European Commission

Scientific Committee on
Health, Environmental and Emerging Risks
SCHEER

FINAL OPINION ON
tolerable intake of aluminium with regards to adapting the migration limits for aluminium in toys

Scientific Committees
on Consumer Safety
on Health, Environmental and Emerging Risks

The SCHEER adopted this Opinion
on 28 September 2017

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SCHEER

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ABSTRACT

Following a request from the European Commission, the Scientific Committee on Health, Environmental and Emerging Risks (SCHEER) hereby reviews the currently available data on the toxicity of aluminium, taking into account the different tolerable intake levels for aluminium established by the European Food Safety Authority in 2008 and by the Joint FAO/WHO Expert Committee on Food Additives in 2011, and presents its recommendation for a tolerable intake level for aluminium based on most recent data that could be used to adapt the migration limits for aluminium in the Toy Safety Directive 2009/48/EC, taking into account the exposure to aluminium from sources other than toys.

The SCHEER is of the opinion that for the time being the study by Poirier *et al.* from 2011 is the fundamental study for the derivation of a health-based limit value. Using the NOAEL of 30 mg/kg bw/d from this study (based on neuro-developmental effects seen at 100 mg/kg bw/d) as the Point of Departure and applying the default assessment factor of 100, a tolerable daily intake (TDI) of 0.3 mg/kg bw/d is considered appropriate by the SCHEER for the calculation of migration limits for aluminium from toys.

The resulting migration limits for aluminium from toys, calculated according to the current legislation, which allocates 10% of the tolerable daily intake to toys, are 2250 mg aluminium/kg of dry, brittle, powder-like or pliable toy material, 560 mg aluminium/kg of liquid or sticky toy material and 28130 mg aluminium/kg of scraped-off toy material.

However, the SCHEER noted that exposure to aluminium from sources others than toys, in particular from diet, which is by far the major source of chronic exposure, may already exceed the reference value for tolerable weekly intake as derived by JECFA. Therefore, the SCHEER recommends that the additional exposure from toys should be minimised.

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1. MANDATE FROM THE EU COMMISSION SERVICES

1.1. Background as provided by the Commission

The Toy Safety Directive2009/48/EC[1] establishes migration limits for 19 elements in toys or components of toys, depending on the type of toy material used: dry, brittle, powder-like or pliable toy material; liquid or sticky toy material; and scraped-off toy material. These migration limits, listed in point 13 of Section III of Annex II of the Directive, must not be exceeded.

The migration limits were based on a 2008 Report[2] listing available Tolerable Daily Intake (TDI) data for each of the 19 elements.[3] For aluminium, the TDI was given as 0.75 mg/kg bw/d, derived from data of the Office of Environmental Health Hazard Assessment (OEHHA) with own considerations added.[4] This TDI corresponds to 5.25 mg/kg bw/w.

The migration limits in Directive 2009/48/EC were calculated by taking 10 % of the TDI (in order to take account of the exposure to aluminium from sources other than toys), multiplied by the bodyweight of a child (7,5 kg for a child below 3 years of age) and divided by the quantity of toy material ingested per day: 100 mg for dry, brittle, powder-like or pliable toy material, 400 mg for liquid or sticky toy material, and 8 mg for scraped-off toy material. These daily ingestion amounts were recently confirmed by SCHER.[5] The current migration limits for aluminium in Directive 2009/48/EC are thus: 5625 mg/kg in dry, brittle, powder-like or pliable toy material, 1406 mg/kg in liquid or sticky material, and 70000 mg/kg in scraped-off toy material.

The European Food Safety Authority (EFSA) established in 2008 a Tolerable Weekly Intake (TWI) of 1 mg aluminium/kg bw/w, based on the combined evidence from several studies in mice, rats and dogs that used dietary administration of aluminium compounds.[6] In view of the cumulative nature of aluminium in the organism after dietary exposure, EFSA considered it more appropriate to establish a TWI rather than a TDI.

To note that under Regulation (EU) No 10/2011 on plastic materials and articles intended to come into contact with food, a new aluminium limit has recently been established[7], based on the above EFSA TDI. Due to the high dietary exposure of a significant part of the European Union's population to aluminium (see the EFSA Opinion in footnote 6), the

[1] Directive 2009/48/EC of the European Parliament and of the Council of 18 June2009 on the safety of toys. OJ L 170, 30.06.2009, p. 1: http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:02009L0048-20140721&rid=1

[2] RIVM advisory report of 2008, Chemicals in toys. A general methodology for assessment of chemical safety of toys with a focus on elements. http://www.rivm.nl/bibliotheek/rapporten/320003001.pdf

[3] RIVM advisory report of 2008 (see footnote above), Table 2-2 on p. 26, Table 8-1 on p. 114.

[4] OEHHA (2000) Public health goal for aluminium in drinking water. Pesticide and Environmental Toxicology Section Office of Environmental Health Hazard Assessment California Environmental Protection Agency. DRAFT dated February 2000. Referred to in the RIVM advisory report of 2008 (see footnote above), section II.1.6, p. 145.

[5] Scientific Committee on Health and Environmental Risks (SCHER) Opinion on Estimates of the amount of toy materials ingested by children. Adopted on 8 April 2016.

[6] European Food Safety Authority (EFSA) Panel on Food Additives, Flavourings, Processing Aids and Food Contact Materials (AFC) (2008) Scientific Opinion on Safety of aluminium from dietary intake. The EFSA Journal (2008) 754, 1-34: http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2008.754/pdf

[7] Commission Regulation (EU) 2016/1416. OJ L 203, 25.8.2016, p. 22: http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32016R1416&from=EN

contribution from exposure by food contact materials to the overall exposure was calculated by applying an allocation factor of 10 % to the conventionally derived migration limit.

The Joint FAO/WHO Expert Committee on Food Additives (JECFA) evaluated available data for aluminium in 2011.[8] The Committee concluded that a No Observed Adverse Effect Level (NOAEL) of 30 mg/kg bw/d was appropriate for establishing a Provisional Tolerable Weekly Intake (PTWI) for aluminium compounds. Because long-term studies on the relevant toxicological endpoints had become available, there was no longer the need for an additional uncertainty factor for deficiencies in the database. The Committee therefore established a PTWI of 2 mg/kg bw/w from the NOAEL of 30 mg/kg bw/d by applying an uncertainty factor of 100 for interspecies and intraspecies differences.

Thus, both EFSA and JECFA established tolerable intake levels for aluminium that are notably lower than the level that was the basis for the migration limits for aluminium in the Toy Safety Directive 2009/48/EC. This suggests that the migration limits might need to be adapted.

1.2. Terms of reference

SCHEER is asked:

1. To review the available data on the toxicity of aluminium that are currently available, taking into account the different tolerable intake levels for aluminium established by EFSA in 2008 and JECFA in 2011;

2. To advise on a tolerable intake level for aluminium based on most recent data that could be used to adapt the migration limits for aluminium in the Toy Safety Directive 2009/48/EC, taking account of the exposure to aluminium from sources other than toys.

Timeline

Preliminary opinion – May 2017

Final opinion – autumn 2017

[8] WHO (2011) Technical Report 966 – Evaluation of certain food additives and contaminants. 74th report of the Joint FAO/WHO Expert Committee on Food Additives. P. 16: http://apps.who.int/iris/bitstream/10665/44788/1/WHO_TRS_966_eng.pdf

2. OPINION

The SCHEER is requested to review the available data on the toxicity of aluminium that are currently available, taking into account the different tolerable intake levels for aluminium established by EFSA in 2008 and JECFA in 2011.

When deriving a tolerable intake level for aluminium, EFSA (2008) took into account available studies, although they were characterised by a number of limitations. Applying a weight of evidence approach, the EFSA Panel combined results from mice, rats and dogs after dietary administration of aluminium compounds and compared results by using both the lower end of the lowest observed adverse effect level (LOAEL) range (50 mg aluminium/kg bw/d) as well the lowest NOAEL (10 mg aluminium/kg bw/d) as the Point of Departure (PoD). When the LOAEL of 50 mg aluminium/kg bw/d was used, a tolerable daily intake (TDI) of 0.17 mg aluminium/kg bw/d was obtained by applying an assessment factor of 100 (accounting for inter- and intraspecies variations) and an additional factor of 3 for using a LOAEL instead of a NOAEL. Alternatively, when the lowest NOAEL of 10 mg aluminium/kg bw/d for neurodevelopmental toxicity in mice was used, a TDI of 0.10 mg aluminium/kg bw/d could be established, applying the assessment factor of 100. The EFSA Panel considered it more appropriate to establish a tolerable weekly intake (TWI) rather than a TDI, due to the aluminium accumulation in the body after dietary exposure. The TWI values obtained considering the LOAEL and the NOAEL approaches were 1.2 mg/kg bw/w and 0.7 mg/kg bw/w, respectively. Due to the limitations of the available studies, significant uncertainties in defining reliable NOAELs and LOAELs and the lack of evidence of a clear dose response, the EFSA Panel concluded that a value of 1 mg aluminium/kg bw/w, representing a rounded value between the TWIs provided by the LOAEL and NOAEL approaches, should be established as the TWI.

In 2011, JECFA revised its previous Opinion on aluminium taking into account a new 12-month neuro-developmental toxicity study on aluminium citrate, administered via drinking water to Sprague-Dawley rats (Poirier *et al.* 2011). From this study, considered as the reference, a LOAEL of 100 mg/kg bw/d for neurodevelopmental effects, specifically on hind limb and fore grip strength, and a NOAEL of 30 mg/kg bw/d were obtained. Based on the higher bioavailability of aluminium citrate when compared to other aluminium compounds, JECFA concluded that the NOAEL of 30 mg/kg bw/d could be considered as appropriate for other aluminium compounds. By applying the default assessment factor of 100, a PTWI of 2 mg/kg bw/w was established from the NOAEL of 30 mg/kg bw/d. As a consequence, the previous PTWI of 1 mg/kg bw/w derived by JECFA in 2007 was withdrawn.

Taking into account the different approaches by EFSA and JECFA and considering the available data on toxicity of aluminium, the SCHEER is of the opinion that the study by Poirier *et al*. from 2011 is the fundamental study for the derivation of a health-based limit value for migration limits for aluminium from toys. Renal pathology, most prominently in the male pups, was mostly observed in the high dose group, where higher mortality and significant morbidity occurred. A dose–dependent neuromuscular functions impairment—hind-limb and fore-limb grip strength—was observed at the high- (300mg/kg bw/d) and to a lesser extent at mid-dose (100 mg/kg bw/d) aluminium-treated groups, in both males and females. This effect, which was more pronounced in young animals, was taken as the critical effect. No other treatment-related neurobiological effects were observed in the different groups. Therefore, taking the NOAEL of 30 mg/kg bw/d from this study as the PoD and applying the default assessment factor of 100, a TDI of 0.3 mg/kg bw/d should be the base

for the calculation of migration limits for aluminium from toys. The same PoD was used by JECFA for the derivation of the PTWI.

The SCHEER is requested to advise on a tolerable intake level for aluminium based on most recent data that could be used to adapt the migration limits for aluminium in the Toy Safety Directive 2009/48/EC, taking account of the exposure to aluminium from sources other than toys.

Based on (1) a TDI of 0.3 mg/kg bw/d and (2) the SCHER (2010) Opinion which recommends allocating a maximum of 10% of the TDI to exposure from toys, the corresponding migration limits for aluminium from toys should be set to 2250 mg aluminium/kg dry, brittle, powder-like or pliable toy material, 560 mg aluminium/kg liquid or sticky toy material and 28130 mg aluminium/kg scraped-off toy material. The calculation of the migration limits is carried out according to the following equation:

$$ML = \frac{10\%\, TDI \cdot BW}{A_{TM}} \text{ mg element/mg toy material}$$

where:

ML	=	migration limit (mg element /mg toy material)
TDI	=	Tolerable Daily Intake (mg/kg bw/d)
BW	=	body weight (default 7.5 kg)
A_{TM}	=	amount of toy material ingested (8, 100, or 400 mg)

However, the SCHEER recognises that dietary aluminium intake for children, although variable and dependent on the specific diet, in many cases exceeds the reference values established by EFSA and JECFA. This is especially true, but not limited, to children fed with soy-based infant-formulas.

Drinking water represents an additional, although minor, source of chronic exposure. Intermittent exposure from the use of aluminium compounds in consumer products (e.g. cosmetic and antiperspirant via dermal absorption) or exposure via inhalation, related to dust can occur. In addition, there may also be intermittent exposure to aluminium from pharmaceuticals via the oral and parenteral route.

Taking into account the high exposure to aluminium from diet and other sources, exceeding the PTWI as derived by both EFSA as well as JECFA, the SCHEER is of the opinion that the additional exposure from toys should be minimised.

3. MINORITY OPINIONS

None.

4. DATA AND METHODOLOGIES

Scientific data on the toxicity of aluminium and information regarding approaches to derive NOAEL values were collected from available open literature, websites and from documents of other Scientific Committees and International Organisations (e.g. WHO, EPA, EFSA, JECFA).

4.1. Literature search

A literature research was undertaken in order to determine whether there were any key publications since 2008 that needed to be considered in forming this Opinion. The search terms were provided to the European Commission Library and e-Resources Centre. The results are based on open access articles from Find-eR and PubMed to obtain an indication of the numbers of possible publications. The following terms were used in carrying out the literature review and the terms were searched in the title, abstract, key word fields:

- Aluminium OR aluminum AND toxicology
- Aluminium OR aluminum AND *toxicity
- Aluminium OR aluminum AND risk assessment
- Aluminium OR aluminum AND children
- Aluminium OR aluminum AND susceptible individuals
- Aluminium OR aluminum AND susceptible groups
- Aluminium OR aluminum AND exposure
- Aluminium OR aluminum AND toxicokinetics
- Aluminium OR aluminum AND absorption
- Aluminium OR aluminum AND paediatric population
- Aluminium OR aluminum AND exposure scenarios
- Aluminium OR aluminum AND safety
- Aluminium OR aluminum AND consumer products

The literature review included the following types of documents: peer-reviewed articles, journal entries, book chapters and government and non-government funded publications. The period covered was from 01/01/2008 until 31/01/2017.

A total of 47 publications were identified by the European Commission Library search. Out of these, the titles/abstracts were scrutinised and 30 publications were selected as being relevant for the development of the Opinion by giving additional information e.g. on bioavailability of aluminium compounds, on effects of aluminium on the immune system or on the central nervous system and by reviewing existing information. References are given mainly in chapters 5.2 and 5.3. Within these publications, however, there was no additional study on chronic toxicity of aluminium from which a NOAEL could have been derived.

In addition, the SCHEER took into account further relevant publications available on the topic, and also evaluated relevant reports or Opinions from the other regulatory bodies.

4.2. Evaluation of scientific information

The literature review was conducted by the members of the SCHEER who evaluated the papers and documents independently and then discussed them as a group to reach conclusions. The review considered toxicity studies and published health-based limit values that could be used to derive migration limits for aluminium from toys. The migration limits

were calculated according to the procedure used in the Toy Safety Directive (TSD) and 10% of the relevant health-based limit value was allocated to exposure from toys. In addition, information on significant exposure from sources other than toys was also evaluated.

5. ASSESSMENT

5.1. Introduction and RIVM approach

The TSD establishes migration limits for 19 elements in toys or components of toys, depending on the toy material used. The migration limits must not be exceeded. However, they do not apply if the toy or the components of the toy clearly exclude any hazard due to sucking, licking, swallowing or prolonged contact with the skin when used as intended or in a foreseeable way, bearing in mind young children's proclivity for mouthing objects.

The migration limits are based on a report from the Netherlands National Institute for Public Health and the Environment (RIVM, 2008). In this report, the approach to allocate a certain percentage (5%, 10%, or 20%) of a health-based limit value to the exposure from toys is proposed. For the different elements values for the tolerable daily intake (TDI) are listed. The Scientific Committee on Health and Environmental Risks (SCHER) supported the RIVM approach as a starting point for risk assessment of chemical elements in toys, namely that the basis for all approaches presented in the report is the TDI as a health-based limit value (SCHER, 2010). In accordance with an earlier Opinion by the Scientific Committee on Toxicity, Ecotoxicity and the Environment (CSTEE, 2004) the SCHER also recommended that the amount allocated to exposure from toys should be limited to a maximum of 10% of the health-based limit value.

When establishing migration limits for aluminium, RIVM considered human data the most suitable basis for the evaluation and derived the TDI from the study by Bishop *et al.* (1997). The same data were also used by the Office of Environmental Health Hazard Assessment (OEHHA) to derive the Public Health Goal (PHG) for aluminium in drinking water (OEHHA, 2000).

In this study, 227 premature infants with gestational ages of less than 34 weeks and birth weights of less than 1850 g received standard intravenous feeding solutions at an aluminium intake level of 45 µg/kg bw/d, or an aluminium-depleted feeding solution at an aluminium dose of 4 to 5 µg/kg bw/d. Neurologic development was tested at 10 months of age in 182 surviving infants. The 90 infants who received the standard feeding solutions had a mean (± SD) Bayley Mental Development Index (BMDI) of 95 ± 22, as compared with 98 ± 20 for 92 infants who received aluminium-depleted feeding solutions ($p = 0.39$). A subgroup of infants in whom duration of i.v. feeding exceeded the median and who did not exhibit neuromotor impairment, had BMDI values of 92 ± 20 ($n = 41$) for the standard solution and 102 ± 17 ($n = 39$) for aluminium-depleted solution ($p = 0.02$). For all 157 infants without neuromotor impairment, increasing aluminium exposure was associated with a reduction in the BMDI ($p = 0.03$), with an adjusted loss of one index point per day of i.v. feeding of infants receiving the standard solutions.

An intravenous LOAEL of 0.045 mg/kg bw/d was derived from this study base on impaired neurologic development observed in infants receiving the standard feeding solution for more than 10 days. Using an oral absorption factor of 0.002 the intravenous LOAEL of 0.045

mg/kg bw/d was converted to an oral LOAEL of 22.5 mg/kg bw/d. An uncertainty factor of 30 (10 for extrapolation from a LOAEL to a NOAEL, 3 for extrapolation from short-term to longer-term exposure, no inter-individual factor as premature infants are considered the most sensitive subgroup) was applied leading to the TDI of 0.75 mg/kg bw/d proposed by RIVM.

Migration limits laid down in the TSD are based on the assumption that a toy material can be considered safe with respect to the oral route if the bioaccessible amounts of the regulated elements do not exceed 10% of the TDI. Migration limits are calculated for different toy materials assuming ingested amounts of 100 mg dry, pliable or powder-like toy material, 400 mg liquid or sticky material and 8 mg scraped-off toy material and a body weight of 7.5 kg (based on 6-9 months of age) by using the following formula:

$$ML = \frac{10\% \, TDI \cdot BW}{A_{TM}} \qquad \text{mg element/mg toy material}$$

where:

ML	=	migration limit (mg element /mg toy material)
TDI	=	Tolerable Daily Intake (mg/kg bw/d)
BW	=	body weight (default 7.5 kg)
A_{TM}	=	amount of toy material ingested (8, 100, or 400 mg)

For aluminium the current migration limits, based on the above-mentioned assumptions, are 5625 mg aluminium/kg for dry, brittle, powder-like or pliable toy material, 1406 mg aluminium/kg for liquid or sticky toy material and 70000 mg aluminium/kg for scraped-off toy material.

5.2. Evaluation of aluminium health effects by other regulatory bodies

Many reports have been published which include extensive review of the effects of aluminium on health (EFSA, 2008; ATSDR, 2008; JECFA, 2007 and 2011; WHO, 2010; SCCS, 2014). Most of them commented on the limitations of the available animal studies, until a new multigenerational/developmental toxicity study (Poirier *et al.*, 2011) was made available and used in the 2011 JECFA evaluation. The approach followed by some of them for deriving reference value is briefly reported here.

The EFSA Opinion (2008)

EFSA published a scientific Opinion on the safety of aluminium from dietary intake (EFSA, 2008) considering that diet is the major route of exposure to aluminium for the general population.

The oral bioavailability of the aluminium ion highly depends on the chemical form and on the degree of water solubility of the ingested aluminium compound. Experimental data indicate that oral absorption is ≈0.3% when aluminium is ingested as dissolved in drinking water, and even less when it is contained in food and beverages (0.1%). The oral bioavailability of aluminium is related to solubilisation of aluminium compounds by acid digestion in the stomach. It is limited by the formation of insoluble aluminium hydroxide, expected to precipitate in the intestine with pH increase to neutral values. The bioavailability of aluminium is higher when administered via the parenteral route as well as by gavage.

After absorption, aluminium binds to transferrin and distributes to all tissues, accumulating in some, and especially in the bone where it can persist for a very long time. Normal levels of aluminium in serum are approximately 1–3 µg/L, whereas the total body burden in healthy human subjects has been reported to be approximately 30–50 mg/kg bw, half of which is in the skeleton. Aluminium is able to cross the blood-brain barrier entering the brain and the placenta to reach the foetus. Unabsorbed aluminium is excreted in the faeces, whereas the route of excretion of absorbed aluminium is via urine.

Data on sub chronic toxicity indicated a NOAEL of 52 mg aluminium nitrate/kg bw/d based on decreased body weight in rats, when aluminium nitrate was administered via drinking water for 28 days. On the contrary, administration of sodium aluminium phosphate (SALP) to rats for 28 days resulted in no effects up to 300 mg aluminium/kg bw/d (the highest dose tested). Dietary administration of SALP to dogs for 26 weeks indicated in one study that no effects were observed up to around 90 mg aluminium/kg bw/d but a NOAEL of 27 mg aluminium/kg bw/d, based on some histopathological effect in the liver and kidney of males, with no effects seen in females in the second study.

Aluminium compounds were non-mutagenic in bacterial and mammalian cell systems. Some DNA damage *in vitro* and clastogenic effects *in vivo* were observed at relatively high doses or after application by the intraperitoneal route and were explained by indirect mechanisms of genotoxicity. The EFSA Panel concluded that genotoxic effects are unlikely to be of relevance for humans exposed to aluminium via the diet.

Based on epidemiological data on individuals occupationally exposed by inhalation to aluminium dust and aluminium compounds, the International Agency for Research on Cancer (IARC) concluded that "*the available epidemiological studies provide limited evidence that certain exposures in the aluminium production industry are carcinogenic to humans, giving rise to cancer of the lung and bladder."* However, the EFSA Panel noted that in those studies co-exposure to other carcinogenic agents (polycyclic aromatic hydrocarbons, aromatic amines, nitro compounds and asbestos) was a relevant confounding factor. In addition, no evidence of increased cancer risk was reported in individuals therapeutically exposed to aluminium compounds and no carcinogenic potential of SALP was evidenced in mice administered up to 850 mg aluminium/kg bw/d in the diet. On this basis, the Panel concluded that aluminium is unlikely to be a human carcinogen at exposures relevant to dietary intake.

The observation on aluminium-induced neurotoxicity in dialysis patients (hence chronically exposed to the metal via a parenteral route, with a relatively high bioavailability), indicated a possible role for aluminium in the aetiology of neurodegenerative diseases in humans. Since these hypotheses remain controversial and the internal exposure in patients undergoing dialysis is much higher than the levels taken up via diet, the Panel did not consider exposure to aluminium via the food to constitute a risk for developing Alzheimer's disease.

The methodological and reporting limitations shown by neurotoxicity and neuro-developmental studies in rodents available in 2008 made it difficult to observe any dose-response relationships and to determine a NOAEL for the observed effects. For this reason, the EFSA Panel applied a weight of evidence approach, combining results from mice, rats and dogs receiving dietary administration of aluminium compounds, instead of using a single reference study to derive a tolerable intake value. The range of LOAELs related to the

more relevant endpoints, i.e. neurotoxicity, effects on testes, embryotoxicity, and effects on the developing nervous system was 50-100 mg aluminium/kg bw/d, the range for NOAELs 10-100 mg aluminium/kg bw/d, respectively.

The EFSA Panel compared results by using both, the lower end of the LOAEL range (50 mg aluminium/kg bw/d) as well the lowest NOAEL (10 mg aluminium/kg bw/d) as PoD. For the LOAEL of 50 mg aluminium/kg bw/d, a TDI of 0.17 mg aluminium/kg bw/d was obtained applying an assessment factor of 100 (accounting for inter- and intraspecies variations) and an additional factor of 3 for using a LOAEL instead of a NOAEL. Alternatively, when the lowest NOAEL of 10 mg aluminium/kg bw/d was used, a TDI of 0.10 mg aluminium/kg bw/d could be established, applying an assessment factor of 100.

In addition, the Panel considered it more appropriate to establish a tolerable weekly intake (TWI) than a TDI due to the aluminium accumulation in the body after dietary exposure. The TWI values obtained considering the two approaches were 1.2 mg/kg bw/w and 0.7 mg/kg bw/w and the EFSA Panel concluded that a value of 1 mg aluminium/kg bw/w, representing a rounded value between the TWIs provided by the LOAEL and NOAEL approaches, should be established as the TWI.

Based on the exposure estimate described in the Opinion, it appears that the TWI of 1 mg/kg bw/w is likely to be exceeded in a significant part of the European population, including children and formula-fed infants.

WHO/JECFA (2007) Opinion

The Joint FAO/WHO Expert Committee on Food Additives (JECFA) Opinion in 2007 was fully in line with the EFSA approach. At that time, the committee concluded that:

- the available studies have many limitations and are not adequate for defining the dose–response relationships,
- significant differences in kinetics limit the relevance of many of the available studies, in which aluminium compounds were administered by gavage,
- basal levels in the feed were generally not reported in the total aluminium exposure,
- the lowest LOELs for aluminium in a range of different dietary studies in mice, rats and dogs were in the region of 50–75 mg/kg bw/d expressed as aluminium,
- a total assessment factor of 300 (100 for inter- and intraspecies differences plus an additional factor of 3 accounting for deficiency in the data base) is appropriate,
- the health-based guidance value should be expressed as a PTWI, because of the potential for bioaccumulation.

On this basis JECFA established a PTWI of 1 mg/kg bw for aluminium, which applies to all aluminium compounds in food, including additives.

Based on the available exposure study, the Committee also concluded that the PTWI was likely to be exceeded in a number of population group, including children and especially infants fed on soy-based formula. In addition, considering the limitation in the data base, the Committee recommended that further studies on aluminium bioavailability and developmental toxicity be carried out.

WHO/JECFA (2011) Opinion

In 2011, JECFA revised its previous Opinion, considering new data. The new studies conducted on the bioavailability of aluminium compounds confirmed that absorption of

aluminium compounds is 0.01–0.3% in rats, with the more water-soluble aluminium compounds being better absorbed. The newly available data indicate that absorption in humans is likely to vary widely, but did not support an estimation of bioavailability.

New studies in rats also confirmed that i) absorbed aluminium accumulates in bone, the kidney and the spinal cord; ii) aluminium is able to cross the placental barrier reaching the fetal brain; iii) newborns can be also exposed via lactation. However, although new data were produced, the committee concluded that they were not sufficient to derive any chemical-specific adjustment factor for either interspecies or intraspecies differences in toxicokinetics.

The new multigeneration reproductive studies conducted with aluminium sulphate and aluminium ammonium sulphate administered to rats in the drinking-water did not provide evidence of reproductive toxicity. Although some developmental effects were observed (e.g. delayed maturation of the female offspring, decreased bodyweight gain and changes in some organ weights), the Committee concluded that they are likely secondary to effects on the dams (decrease in maternal fluid and feed consumption) and therefore that it was not possible to establish a cause-effect relationship with aluminium treatment. No effects on motor activity or learning ability were observed in these studies.

WHO/JECFA considered the study by Poirier *et al.* (2011) as the fundamental one: it is a Good Laboratory Practice (GLP) compliant 12-month neuro-developmental toxicity study of aluminium citrate, administered via the drinking water to Sprague-Dawley rats, at nominal doses of 30, 100 and 300 mg aluminium/kg bw/d, based on an expected water intake of 120 ml/kg bw/d. Due to changes in the water intake over time, the treatment doses differed in the various phases: at the low dose, relevant for the NOAEL derivation, during gestation the target dose was almost respected, whereas during lactation the dams were treated with a dosage higher than 30 mg/kg bw/d (around 40 mg/kg bw/d). During the first week post-weaning, mean dosage of male and female pups was 40.2 and 43.5 mg (again higher than 30). By week 9, when pups become adult animals, mean dosage of low-dose males and females had fallen to 15.4 and 17.4 mg aluminium/kg bw/d, respectively, decreasing to lower values during the rest of the study. Two control groups received either sodium citrate solution at the molar equivalent of the high-dose aluminium citrate or plain water. Dams were exposed from gestational day 6 through lactation and then the offspring was exposed post-weaning until postnatal day 364. The concentration of aluminium in the diets was 7–8.5 ng/ml, which corresponds to less than 1 µg/kg bw/d and was not relevant with respect to the treatment. After delivery, 20 litters per dose group were culled to four males and four females. Water consumption, body weight, a functional observational battery, morbidity and mortality were checked in dams; observations on the pups included body weight, fluid consumption and a functional observational battery on all pups several times before weaning and twice weekly on the 1-year group until sacrifice. Motor activity, startle response and performance in a T-maze test and the Morris water maze test were assessed at various times. At each sacrifice time (PNDs 23, 64, 120 and 364), half of the pups of each group were processed for neuro-histopathological examination, and the other half was subjected to a regular necropsy followed by brain weight measurement, clinical chemistry, haematology, and collection of tissues and blood for measurement of aluminium and other metals.

Evidence of aluminium-induced renal toxicity (hydronephrosis, urethral dilatation, obstruction and/or presence of calculi) was demonstrated in the high-dose group (300

mg/kg bw/d of aluminium) resulting in high mortality in the male offspring and to a lesser extent, the mid-dose group (100 mg/kg bw/d of aluminium).

No major neurological pathology or neurobehavioural effects were observed, except for alterations in neuromuscular measurements (hind-limb and fore-limb grip strength) in both males and females from 100 mg/kg bw, which were partly considered secondary to body weight changes. However, since effect on grip strength was more pronounced in younger animals, JECFA hypothesized that exposure in utero and/or during lactation exposure could be more important than exposure during the later stage. These are indeed the most relevant windows of exposure of pups in relation to the developmental effects used as the critical end-point for the NOAEL derivation; during gestation and lactation periods dams were treated with the target dose or higher. Therefore, the lowering in the treatment dose noted in adult pups was not considered to impact on the study results.

Lesions seen on histopathological examination of brain tissues at study termination (364-day group) were present both in treated and in control group animals, therefore they were not attributed to aluminium-treatment and were likely due to aging. Regarding the distribution of aluminium in tissues, it was found that bone is the tissue that accumulated aluminium over time in the high-, mid- and low-dose groups.

Based on the Poirier *et al.* study (2011), the LOAEL was set at 100 mg/kg bw/d and the NOAEL at 30 mg/kg bw/d. Considering the high bioavailability of aluminium citrate when compared to the other aluminium compounds, JECFA concluded that the NOAEL of 30 mg/kg bw/d could be considered as appropriate for other aluminium compounds.

The NOAEL of 30 mg/kg bw/d was considered appropriate as PoD for establishing a Provisional Tolerable Weekly Intake (PTWI) for aluminium compounds. By applying the default assessment factor of 100, a PTWI of 2 mg/kg bw/w was established.

WHO Drinking Water Guidelines (2010)

To derive a health-based value for drinking water, the WHO based its evaluation on the JECFA Opinion adopted in 2007 described above and the PTWI of 1 mg/kg bw/d. On that basis, and considering an allocation of 20% of the PTWI to drinking water as well as the default assumptions (60 kg bw for adults; 2 litres of water consumption/d) a Guidance value of 0.9 mg/L (rounded value) was derived. The WHO however underlined the uncertainties linked to the extent of aluminium absorption from drinking water and also the beneficial effects of the use of aluminium as a coagulant in water treatment to prevent microbial contamination. In relation to this latter factor, practicable levels based on optimization of the coagulation process in drinking-water plants using aluminium-based coagulants are 0.1 mg/L or less in large water treatment facilities and 0.2 mg/L or less in small facilities.

SCCS Opinion on aluminium in cosmetics (2014)

The SCCS was requested by the Commission to assess the possible risk for human health from the presence of aluminium in cosmetics, considering the exposure from other sources, such as food and food supplements. The request was made after three different reports had been received:

- a report submitted by the Agence française de sécurité sanitaire des produits de santé (AFSSAPS) which raises concern on the use of aluminium in antiperspirants and deodorants in September 2011,

- a "*Scientific discussion paper on systemic exposure to aluminium from dermal exposure to soluble salts*" by Cosmetics Europe, in October 2012,
- a dossier on "*The risk assessment of aluminium exposure through food and the use of cosmetic products in the Norwegian population*" by the Norwegian Scientific Committee for Food Safety in June 2013.

The SCCS (2014) revised the already performed risk assessment and the new study available, especially in relation to dermal absorption, relevant for their mandate. The SCCS concluded that:

- the available studies on dermal absorption of aluminium are of poor quality and do not allow conclusions to be drawn on the internal exposure to aluminium following cosmetic use,
- aluminium is not genotoxic, in agreement with EFSA Opinion,
- due to the lack of carcinogenicity at high dietary doses (up to 850 mg aluminium/kg bw/d) in animal studies, carcinogenicity is not expected at exposure levels which are achieved via cosmetic use,
- the NOAEL of 30 mg/kg bw/d used by JECFA for PTWI derivation is an appropriate PoD for systemic effects,
- aluminium is a neurotoxicant in experimental animals, although most of the animal studies performed have several limitations and therefore cannot be used for quantitative risk assessment,
- the information available in humans was inconsistent and did not support a causal association between aluminium exposure and Alzheimer's disease or other chronic neurological diseases,
- infants may be exposed to aluminium compounds through inhalation of dust, ingestion of soil and from the diet. Use of aluminium-containing cosmetic products (lipstick and lip gloss, antiperspirants and whitening toothpaste) is unlikely in this age group. The diet is likely to be the main source (COT, 2013).

5.3. Additional information from relevant recent publications

The relevant information published after 2011 is summarised in the following, although no additional retrieved data impacted on the reference value as derived by JECFA in 2011.

A systematic review of potential health risks posed by pharmaceutical, occupational and consumer exposures to metallic and nanoscale aluminium, aluminium oxides, aluminium hydroxide and its soluble salts has been published by a Canadian/USA-group (Willhite *et al.*, 2014). The authors conclusions were fully in line with the ones reported by the more recent evaluations from different Agencies, i.e.:

- wide variations in diet can result in aluminium intakes that are often higher than the recommended values for tolerable weekly intake,
- there is no consistent and convincing evidence to associate the chemical forms of aluminium and concentrations found in food and drinking water in North America and Western Europe with increased risk for Alzheimer's disease,
- there is no clear evidence to show that the use of aluminium-containing underarm antiperspirants or cosmetics increases the risk of Alzheimer's disease or breast cancer,

- metallic aluminium, its oxides, and common aluminium salts have not been shown to be either genotoxic or carcinogenic.

Effects of aluminium on the immune system with a focus on trace elements in the spleen are reviewed by Zhu *et al.* (2014), however, results are generally conflicting and no clear conclusions can be drawn. The possible mechanism for aluminium-induced immunotoxicity remains unclear. Aluminium decreased levels of Zn and Fe, but the effect on Cu-levels was unclear. Aluminium inhibited α-naphthyl acetate esterase (ANAE) positive cells, the production of interleukin (IL)-2 and macrophages function. While aluminium suppressed production of TNF-a *in vitro*, effects of aluminium on the TNF-a *in vivo* were elusive. Effects of aluminium exposure on the IgG, IgM and IgA levels were also conflicting. Therefore, these pieces of information do not change the conclusions about the key event in aluminium-induced toxicity.

Several other publications are related to effects of aluminium on the central nervous system and a possible relationship between aluminium exposure and mental diseases. The central nervous system is particularly sensitive to metal-induced oxidative stress and any impact of aluminium on cell signalling, neurotransmission, and cell redox status have been the most investigated critical effects for the nervous system (Verstraeten *et al.,* 2008; Chaitanya *et al.;* 2012; Shrivastava, 2012; Yuan *et al.,* 2012). The greatest complications of aluminium toxicity are neurotoxic effects such as neuronal atrophy in the locus ceruleus, substantia nigra and striatum (Neeshu *et al.,* 2016).

5.4. Sources of exposure to aluminium

Aluminium has a strong affinity to oxygen. Therefore, it is almost never found in the elemental state. It can be found as aluminium derivatives with:

- chloride (used in the manufacture of rubbers and lubricants, and as an antiperspirant (O'Neil *et al.*, 2001),
- hydroxide (used as an adsorbent, emulsifier, ion-exchanger, mordant in dyeing, and filtering medium, flame retardant in different materials, including children's toys and clothing (e.g. pyjamas)[9], detergents and as a vaccine adjuvant (Baylor *et al.,* 2002; O'Neil *et al,.*2001; Lewis, 2001),
- phosphorous (used for cosmetics, paints and varnishes, pharmaceuticals (antacid), vaccine adjuvants (Malakoff, 2000), emulsifying agent in pasteurized processed food and in refrigerated or frozen products (Chung, 1992; Galembeck *et al.,* 2006),
- sulphur for water purification, vaccine adjuvants (Baylor *et al.*, 2002; Malakoff, 2000).

Other aluminium compounds that are used as food additives include aluminium silicates (anticaking agents) (Saiyed and Yokel, 2005; Krewski *et al.,* 2007; WHO, 1997) and aluminium oxide, used in the manufacturing of ceramics, in electrical insulators, and as a food additive (dispersing agent) (Lewis, 2001).

[9] How Flame-Retardant Polymers in Toys and Pajamas Contribute to Your Child's Safety: https://www.polymersolutions.com/blog/plastics-polymers-rubbers/page/27/,2015

5.5. Dietary exposure

Diet is considered by far the most relevant route of chronic exposure for the general population. The focus of this section is on estimating dietary exposure to children as they are the end-users of toys.

EFSA (2008) conducted an exposure assessment to determine dietary exposures to both children and adults expressed on a body weight basis. Some unprocessed foods contain the highest levels of aluminium concentrations (e.g. tea leaves, herbs, cocoa and cocoa products, and spices). Other foods such as bread, cakes and biscuits, sugar-rich foods baking mixes, most farinaceous products and flours, some vegetables (e.g. mushrooms, spinach, radish), dairy products, sausages, and shellfish have been found to contain mean levels in the range 5 to 10 mg aluminium/kg (EFSA, 2008). Other foods generally have less than 5 mg aluminium/kg. These figures can, at least partially, be due to the use of permitted aluminium-containing food additives and aluminium from food colours. Indeed, some aluminium compounds (e.g. aluminium sulphate, sodium aluminium phosphate, aluminium potassium sulphate) are permitted as food additives under the European Directive 95/2/EC on food additives other than colours and sweeteners. Since the contribution from food is quite high, EFSA considered that migration from food contact materials in which aluminium in its alloys are used would add only a small amount under normal and typical conditions, except when aluminium-based pans, bowls, and foils for foods, vessels and trays for convenience and fast food are used with acidic or salty food (e.g. tomatoes, apple puree, vinegar, salted herring, pickles).

Large individual variations in dietary exposure to aluminium can occur in adults and children depending on the dietary habits. Exposure levels at the 97.5th percentile in children have been estimated to be in the range of 0.7-2.3 mg/kg bw/w for children aged 3-15 years in France as well as 2.3 mg/kg bw/w for 1.5-4.5 years old and 1.7 mg/kg bw/w for 4-18 year olds in the UK (EFSA, 2008).

Potential exposure in breast-fed infants was estimated to be less than 0.07 mg/kg bw/w while potential dietary exposures from infant formulae and food manufactured specially for infants was estimated to be 0.10-0.78 mg/kg bw/w in the period 0-12 months, with soy-based formulae showing the highest levels.

Indeed, the concentration in ready-made milk varies from 176 to 700 µg/L whereas the aluminium content in powders used to make milk formulations can vary from 2.4 to 4.3 µg/g (EFSA, 2008).

According to Burrell and Exley (2010), the average daily ingestion of aluminium from infant formulae for a child of 6 months varies from 200 to 600 µg which is in the range estimated by EFSA. Immature gastrointestinal barrier and kidney excretion functions may influence both the mechanisms and the efficiency of aluminium absorption and excretion in this age group.

The Norwegian Scientific Committee for Food Safety published a dossier on "*the risk assessment of aluminium exposure through food and the use of cosmetic products in the Norwegian population*" (2013), in which reported values related to aluminium uptake in children from the diet were higher in 1- and 2-year-old infants (0.89 mg/kg bw/w as mean value with the 95th percentile at 1.9 mg/kg bw/w and 0.88 mg/kg bw/w as mean value with the 95th percentile at 1.7 mg/kg bw/w for 2 year olds, respectively) and gradually dropped in older children to mean values of 0.53 and 0.35 mg/kg bw/w (with 95th percentiles of 0.90

and 0.66 mg/kg bw/w) in 4- and 9-year-old children, respectively. Intakes in 13-year-old adolescents (mean value of 0.22 mg/kg bw/w and 95th percentile at 0.49 mg/kg bw/w) were similar to the levels reported in adulthood (0.29 mg/kg bw/w).

EFSA (2013) has recently estimated the exposure to aluminium from five permitted food additives, namely aluminium ammonium sulphate (E 523), sodium aluminium phosphates (acidic and basic; E 541), sodium aluminosilicate (E 554), calcium aluminium silicate (E 556) and aluminium silicate (E559). The dietary exposure estimates were calculated using two different scenarios[10], considering the maximum levels recommended by the 45th Codex Committee on Food Additives (CCFA) for the five aluminium-containing food additives, and food consumption data from European countries obtained from the EFSA Comprehensive Food Consumption database. Five population groups (toddlers, children, adolescents, adults and the elderly) were included in the survey: uptakes ranged from 2.3 to 76.9 in mg/kg bw/w at the mean and from 7.4 to 145.9 mg/kg bw/w at the 95th percentile in scenario 1, whereas in scenario 2, values ranged from 18.6 to 156.2 mg/kg bw/w at the mean and from 35.3 to 286.8 mg/kg bw/w at the 95th percentile. For the five population groups considered, the mean and 95th percentile intake values from the 5 additives largely exceeded the TWI of 1mg/kg bw/w established by EFSA (2008).

ATSDR (2008) has reported data from the FDA Total Diet Study (Pennington and Schoen, 1995) in the USA. Dietary intakes for different ages were in the range of 0.10–0.18 mg/kg bw/d (0.7-1.26 mg/kg bw/w). Some details were given for 2- and 6-year-old children and the highest values were 0.35 and 0.30 mg/kg bw/d, respectively.

In the North American diet, the major sources of aluminium were milk and dairy products (36%), fish and crustaceans (29%), cereals (16%), and vegetables (8%) (ATSDR, 2008). Processed foods containing aluminium additives (e.g. processed cheese and grain-based products) have the highest quantities of aluminium and represent the largest contribution to the dietary intake of children. High quantities are also contained in soy-based formula therefore infants fed with such formula would have much higher dietary intakes of aluminium than other children (up to 0.161 mg Al/d) (Pennington and Schoen, 1995).

To summarise, aluminium intake in children varies depending on dietary habits, but as a general rule, dietary intake in children tends to exceed the reference values established by EFSA and JECFA.

5.6. Exposure from other sources

Drinking water represents an additional, although minor, source of chronic exposure. Intermittent exposure from the use of aluminium compounds in consumer products (e.g. cosmetic and antiperspirant via dermal absorption) or exposure via inhalation, related to dust can occur.

In addition, there may also be intermittent exposure to aluminium from pharmaceuticals via the oral and parenteral route. However, the medical application of aluminium compounds in pharmaceuticals is out of the scope of this Opinion.

[10] The 1st one takes into account the recommendation 2 of the electronic Working Group (eWG), namely: recommendation to adopt the maximum levels. The 2nd scenario takes into account recommendations 2, 3 and 4 of the eWG, namely: recommendation to adopt, discuss further and circulate for comments the maximum levels

5.6.1 Drinking water

Aluminium can be found in drinking water, since some compounds (e.g. aluminium sulphate, aluminium polychloride) are used as flocculating agents in the treatment of water intended for human consumption. The concentration of aluminium in tap water after completion of treatment is usually less than 0.2 mg/L. Therefore, based on a daily consumption of 1 L/d, dietary exposure from treated drinking water may be up to 0.2 mg aluminium/d, corresponding to 0.02 mg aluminium/kg bw/d for a child weighing 10 kg (JECFA, 2007).

5.6.2 Food contact materials

The Council of Europe recommends a specific release limit (SRL) of 5 mg/kg food for aluminium from food contact materials (Resolution CM/Res (2013)9 on metals and alloys used in food contact materials and articles). Both EFSA (2008) and ATSDR (2008) concluded that cooking in aluminium containers or preserving food in aluminium-containing cans or pots often results in statistically significant, but not biologically important, increases in the aluminium content of some foods. The migration of aluminium from cookware into food will increase with the acidity of the food and the duration of exposure. Indeed, aluminium migration from these articles depends on temperature, contact time, pH (2.2–7), and salt concentration of the extractant (Fekete *et al.*, 2012).

5.6.3 Dust

Inhalation of aluminium in ambient air represents a small contribution to an individual's exposure (Browning, 1969). Dusts arising from soil, especially in industrial or agricultural areas (Eisenreich, 1980), and from the metal surfaces of air conditioners can contain measurable amounts of aluminium (Crapper and McLachlan, 1989), resulting in high localized concentrations and, subsequently, in higher exposures. However, for the general population, inhalation is likely to be less important as an exposure pathway than is dietary exposure, although it may represent a source of greater exposure in some urban environments.

An in-depth study has been undertaken to quantify estimates of soil ingestion by 2- to 7-year-old children in the USA (Davis *et al.,* 1990). A total of 104 children participated in the study which involved extensive soil and household dust sampling, as well as the recording of duplicate food items consumed and the children's daily activities over four consecutive days. For 101 of those children mean aluminium values in food were 30.2 (with a range of 3.2-91.6) µg/g and the contribution of aluminium from soil (and dust) accounted for a mean percent by weight of 6.6 and a range of 5.1-7.6. The household dust samples resulted in mean aluminium concentrations (percentage by weight) of 1.9%. To evaluate the extent to which aluminium concentrations influence soil ingestion rates, the study recalculated soil values to account for household dust and vacuum cleaner dust, making a number of assumptions so that the estimated daily intakes take into account these sources of aluminium.

5.7. Overall conclusion regarding aluminium exposure in children

When estimating the total exposure of infants and children to aluminium, it is important to take into account all significant sources of exposure, i.e. to include dietary exposure typical of different age groups and exposure from further specific sources.

Dietary aluminium intake alone, although variable and dependent on the specific diet, in some cases already exceeds the reference values established by EFSA (TWI of 1 mg/kg bw/w) and JECFA (PTWI of 2 mg/kg bw/w).

The uptake of aluminium from other voluntary sources – such as toys – should therefore be minimised.

6. CONSIDERATION OF RESPONSES RECEIVED IN PUBLIC CONSULTATION

A public consultation on this Opinion was opened on the website of the non-food scientific committees from 7 July to 10 September 2017. Information about the public consultation was broadly communicated to national authorities, international organisations and other stakeholders.

Nine contributors from industry and public institutes participated in the public consultation, providing input to different chapters and subchapters of the Opinion. Ten comments in total were submitted.

Each submission was carefully considered by the SCHEER, but the SCHEER did not feel that any of them indicated a necessity for making changes to the final Opinion. The comments from the public consultation and SCHEER responses are available at:

https://ec.europa.eu/health/scientific_committees/consultations/public_consultations/scheer_consultation_04_en

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8. LIST OF ABBREVIATIONS

AFSSAPS	Agence française de sécurité sanitaire des produits de santé
ANAE	α-naphthyl acetate esterase
ATSDR	Agency for Toxic Substances and Disease Registry
BMDI	Bayley Mental Development Index
bw	body weight
CSTEE	Scientific Committee on Toxicity, Ecotoxicity, and the Environment
d	Day
DTaP	diphtheria-tetanus-acellular pertussis
EFSA	The European Food Safety Authority
IARC	International Agency for Research on Cancer
JECFA	The Joint FAO/WHO Expert Committee on Food Additives
kDA	Kilodalton
LOAEL	Lowest Observed Adverse Effect Level
NOAEL	No Observed Adverse Effect Level
OEHHA	Office of Environmental Health Hazard Assessment
PHG	Public Health Goal
PND	Postnatal day
PoD	Point of Departure
PTWI	Provisional Tolerable Weekly Intake
RIVM	Netherlands National Institute for Public Health and the Environment
SALP	sodium aluminium phosphate
SCCS	Scientific Committee on Consumer Safety
SCHEER	Scientific Committee on Health, Environmental and Emerging Risks
SCHER	Scientific Committee on Health and Environmental Risks
SCIT	Subcutaneous immunotherapy
SD	standard deviation
TDI	Tolerable Daily Intake
TSD	Toy Safety Directive
TWI	Tolerable Weekly Intake
w	Week
WHO	World Health Organisation