant tasks and subsequently delayed spatial alternation or discrimination reversal testing; n=1 sex/litter/test).

No effect on maternal weight at birth, gestation length, litter size, pup weight at birth, and pup weight at post-natal days 21, 50, or 150-170, and pup organ weights were observed. In pups fed diets containing 1000 mg/kg, increased cage mate aggression was observed. Long-term effects on behavioural parameters, including decreases in forelimb and hind limb grip strength, were observed in the offspring at 500 and 1000 mg/kg. These effects were not dose dependent and were not further intensified by continuing exposure as adults (Golub *et al.*[33]).

Pregnant Swiss Webster mice (n=30-40/group) were given diets containing 7 mg Al/kg diet (background concentration in control diet; i.e., according to Golub and German <1 mg Al/kg bw/day) and 100, 500, or 1000 mg aluminium lactate/kg diet (according to Golub and German ca. 10, 50, 100 mg Al/kg bw/day) from gestational day 1 until weaning. After weaning on post-natal day 21, mice continued to be fed the same diet as their dams until post-natal day 35. Female offspring (n=16) were evaluated in a cognitive task test (Morris water maze) at 3 months of age and male offspring (n=20) in a motor activity test battery at 5 months of age. No effects were observed on the number of dams surviving pregnancy, gestation length, weight gain during pregnancy, litter size at birth, or birth weight. At post-natal day 21, male and female offspring weights were statistically significantly less in the groups given 500 and 1000 mg/kg compared to the control group. In females, body weights were statistically significantly decreased in the high-dose group at 35 days and 3 months of age when compared to controls. Except for increased absolute and relative brain weights at the low dose and decreased absolute and increased relative brain weights at the high dose, no effects were observed on relative organ weights of the female offspring at sacrifice after 3 months. In males, body weights were statistically significantly lower at the mid and high dose at all time points, including at 5 months of age, when compared to controls. Female offspring of the 1000 mg/kg group were slower in learning the Morris maze and male offspring performed slightly less in the motor activity tests than controls (Golub and German[34]).

Gavage

Sprague-Dawley rats (n=10/group) were given aluminium nitrate nonahydrate (0, 180, 360, 720 mg/kg bw/day; i.e., o, 13, 26, 52 mg Al/kg bw/day) from gestational day 14 to post-natal day 21 and sacrificed on post-natal day 21. Maternal toxic effects were not described. No statistically significant dose-dependent effects on pregnancy rate and live pups per litter were observed on post-natal day 1. Pup weights were decreased on post-natal day 1 (at 720 mg/kg bw), 4 (at 180

and 720 mg/kg bw), and 21 (all treated groups). Body length was decreased on post-natal day 1 (at 360 and 720 mg/kg bw) and 4 (at 720 mg/kg bw). Tail length was decreased on post-natal day 1 and 4 (at 720 mg/kg bw) and 21 (all treated groups). No treatment-related effects were observed on relative organ weights (Domingo *et al*.[35]).

Pregnant THA rats (n=4/group) were given aluminium chloride (0, 90, 180, 360 mg/kg bw/day; i.e., 0, 18, 36, 72 mg Al/kg bw/day) from gestational days 8-20. On post-natal day 1, litters were culled and sex-balanced to a maximum size of 8 pups. Male pups (n=10-20) were used for neurodevelopmental and behavioural examinations. No effect was observed on body weights of dams, maternal behaviour, and reproductive parameters. No effects were seen on pup developmental parameters (weight, pinna detachment, incisor eruption, eye opening), but effects were observed on pivoting (delay at day 7 - not at day 9 and 11 - at 360 mg/kg bw) and urination (increased frequency at 180 and 360 mg/kg bw) (Misawa and Shigeta[36]).

Pregnant THA rats (n=3-4) were given single doses of aluminium chloride (0, 900, 1800 mg/kg bw/day; i.e., 0, 180, 360 Al/kg bw/day) on gestational day15. Pups were weaned on post-natal day 21 and tested for neurodevelopmental and behavioural effects at an age of 4 weeks. Two out of three rats of the high-dose group died immediately after dosing. In the remaining dams, no maternal toxic effects were observed. There were no effects on the number of implantation sites, birth rate, and litter size among the groups. In the offspring of both treatment groups, effects were seen on pup body weights, timing of pinna detachment (females), and eye opening (females). Furthermore, pups of treated dams performed less well in an auditory startle test (males), while pivoting was not affected (see above). Finally, effects were seen on ambulation (decrease in high-dose females) but not on urination (see above) (Misawa and Shigeta[37]).

In two experiments, a total of 31 pregnant Charles River CD rats (n=3/group) were treated by gavage with 0, 5, 25, 50, 250, 500, and 1000 mg aluminium/kg bw/day (as aluminium lactate) from gestational days 5-15. Maternal toxicity was not described. Except for a transient disturbance of oestrous cycle regularity in the female offspring, no consistent or reproducible effects were observed in the offspring on birth weight, anogenital distance, testicular weight, vaginal opening, duration of pseudopregnancy, number of superovulated oocytes, and ovarian weight (Agarwal *et al*.[38]).

Intraperitoneal

Pregnant CBA mice (number not specified) were injected intraperitoneally with aluminium sulphate (200 mg/kg bw/day; i.e., 32 mg Al/kg bw/day) from gestational days 10-13. To differentiate between direct effects of prenatal exposure and effects arising from alterations in maternal behaviour or physiology, pups were cross-fostered 1 day after birth (post-natal day 1) so that each mother reared two control pups and two treated pups. Pups were tested for neurobehavioural development. During the exposure period, a transient decrease in maternal body weight was observed. Furthermore, effects of prenatal aluminium exposure on maternal care (nursing, licking, pup retrieval) were observed. No effects on reproduction were seen. Birth weights of pups of aluminium treated dams were statistically significantly decreased and persisted for those pups reared by treated mothers only. Body weights of control pups fostered to treated dams were also lower than body weights of control pups reared by control mothers. Furthermore, neurobehavioural (forelimb grasping, righting reflex, screen climbing, locomotor coordination, ultrasonic vocalisations, radial maze test) and neurochemical (decreased activity of choline acetyltransferase) alterations in the offspring of treated dams were described that persisted until pups were adults (Rankin *et al*.[39]).

Pregnant C57B1/6J mice (number not specified) were given intraperitoneal injections of aluminium sulphate (200 mg/kg bw/day; i.e., 32 mg Al/kg bw/day) from gestational days 10-13. At birth, pups were cross-fostered so that each mother received two control and two treated pups and subsequently, at an age of 10 weeks, male mice (n=14/group) were tested in an eight-arm radial maze on post-natal day 70. Treatment of the mothers affected the performance of the offspring. Pups of treated mothers cross-fostered to treated mothers during lactation performed less efficiently when compared to all other groups (Santucci *et al*.[40]).

Subcutaneous

Pregnant New Zealand White rabbits (n=8-23) received 20 subcutaneous injections of aluminium lactate (0, 25, 100, 400 µmol/kg bw/injection; i.e., 0, 0.7, 2.7, 10.8 mg Al/kg bw/injection) from gestational days 2-27. On post-natal day 2, litters were culled to 6, and 3 pups of each treated dam were cross-fostered to a non-treated dam and vice versa. Body weights of dams of the mid- and high-dose groups were decreased. The incidences of stillborn foetuses or pups that died before post-natal day 2 in the low-, mid-, and high-dose group were 4, 12, and

58%, respectively, vs. 7% in the controls. In the low-dose group, body weight gain of pups of treated dams was increased, whereas in the high-dose group, body weight gain of pups of treated dams and of control pups cross-fostered to treated dams was decreased. Aluminium concentrations in various organs of pups that died before post-natal day 2 were a function of the aluminium concentration and were lower than the concentrations in the placentas and in organs of dams. Learning and memory were facilitated by lower (25 µmol) and impaired by higher (400 µmol) aluminium concentrations (see also lactation) (Yokel[41])

Gonda *et al*.[42] treated pregnant SPRD rats (n=7-10) with aluminium lactate (0, 2.45, 4.9, 9.8 mg aluminium lactate/kg bw/day; i.e., 0, 0.2, 0.4, 0.9 mg Al/kg bw/day) by subcutaneous injections from gestational days 7-15. After delivery, litter size was adjusted to 10. Pups were weaned on post-natal day 22. Only the male pups were used for a conditioned taste aversion test on post-natal day 37 and a passive avoidance learning test on post-natal day 56. No maternal toxic effects were observed. There were no effects on litter size, pup weights at birth, mortalities, and eye and ear opening. However, weight gain during lactation was lower in pups of all the aluminium-treated rats resulting in lower weights at weaning. No effects were seen in the conditioned taste aversion test, but in a passive avoidance task, the learning ability of pups of dams given 9.8 mg/kg bw/day was impaired.

4.4 Conclusions

No human studies on fertility effects of soluble aluminium compounds were available.

In animal studies, administration of aluminium chloride via the drinking water did not induce effects on reproduction.[15-17] The number of pregnant untreated mice that were mated with males treated with aluminium nitrate administered intraperitoneally at a general toxic dose level was decreased. In these males, the concentration of sperm cells in the testis and epididymis was decreased and histopathological effects were observed in the testis.[18] The study of Ondreicka *et al*.[15] was poorly reported and in the studies of Dixon *et al*.[16], Bataineh *et al*.[17], and Llobet *et al*.[18], the effects on male fertility only were studied. Furthermore, the route of administration of aluminium (intraperitoneally) in the study of Llobet *et al*.[18] was of less importance for human exposure.

Therefore, the committee proposes not to classify soluble aluminium compounds for fertility due to a lack of appropriate data.

Except for an increased prevalence of children showing talipes, no effects in humans were observed in the study of Golding *et al*.[11], describing the developmental effects of high but not specified concentrations of aluminium sulphate in drinking water.

In prenatal developmental toxicity studies with experimental animals and oral administration of soluble aluminium compounds at dose levels that did not induce general toxic effects, no effects were observed in the foetuses.[19] In the foetuses of dams orally treated with soluble aluminium compounds at dose levels inducing general toxicity, decreased foetal weights and retarded ossification were seen.[6,20-22] In general, it was shown that aluminium reached the foetuses by placental transport after *in utero* exposure to soluble aluminium compounds.[6,25,42]

The effects of soluble aluminium compounds were widely investigated in a series of post-natal developmental toxicity studies. In these studies, neurodevelopmental and/or behavioural effects of water-soluble aluminium compounds were investigated in the offspring of dams treated during gestation[27,28,30,36-42] or during gestation and lactation.[24,29,31-35] In post-natal developmental toxicity studies with soluble aluminium compounds, no effects were observed on reproductive parameters (pregnancy rate, absorptions, implantation sites, litter size, and pup weight at birth). In these studies, aluminium exposure at dose levels that caused general toxic effects generally resulted in decreased pup weight gain, increased pup mortality, and impaired neurodevelopment and behavioural effects. However, increased pup mortality and neurodevelopmental and behavioural effects were also observed after oral administration of soluble aluminium compounds at concentrations that did not induce general toxic effects. [27,29,30,32-34,36,37]

In conclusion, based on the post-natal developmental effects found in two species, viz., rats and mice, in the absence of general toxic effects, the committee proposes to classify water-soluble aluminium compounds in category 2 (*substances which could be regarded as if they cause developmental toxicity in humans*) and to label the compounds with R61 (*may cause harm to the unborn child*).

Proposed classification for fertility

Lack of appropriate data precludes assessment of soluble aluminium compounds for fertility.

Proposed classification for developmental toxicity

Category 2, R61.

Proposed labelling for effects during lactation

See Chapter 5.

Chapter 5

Lactation

5.1 Human studies

Baxter *et al*.[44] assessed the concentrations of aluminium in soya-based and cows' milk-based infant formulae and compared them with the concentration of aluminium in human breast milk. Aluminium concentrations in soya-based infant formulae (n=3) and in cows' milk-based formulae (n=7) ranged from 530 to 640 µg/L and 27 to120 µg/L, respectively. Aluminium levels in breast milk ranged from 3 to 79 µg/L (n=8). Six of the samples were between 3 and 21 µg/L. As to the two remaining samples of 69 and 72 µg/L, Baxter *et al*. wondered whether the amounts found reflected the concentration in the milk prior to sampling or contamination during sampling by, e.g., aluminium-containing deodorants on the mother.

Bougle *et al*.[45] showed that aluminium levels in human milk of 14 women ranged from 0.6 to 2.4 µmol/L (mean 1.5 µmol/L) (equivalent to 16.2-64.8 µg/L, mean 40.5 µg/L). In infants who had always been enterally fed (n=25), mean aluminium intake was 0.56 ± 0.08 µmol/kg bw/day (equivalent to 15.1±2.2 µg/kg bw/day) with aluminium levels in plasma and urine of 0.33±0.10 µmol/L (equivalent to 8.9±2.7 µg/L) and 0.47±0.09 µmol/mmol of creatine (equivalent to 12.68±2.4 µg/mmol of creatine), respectively.

In a study to assess reference values for various minor and trace elements in human milk of Italian urban and rural populations, subdivided into smokers and non-smokers, Coni *et al*.[46] found aluminium concentrations ranging between 39 and 1413 µg/g (n=59; mean: 239 µg/g; no standard deviation given). No individual levels were given, but in the groups of urban smoking mothers and of rural non-smoking mothers maximum levels were 1115 and 1413 µg/g, respectively. Coni *et al*. used a strategy to minimise the risk of chemical contamination, viz., cleansing the nipple and the areola with doubly distilled water before sampling.

Hawkins *et al*.[47] measured aluminium concentrations in samples of plasma obtained from 74 infants (14-112 days old) fed various diets (breast milk (n=15) or whey-based (n=24), fortified whey-based (n=14), preterm (n=7), soy (n=7), and casein hydrolysate infant formulae (n=7)) for at least 2 weeks before the study. Mean aluminium concentrations were 9.2 µg/L (95% CI: 5.6-12.7 µg/L) in breast milk and 165 µg/L (95% CI: 150-180 µg/L) in whey-based, 161 µg/L (95% CI: 143-180 µg/L) in fortified whey-based, 300 µg/L (95% CI: 272-328 µg/L) in preterm, 534 µg/L (95% CI: 470-598 µg/L) in soy, and 773 µg/L (95% CI: 632-914 µg/L) in casein hydrolysate infant formulae. Mean aluminium concentrations in infant plasma were 8.6 µg/L when fed breast milk and 9.2 µg/L, 10.3 µg/L, 9.7 µg/L, 12.5 µg/L, and 15.2 µg/L when given whey-based, fortified whey-based, preterm, soy, and casein hydrolysate infant formulae, respectively.

Krachler *et al*.[48] found aluminium concentrations of <10 to 380 µg/L in breast milk samples obtained from 27 Austrian mothers (median: 67 µg/L). Before collecting the milk, breasts were cleaned with doubly distilled water and air dried. Krachler stated that the highest level might be due to contamination of the specimen during collection or sample preparation.

Mandić *et al*.[49] reported aluminium levels in breast milk collected during the winter period of 1992/1993 from 42 Eastern-Croatian and Bosnia-Herzegovinian women ranging from 4 to 2670 µg/L (mean: 380±380 µg/L). Although no individual levels were given, ranges presented for various subgroups showed that at least 4 samples contained aluminium levels >1000 µg/L. The levels in the Bosnia-Herzegovinian women, a refugee population, were somewhat lower (range: 70-1010 µg/L; mean: 300±200 µg/L) when compared to those in the Eastern-Croatian group (range: 4-2670 µg/L; mean: 450±600 µg/L), a local population, but the difference was not statistically significant. Mandić *et al*. noticed that the levels found were significantly higher than those reported in the period 1989-

1991 for Italian, British, and American women but could not find an explanation for these differences.

The committee considered 710 µg aluminium/L breast milk to be the tolerable level for aluminium (all compounds) in breast milk, based on a provisional tolerable weekly intake (PTWI) of 1.0 mg/kg body weight as recommended by JECFA (see Annex E for calculations).[14]

5.2 Animal studies

The committee found studies in which the effects of subcutaneous or intravenous injection of aluminium lactate or aluminium chloride into lactating rabbits or rats was examined.[25,41,50,51] However, in view of the less relevant administration routes and the aforementioned human data indicating that human breast milk can contain aluminium concentrations in excess of levels considered to be safe, these animal studies do not contribute to a recommendation for labelling and are not further discussed.

5.3 Conclusion

In several human studies, aluminium concentrations in breast milk were reported.[44-51] In two of them[46,49], several samples exceeded 710 µg/L which the committee considers to be tolerable(see Annex E).

In conclusion, two human studies reported for several breast milk samples amounts of aluminium which exceeded the tolerable level derived by the committee. The committee is of the opinion that it is reasonable to assume that the presence of aluminium in the breast milk is due to long-term exposure to soluble aluminium compounds and that there is no relevant contribution by insoluble 'aluminium' because of its poor bioavailablity. Therefore, the committee proposes to label soluble aluminium compounds for effects during lactation; labelling of metallic aluminium and insoluble aluminium compounds is not indicated.

Proposed labelling for effects during lactation for metallic aluminium and insoluble compounds

Labelling for effects during lactation for metallic aluminium and insoluble aluminium compounds is not indicated

Proposed labelling for effects during lactation for soluble aluminium compounds

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A	The committee
B	Directive (93/21/EEG) of the European Community
C	Comments on the public draft
D	Fertility and developmental toxicity studies
E	Calculation safe level of aluminium in human breast milk

Annexes

Annex **A**

The committee

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The first draft of the present document was prepared by A.P.M. Wolterbeek from TNO Quality of Life, Zeist, the Netherlands.

The Health Council and interests

Members of Health Council Committees – which also include the members of the Advisory Council on Health Research (RGO) since 1 February 2008 – 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 President 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 establishment meeting the declarations issued are discussed, so that all members of the Committee are aware of each other's possible interests.

Annex **B**

Directive (93/21/EEC) of the European Community

4.2.3 Substances toxic to reproduction

4.2.3.1 For the purposes of classification and labelling and having regard to the present state of knowledge, such substances are divided into 3 categories:

Category 1:

Substances known to impair fertility in humans

There is sufficient evidence to establish a causal relationship between human exposure to the substance and impaired fertility.

Substances known to cause developmental toxicity in humans

There is sufficient evidence to establish a causal relationship between human exposure to the substance and subsequent developmental toxic effects in the progeny.

Category 2:

Substances which should be regarded as if they impair fertility in humans:

There is sufficient evidence to provide a strong presumption that human exposure to the substance may result in impaired fertility on the basis of:

- Clear evidence in animal studies of impaired fertility in the absence of toxic effects, or, evidence of impaired fertility occurring at around the same dose levels as other toxic effects but which is not a secondary non-specific consequence of the other toxic effects.
- Other relevant information.

Substances which should be regarded if they cause developmental toxicity to humans:

There is sufficient evidence to provide a strong presumption that human exposure to the substance may result in developmental toxicity, generally on the basis of:

- Clear results in appropriate animal studies where effects have been observed in the absence of signs of marked maternal toxicity, or at around the same dose levels as other toxic effects but which are not a secondary non-specific consequence of the other toxic effects.
- Other relevant information.

Category 3:

Substances which cause concern for human fertility:

Generally on the basis of:

- Results in appropriate animal studies which provide sufficient evidence to cause a strong suspicion of impaired fertility in the absence of toxic effects, or evidence of impaired fertility occurring at around the same dose levels as other toxic effects, but which is not a secondary non-specific consequence of the other toxic effects, but where the evidence is insufficient to place the substance in Category 2.
- Other relevant information.

Substances which cause concern for humans owing to possible developmental toxic effects:

Generally on the basis of:

- Results in appropriate animal studies which provide sufficient evidence to cause a strong suspicion of developmental toxicity in the absence of signs of marked maternal toxicity, or at around the same dose levels as other toxic effects but which are not a secondary non-specific conse-

quence of the other toxic effects, but where the evidence is insufficient to place the substance in Category 2.

- Other relevant information.

4.2.3.2 The following symbols and specific risk phrases apply:

Category 1:

For substances that impair fertility in humans:
T; R60: May impair fertility

For substances that cause developmental toxicity:
T; R61: May cause harm to the unborn child

Category 2:

For substances that should be regarded as if they impair fertility in humans:
T; R60: May impair fertility

For substances that should be regarded as if they cause developmental toxicity in humans:
T; R61: May cause harm to the unborn child.

Category 3:

For substances which cause concern for human fertility:
Xn; R62: Possible risk of impaired fertility

For substances which cause concern for humans owing to possible developmental toxic effects:
Xn; R63: Possible risk of harm to the unborn child.

4.2.3.3 Comments regarding the categorisation of substances toxic to reproduction

Reproductive toxicity includes impairment of male and female reproductive functions or capacity and the induction of non-inheritable harmful effects on the progeny. This may be classified under two main headings of 1) Effects on male or female fertility, 2) Developmental toxicity.

1) *Effects on male or female fertility,* includes adverse effects on libido, sexual behaviour, any aspect of spermatogenesis or oogenesis, or on hormonal activity or physiological response which

would interfere with the capacity to fertilise, fertilisation itself or the development of the fertilised ovum up to and including implantation.

2) *Developmental toxicity*, is taken in its widest sense to include any effect interfering with normal development, both before and after birth. It includes effects induced or manifested prenatally as well as those manifested postnatally. This includes embrytoxic/fetotoxic effects such as reduced body weight, growth and developmental retardation, organ toxicity, death, abortion, structural defects (teratogenic effects), functional defects, peri-postnatal defects, and impaired postnatal mental or physical development up to and including normal pubertal development.

Classification of chemicals as toxic to reproduction is intended to be used for chemicals which have an intrinsic or specific property to produce such toxic effects. Chemicals should not be classified as toxic to reproduction where such effects are solely produced as a non-specific secondary consequence of other toxic effects. Chemicals of most concern are those which are toxic to reproduction at exposure levels which do not produce other signs of toxicity.

The placing of a compound in Category 1 for effects on Fertility and/or Developmental Toxicity is done on the basis of epidemiological data. Placing into Categories 2 or 3 is done primarily on the basis of animal data. Data from *in vitro* studies, or studies on avian eggs, are regarded as 'supportive evidence' and would only exceptionally lead to classification in the absence of *in vivo* data.

In common with most other types of toxic effect, substances demonstrating reproductive toxicity will be expected to have a threshold below which adverse effects would not be demonstrated. Even when clear effects have been demonstrated in animal studies the relevance for humans may be doubtful because of the doses administrated, for example, where effects have been demonstrated only at high doses, or where marked toxicokinetic differences exist, or the route of administration is inappropriate. For these or similar reasons it may be that classification in Category 3, or even no classification, will be warranted.

Annex V of the Directive specifies a limit test in the case of substances of low toxicity. If a dose level of at least 1000 mg/kg orally produces no evidence of effects toxic to reproduction, studies at other dose levels may not be considered necessary. If data are available from studies carried out with doses higher than the above limit dose, this data must be evaluated together with other relevant data. Under normal circumstances it is considered that effects seen only at doses in excess of the limit dose would not necessarily lead to classification as Toxic to Reproduction.

Effects on fertility

For the classification of a substance into Category 2 for impaired fertility, there should normally be clear evidence in one animal species, with supporting evidence on mechanism of action or site of

action, or chemical relationship to other known antifertility agents or other information from humans which would lead to the conclusion that effects would be likely to be seen in humans. Where there are studies in only one species without other relevant supporting evidence then classification in Category 3 may be appropriate.

Since impaired fertility may occur as a non-specific accompaniment to severe generalised toxicity or where there is severe inanition, classification into Category 2 should only be made where there is evidence that there is some degree of specificity of toxicity for the reproductive system. If it was demonstrated that impaired fertility in animal studies was due to failure to mate, then for classification into Category 2, it would normally be necessary to have evidence on the mechanism of action in order to interpret whether any adverse effect such as alteration in pattern of hormonal release would be likely to occur in humans.

Developmental toxicity

For classification into Category 2 there should be clear evidence of adverse effects in well conducted studies in one or more species. Since adverse effects in pregnancy or postnatally may result as a secondary consequence of maternal toxicity, reduced food or water intake, maternal stress, lack of maternal care, specific dietary deficiencies, poor animal husbandry, intercurrent infections, and so on, it is important that the effects observed should occur in well conducted studies and at dose levels which are not associated with marked maternal toxicity. The route of exposure is also important. In particular, the injection of irritant material intraperitoneally may result in local damage to the uterus and its contents, and the results of such studies must be interpreted with caution and on their own would not normally lead to classification.

Classification into Category 3 is based on similar criteria as for Category 2 but may be used where the experimental design has deficiencies which make the conclusions less convincing, or where the possibility that the effects may have been due to non-specific influences such as generalised toxicity cannot be excluded.

In general, classification in category 3 or no category would be assigned on an ad hoc basis where the only effects recorded are small changes in the incidences of spontaneous defects, small changes in the proportions of common variants such as are observed in skeletal examinations, or small differences in postnatal developmental assessments.

Effects during Lactation

Substances which are classified as toxic to reproduction and which also cause concern due to their effects on lactation should in addition be labelled with R64 (see criteria in section 3.2.8).

For the purpose of classification, toxic effects on offspring resulting *only* from exposure via the breast milk, or toxic effects resulting from *direct* exposure of children will not be regarded as 'Toxic to Reproduction', unless such effects result in impaired development of the offspring.

Substances which are not classified as toxic to reproduction but which cause concern due to toxicity when transferred to the baby during the period of lactation should be labelled with R64 (see criteria in section 3.2.8). This R-phrase may also be appropriate for substances which affect the quantity or quality of the milk.

R64 would normally be assigned on the basis of:

a) toxicokinetic studies that would indicate the likelihood that the substance would be present in potentially toxic levels in breast milk, and/or
b) on the basis of results of one or two generation studies in animals which indicate the presence of adverse effects on the offspring due to transfer in the milk, and/or
c) on the basis of evidence in humans indicating a risk to babies during the lactational period. Substances which are known to accumulate in the body and which subsequently may be released into milk during lactation may be labelled with R33 and R64.

Annex **C**

Comments on the public draft

A draft of the present report was released in 2008. The following persons and organisations have commented on the draft document:

- D. de Halleux, European Chemical Industry Council – Cefic aisbl, Brussels, Belgium
- G. Jonkers, Vereniging van Verf- en Drukinktfabrikanten (VVVF), Leidschendam, the Netherlands
- E. Nordheim, European Aluminium Association AISBL, Brussels, Belgium
- B. Sjögren, Karolinska Institutet, Stockholm, Sweden
- J.J. Tellekamp, Arbo Unie Zeeland, Middelburg, the Netherlands
- R.T.H. van Welie, Nederlandse Cosmetica Vereniging, Zeist, the Netherlands
- R.D. Zumwalde, National Institute for Occupational Safety and Health (NIOSH), Cincinnati, USA

Annex **D**

Fertility and developmental toxicity studies

Table 1 Fertility studies in animals with water-insoluble aluminium compounds

Authors	Species	Experimental period/design	Dose/route	General toxicity	Effects on reproductive organs/effects on reproduction
Pettersen (1990)	Beagle dogs (n=4/sex/group)	Dogs were treated for 26 w.	0, 3, 10, 30 g KASAL/kg diet (KASAL = basic sodium aluminium phosphate) (including Al in basal diets, mean elemental Al levels were 4, 10, 27, 75 mg Al/kg bw/d in males, and 3, 10, 22, 80 mg Al/kg bw/d in females	Decreased food consumption and body weights in 30 g/kg group.	In 30 g/kg group decreased absolute testis weight and histopathological effects in testes of 2 of 4 males.

Table 2 Developmental toxicity studies in animals with water-insoluble aluminium compounds

Authors	Species	Experimental period/design	Dose/route	General toxicity	Developmental toxicity	Remarks
Domingo (1989)	Swiss mice (n=18-20/ group)	Mice were treated from GD 6-15 and sacrificed on GD 18 for foetal examinations.	0, 66.5, 133, 266 mg/kg bw/d $Al(OH)_3$ (i.e., 0, 23, 46, 92 mg Al/ kg bw/d); gavage.	No effects on food consumption, body weights, organ weights, appearance and behaviour.	No effects on number of implanation sites, resorptions, number of live and dead foetuses, sex ration, foetal weights, foetal lengths, and external, soft-tissue, skeletal abnormalities.	-
Gomez (1990)	Wistar rats (n=18-19 / group)	Rats were treated from GD 6-15 and sacrificed on GD 20 for foetal examinations.	0, 192, 384, 768 mg/kg bw/d $Al(OH)_3$ (i.e., 0, 66, 133, 266 mg Al/kg bw/d); gavage.	No effects on body weight. Food consumption slightly decreased. No effects on liver and kidney weights.	No effects on pregnancy rate, implantation sites, resorptions, live- and dead foetuses, foetal weight, and external, soft-tissue, skeletal abnormalities.	No differences in aluminium concentration of liver, brain and bone of dams and placentas. No aluminium detected in foetuses
Gomez (1991)	Sprague-Dawley rats (n=15-18 / group)	Rats were treated from GD 6-15 and sacrificed on GD 20 for foetal examinations.	384 mg/kg bw/d $Al(OH)_3$; 1064 mg/kg bw/d Al citrate (i.e., 133 mg Al/kg bw/d for both compounds); gavage	No effects on body weights, food consumption, liver, kidney and brain weights.	No effects on pregnancy rate, implantations, resorptions, live- and dead foetuses, foetal weight. Except for increased incidence of foetuses treated with aluminium citrate of which xiphoides was absent no effects on external, soft-tissue, skeletal abnormalities.	No aluminium was detected in foetuses. Effects on foetal weights and skeletal abnormalities were observed after concurrent citric acid and aluminium hydroxide treatment.
Colomina (1992)	Swiss mice (n=10-13 / group)	Mice were treated from GD 6-15 and sacrificed on GD 18 for foetal examinations.	166 mg/kg bw/d of $Al(OH)_3$; 627 mg/kg bw/d of Al lactate (i.e, 57 mg Al/kg bw/d for both compounds); gavage.	$Al(OH)_3$: No effects in body weights and food consumption Al lactate: decreased food food consumption and body weights.	No effects on pregnancy rate, implantations, resorptions, live and dead foetuses. Al lactate: Foetal weight decreased, increased incidence if cleft palate, delayed ossification.	Concentration of Al in foetuses of Al lactate group was higher than in $Al(OH)_3$foetuses of group.
Colomina (1994)	Swiss mice (n=not specified)	Mice were treated from GD 6-15 and sacrificed on GD 18 for foetal examinations.	300 mg/kg bw/d of $Al(OH)_3$ (i.e., 104 mg Al/kg bw/d) with or without ascorbic acid (85 mg/kg bw/d); gavage.	Decreased food consumption of dams treated with Al alone. No effects on body weights	No effects on number of implantations, resorptions, live foetuses, implantation loss, sex ratio, foetal body weights, and external, soft-tissue, skeletal abnormalities	Concentration of Al in foetuses was not increased. No effects of ascorbic acid.

Table 3 Fertility studies in animals with water-soluble aluminium compounds

Authors	Species	Experimental period/design	Dose/route	General toxicity	Effects on reproductive organs/effects on reproduction
Ondriecka (1966)	Dobra Voda mice (n=10/group)	Mice were treated from 4 w of age for several generations.	0, 19.3 mg Al/kg bw/d as $AlCl_3$; drinking water	No effects on body weights in first 2 generations. In subsequent generations decreased growth. No effects on red blood cell count and histopathology of liver, spleen and kidneys.	No effects on number of litters of offspring.
Dixon (1979)	Male Sprague Dawley rats (n=31/group)	Rats were treated for up to 90 d. On day 30, 60 and 90 seven rats/group were sacrificed. From day 90 onwards remaining rats were not treated and used for 10 serial matings with untreated females.	0, 44.8, 447.6, 4476 mg $AlCl_3.6H_2O$ /L in drinking water (0, 5, 50, 500 mg Al/L)	No histopathological effects in liver, lung, spleen, kidneys, brain, heart.	No histopathological effects in testes. Reproductive capacity of male was not affected. No effect on plasma concentration of LH and FSH.
Llobet (1995)	Male Swiss mice (n=18/group)	Mice were treated for 4 w. and mated with untreated females or sacrificed.	0, 50, 100, 200 mg/kg bw/d $Al(NO)_3.9H_2O$ (i.e., 0, 3.6, 7.2, 14.4 mg Al/kg bw/d); intraperitoneal injections.	Decreased body weights in all treatment groups.	Decreased number of pregnant females in 100 and 200 mg/kg groups. No effects on implantations, resorptions, live and dead foetuses. Absolute weight of testes and epididymal weight decreased. No effects on relative weights. Sperm cell concentration decreased in testes (100 and 200 mg/kg) and epididymides (200 mg/kg). No effects on sperm motility and morphology. Histopathological changes in testes (100 and 200 mg/kg)
Bataineh (1998)	Male Sprague Dawley rats (n=10-13/group)	Rats were treated for 12 weeks and mated with untreated females	0, 1000 mg $AlCl_3.6H_2O$ /L drinking water (i.e., 0, 9 mg Al/kg bw/d, calculated from a bw of 309 g and an assumed water intake of 25 mL/d)	Decreased body weights	Sexual- and aggressive behaviour was suppressed. No effects on reproduction. Absolute weight of testes and seminal vesicles decreased. No effects on relative weights.

Table 4 Prenatal developmental toxicity studies in animals with water-soluble aluminium compounds

Authors	Species	Experimental period/design	Dose/route	General toxicity	Developmental toxicity	Remarks
McCormack (1979)	Sprague Dawley rats (n=6-8/ group)	Rats were treated from GD 6-19 and sacrificed on GD 19 for foetal examinations.	119 (control), 500, 1000 mg $AlCl_3$/kg diet	Not described	No effects on the number of live foetuses, resorptions, foetal weight, foetal crown-rump length, whole carcass aluminium concentration and external, soft-tissue, skeletal abnormalities.	-
Wide (1984)	NRMI mice (n=8-28/ group)	Mice were treated on GD 3 or GD 8 and sacrificed on GD 17 for foetal examinations.	0, 50, 100 mM and 0, 50 mM of $AlCl_3.6H_2O$ on GD 3 and GD 8, respectively (i.e., 0, 4.5, 9 mg Al/kg bw, assuming a bw of 30 g); intravenous injection	Not described	No effects on pregnancy rate, resorptions, number of foetuses per litter, foetal weight, external abnormalities. GD 3, 100 mM: increased incidence of foetuses with abdominal haemorrhages. GD 8, 50mM: Increased incidence of foetuses with retarded skeletal ossification and abdominal haemorrhages.	-
Golub (1987)	Swiss Webster mice (n=10/ group)	Mice were treated on GD 3, 5, 7, 9, 11, 13 and 15 and sacrificed on GD 18 for foetal examinations.	0, 10, 20, 40 mg Al/kg bw (as Al lactate); subcutaneous injection.	No effects on body weight, food consumption, mortalities. (Severe) necrotic skin lesions near injection sites. Increased spleen and liver weight in 20 mg/kg bw group.	Dose-related decreased pregnancy rate. No effects on foetal resorptions, number of foetuses per litter, uterine weight, foetal weight, and external, soft-tissue, skeletal examinations. Crown-rump length decreased in 20 mg/kg bw group.	Due to severe necrotic skin lesion sand very low pregnancy rate data from highest dose group not presented.
Paternain (1988)	Sprague Dawley rats (n=7-10)	Rats were treated from GD 6-14 and sacrificed on GD 20 for foetal examinations.	0, 180, 360, 720 mg/kg bw/d $Al(NO)_3.9H_2O$ (i.e., 0, 13, 26, 52 mg Al/kg bw/d); gavage.	Bodyweight gain decreased in all treatment groups.	No effects on implantations, resorptions, live- and dead foetuses. Foetal body weight decreased and effects on skull, ribs, sternebrae in all treatment groups. Increased incidence of foetuses with haematomas in abdomen, thorax and limbs in 720 mg/kg bw group.	-

Colomina (1998)	Swiss mice (n=10-14 / group)	Mice were treated from GD 6-15 and sacrificed on GD 18 for for foetal examinations	0, 37.5, 75 mg/kg bw/d of $AlCl_3$ (i.e., 0, 7.6, 15 mg Al/kg bw/d); intraperitoneal injection.	No effects on food consumption and body weight. One and 2 mice died in 37.5 and 75 mg/kg bw/d groups, respectively. No effects on liver and kidney weights.	Gravid uterine weight and foetal weights was decreased in both groups. No effects on pregnancy rate, implantations, resorptions, live and dead foetuses. No effects on external, soft-tissue, skeletal examinations.	-
Bellés (1999)	CD 1 mice (n=10-32 / group)	Mice were treated from GD 6-15 and sacrificed on GD 18 for foetal examinations.	0, 398 mg/kg bw/d of $Al(NO)_3.9H_2O$ (i.e., 0, 29 mg Al/kg bw/); gavage.	Decreased food consumption and body weight gain during gestation. Incidence of dead females in treatment group was 56%.	No effects on resorptions, live- and dead foetuses and sex ratio. Foetal weights were decreased. No effects on external, soft-tissue examinations. Retarded ossification of various bones.	-
Albina (2000)	CD1 mice (n=10-14 / group)	Mice were treated on GD 8, 9, 10, 11, or 12 and sacrificed on GD 18 for foetal examinations.	995 mg/kg bw/d of $Al(NO)_3.9H_2O$ (i.e., 72 mg Al/kg bw/d); gavage.	Decreased body weight gain during gestation.	Except for females treated on GD 11 the number of females with live foetuses was decreased. No effects on resorptions, live- and dead foetuses, and sex ratio. Foetal weights decreased. No effects on external, soft-tissue examinations. Retarded skeletal ossification.	-
Yumoto (2001)	Wistar rats (n=3)	Rats were treated on GD 16 and sacrificed on GD 21 for determination of placental transfer.	705 pg of $^{26}AlCl_3$ and 0.28 mg $^{27}AlCl_3$; subcutaneous injection	No maternal toxicity	No foetal toxicity. About 0.23% of the aluminium injected into the dam was transferred to the foetus by placental transfer.	-

Table 5 Post-natal developmental toxicity studies in animals with water-soluble aluminium compounds

Authors	Species	Experimental period/design	Dose/route	General toxicity	Developmental toxicity
Yokel (1985)[34]	New Zealand White rabbits (n=8-23 / group)	Rabbits were treated on GD 2-6, 9-13, 16-20, 23-27. On PN day 2, litters were culled to 6 and pups were cross fostered from control to treated dams and vice versa. Pups were used for testing of effects on learning and memory.	0, 25, 100, 400 µmol Al/kg bw/ injection (i.e., 0, 0.7, 2.7, 10.8 mg Al/kg bw/ injection) as Al lactate; subcutaneous injection	Body weight of dams of 100 and 400 µmol groups were decreased.	Incidence of stillborn pups and pups that died before PN 2 was increased. Pups body weights increased in 25 µmol group and decreased in 400 µmol group. Milk consumption was dose-related decreased. Learning and memory were facilitated in the 25 µmol group and impaired in the 400 µmol group.
Bernuzzi (1986)	Wistar rats (n=12-14 / group)	Rats were treated from GD 8-21 and pups were used in a series of neuromotor developmental tests.	0, 160, 200 mg Al/kg bw/d as $AlCl_3$; diet.	No maternal toxic effects.	No effect on litter size at birth. Pup mortality from PN 1-18 increased in both treatment groups. Pup weights decreased between PN 1-7. Decreased performance in righting reflex, negative geotaxis test. No effects in grasping reflex, suspension test and locomotor coordination test.
Domingo (1987)	Sprague Dawley rats (n=10/ group)	Rats were treated from GD 14-PN 21.	0, 180, 360, 720 mg/kg bw/d of $Al(NO)_3.9H_2O$ (i.e., 0, 13, 26, 52 mg Al/kg bw/d); gavage	Not described	No effect on pregnancy rate and live pups/litter. Decreased pup weights and tail length in all groups. Decreased pup length in 360 and 720 mg/kg groups. No effects on relative organ weights.
Golub (1987)	Swiss Webster mice (n=6-14 / group)	Mice were treated during gestation and lactation. Pups were used for neurobehavioural testing. Pair-fed control group included.	100 (control), 500, 1000 mg Al/kg diet (i.e., 15-60, 95-275, 170-390 mg Al/kg bw/d, calculated from data provided by Golub) as Al lactate.	No effects on body weight at parturition. 500 and 1000 mg/kg: Decreased food consumption and body weight gain during lactation. Ataxia. 1 and 4 dead dams.	No effect on litter size. Dose-dependent effects on pup weights and crown-rump length. Weight of liver and spleen decreased in 1000 mg/kg group. Slight reduced performance in neurobehavioural performance.
Bernuzzi (1989)	Wistar rats (n=5-12 / group)	Rats were treated during the entire gestation period. Pups were used for neuromotor development testing within 2 weeks after birth.	0, 100, 300, 400 mg Al/kg bw/d as $AlCl_3$ or Al lactate; diet.	On GD 18, decreased body weights in 300 and 400 mg/kg chloride and 400 mg/kg lactate groups.	No effect on litter size. Pup mortality increased and pup weights decreased in 300 and 400 mg/kg chloride and 400 mg/kg lactate groups. Neuromotor development delayed.

Donald (1989)	Swiss Webster mice (n=16 in 3 groups)	Mice were treated during gestation and lactation and pups were used for (neurobehavioural) development testing.	25 (control), 500, 1000 mg Al/kg diet (i.e., 5-10, 100-210, 200-420 mg Al/kg bw/d; according to Donald) as Al lactate	No maternal toxicity.	No effects on pregnancy rate, litter size, sex ratio, birth rate. Pre-weaning: No effects on pup mortality, pup growth. 1000 mg/kg: effect in climbing test. Post-weaning: Effects in foot splay test, fore- and hind limb grip strength, thermal sensitivity. No effects in startle response.
Muller (1990)	Wistar rats (n=6-9 / group)	Rats were treated from GD 1-7, GD 1-14 or GD 1-21. Pups were tested for neuromotor development and learning ability.	400 mg Al/kg diet as Al lactate.	GD 1-21: decreased food consumption and body weight gain.	No effects on litter size, mortality, pup weights. Performance in negative geotaxis test (GD 1-7 and GD 1-14), locomotor coordination test and operant conditioning test (all groups) was decreased.
Misawa (1992)	THA rats (n=4 / group)	Rats were treated from GD 8-20 and male pups were used for (neuro)developmental and behavioural examinations.	0, 90, 180, 360 mg/kg bw/d of $AlCl_3$ (i.e, 0, 18, 36, 72 mg Al/kg bw/d); gavage.	No effects on body weights and maternal behaviour.	No effects on reproductive parameters. No effects on pup developmental parameters. Effects on neuromotor development (180, 360 mg/kg groups)
Golub (1992)	Swiss Webster rats (n=9-14 / group)	Rats were treated during gestation and lactation and pups were used for neurodevelopmental testing. At birth pups were cross-fostered.	25 (control); 1000 mg Al/kg diet (ca. 250 mg Al/kg bw/d; according to Golub) as Al lactate.	No effects during gestation. Food intake and body weights decreased during lactation. Neurotoxic effects in 1 dam. 4 dams died after weaning.	PN day 10 onwards: decreased pup weights. Neurobehavioural effects in all foster groups. No effect on aluminium concentration in liver and brain but concentrations of manganese and iron concentrations decreased in liver.
Misawa (1993)	THA rats (n=3-4/group)	Rats were treated on GD 15 and pups were tested for (neuro)developmental and behavioural effects at an age of 4 weeks.	0, 900, 1800 mg/kg bw of $AlCl_3$ (i.e., 0, 180, 360 mg Al/kg bw); gavage.	1800 mg/kg: 2 rats died after dosing. Remaining rats: no toxic effects.	No effects on implantations, birth rate, litter size. Effects on pup body weights, pinnan detachment, eye opening. Performance in auditory startle test was impaired.
Rankin (1993)	CBA mice (n=not specified)	Mice were treated from GD 10-13. Pups were cross fostered and tested for (neuro)behavioural development.	0, 200 mg/kg bw/d of $Al_2(SO_4)_3$ (i.e., 32 mg Al/kg bw/d); intraperitoneal injection.	Decreased body weight during exposure period. Impaired maternal care.	No effects on reproduction. Decreased pup weights that persisted in pups reared by treated mothers only. Impaired (neuro)behavioural development. Decreased activity of choline acetyltransferase in brain.
Santucci (1994)	C57B1/6J mice (n=not specified)	Mice were treated from GD 10-13 and pups were cross-fostered and used for neurodevelopmental testing.	0, 200 mg/kg bw/d of $Al_2(SO_4)_3$ (i.e., 32 mg Al/kg bw/d); intraperitoneal injection.	Not described	Male offspring performed less in a radial 8-arm maze test at PN day 70.

Golub (1994)	Swiss Webster mice (n=not specified)	Mice were treated during gestation and lactation. At weaning half of the pups of the 1000 mg/kg group were fed control diets, the other half the same diet as their parents. Pups were studied for effects on neurodevelopment.	7 (control), 1000 mg Al/kg diet as Al lactate (i.e., ca. 200-420 and 130 mg Al/kg bw/d in maternal mice and adult offspring, respectively; according to Golub).	No effects.	Reduced auditory startle response on PN 22 and 52. Effect on PN 52 was more pronounced in pups continuously treated with aluminium as compared to pups that were fed control diets after weaning.
Golub (1995)	Swiss Webster mice (n=40/ group)	Mice were treated from GD 1 until weaning. At weaning, pups were given the same diet as their parents or were fed control diets. Pups were studied for effects on neurobehaviour.	7 (control), 500, 1000 mg Al/kg diet as Al lactate (i.e., ca. 1.4-2.9, 100-210, 200-420 mg Al/kg bw/; according to Golub)	No effects	No effects on gestation length, litter size, pup weights, pup organ weights. 1000 mg/kg: increased cage mate aggression. Long-term, not dose-dependent effects on neurobehaviour.
Agarwal (1996)	Charles River CD rats (n = 3/group)	Rats were treated from GD 5-15 and pups were studied for effects on (sexual) development.	0, 5, 25, 50, 250, 500, 1000 mg Al/kg bw/d as Al lactate; gavage.	Not described.	Transient disturbance in oestrous cycle regularity. No effects on birth weight, anogenital distance, testes weight, vaginal opening, duration of pseudopregnancy, number of superovulated oocytes and ovarian weight.
Gonda (1996)	SPRD rats (n=7-10 / group)	Rats were treated from GD 7-15. Male pups were tested in a taste aversion test and a passive avoidance learning test.	0, 2.45, 4.9, 9.8 mg/kg bw/d of Al lactate (i.e., 0, 0.2, 0.4, 0.9 mg Al/kg bw/d); subcutaneous injection	No effects	No effects on litter size, pup weights at birth, mortalities, eye and ear opening. Pup weights gain during lactation decreased in all treatment groups. No effects in taste version test. Passive avoidance test was impaired in pups of 9.8 mg/kg bw group.
Golub and German (2001)	Swiss Webster mice (n=30-40 / group)	Mice were treated from GD 1 until weaning. Offspring was fed the same diets as their parents. Female pups were evaluated in a cognitive task test and male pups in a motor developmental test battery.	7 (control), 100, 500, 1000 mg Al/kg diet as Al lactate (ca. <1, 10, 50, 100 mg Al/kg bw/d; according to Golub/German).	No effects	No effects on litter size or birth weight. 500 and 1000 mg/kg groups: Pup weight gain decreased during lactation. 1000 mg/kg group: Decreased performance in Morris Maze test and motor activity tests.

Annex **E**

Calculation safe level of aluminium in human breast milk

In order to protect up to 6-month-old breastfed children from the effects of aluminium through intake of breast milk, the committee uses the following default values:

- Body weight infant: 4.5 kg
- Intake human breast milk per infant per day: 900 mL
- An infant is as sensitive for the effects of aluminium as an adult

These assumption are used for the calculation of a tolerable level of aluminium in human breast milk. These values are conservative figures estimated from growth curves published for the Netherlands[53,54] and by the WHO[55] and breast milk intake[56]

At the sixty-seventh meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA), a provisional tolerable weekly intake (PTWI) of 1.0 mg/kg bw was recommended.[14]

This corresponds to:

- a tolerable intake of 0.14 mg/kg bw/day
- a tolerable intake of 0.64 mg/infant/day
- a tolerable concentration of aluminium in breast milk of 710 µg aluminium/L

In conclusion, the committee considers 710 µg aluminium/L breast milk as a tolerable level.