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This investigation has been performed by order and for the account of Ministry of Housing, Spatial Planning and the Environment, within the framework of project 711701: Risk in relation to soil quality

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Abstract

Re-evaluation of some human-toxicological Maximum Permissible Risk levels earlier evaluated in the period 1991 - 2001

In 2007 and 2008 RIVM re-evaluated the health-based limit values for humans of ten substances and substance classes (human-toxicological Maximum Permissible Risk levels). It concerns three metals and five organic compounds, and also chloride and sulfate. Six substances/substance classes were earlier evaluated in the period 1991 - 2001; chloride, sulfate, ethyl-*t*-butylether and methyl-*t*-butylether are evaluated for the first time. Some of the new limit values are lower than the former values, but others are higher or remain unchanged. The re-evaluation was justified by new scientific data.

Together with the ecotoxicological limit values the human health-based limit values are the basis for soil intervention values. These soil intervention values are used to determine whether contaminated soils meet the criteria for 'serious soil contamination' as stated in the Dutch Soil Protection Act.

For each re-evaluated compound or compound class a toxicity profile has been compiled. From each of these profiles an updated Maximum Permissible Risk is deduced for oral exposure, and if relevant also for inhalation exposure.

Key words:
soil contaminants, human-toxicological risk levels, oral exposure, inhalation exposure

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Rapport in het kort

Herevaluatie van enkele humaan-toxicologische Maximum Toelaatbare Risicogrenzen eerder geëvalueerd in de periode 1991 - 2001

Het RIVM heeft in 2007 en 2008 voor tien stoffen en stofgroepen in de bodem opnieuw de maximale waarden bepaald waarbij zij geen schade aan de gezondheid van de mens veroorzaken (humaan-toxicologische gezondheidskundige grenswaarden). Het betreft drie metalen en vijf organische verbindingen, alsmede chloride en sulfaat. Sommige waarden zijn gedaald, anderen gestegen of gelijk gebleven. De waarden worden geherevalueerd als nieuwe wetenschappelijke gegevens daar aanleiding voor geven, wat hier het geval was.

De humaan-toxicologische grenswaarden vormen, samen met de ecotoxicologische grenswaarden, de basis voor bodeminterventiewaarden. Als een bodeminterventiewaarde op een verontreinigde locatie wordt overschreden, dient te worden onderzocht of het noodzakelijk is om die locatie te saneren.

Voor elke beoordeelde stof(groep) werden Maximum Toelaatbare Risico's (MTR's) afgeleid voor de blootstelling via de mond, en indien relevant, ook voor de blootstelling via de ademhaling. De tien stoffen en stofgroepen zijn eerder geëvalueerd tussen 1991 en 2001.

Trefwoorden:
bodemverontreinigende stoffen, humaan-toxicologische risicogrenzen, orale blootstelling, inhalatoire blootstelling

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Summary

Soil Intervention Values are generic soil quality standards for contaminating substances based on potential risks to humans and ecosystems. These values are used to determine whether contaminated soils meet the criteria for 'serious soil contamination' as stated in the Dutch Soil Protection Act.
With reference to potential risks to humans, Maximum Permissible Risk (MPR) values, quantifying the human-toxicological risk limits, were derived in the 1991-1998 period for almost 100 chemicals and chemical classes. These MPRs comprise limits on tolerable daily intake, tolerable concentration in air, and oral cancer risk and/or inhalation cancer risk.
In 2001, the first set of almost 50 MPRs were re-evaluated based on new data. The current report re-evaluates some of the priority compounds evaluated in the period 1991-1998.
In total, the compounds comprise three earlier evaluated metals (antimony, tin and vanadium), three earlier evaluated organic compounds and compound classes (1,2-dichloroethene, dioxins and organotin compounds), two organic compounds which were not evaluated earlier (ethyl-*t*-butylether and methyl-*t*-butylether), and finally short evaluations of chloride and sulfate.
A toxicity profile has been compiled for each compound or compound class. It consists of a concise summary of the available toxicity data, information on background exposure and a survey of existing limit values derived by other organisations. An updated MPR for each compound (or class of compounds) in question is deduced from the respective profile.

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1 Introduction

The Intervention Values for soil, sediment and groundwater are one of the instruments of the Dutch Soil Protection Act: based on these values decisions are made regarding the clean-up of contaminated soils.
In 1991, proposals have been published for the first series of Intervention Values for about 60 (groups of) compounds (Vermeire et al., 1991; Vermeire, 1993). In 1995 Intervention Values for the second and third series of compounds (26 in total) were reported (Janssen et al., 1995), followed by the fourth series (13 compounds) in 1998 (Janssen et al., 1998).
The Directorate General of Environment of the Ministry of Housing, Spatial Planning and the Environment commissioned RIVM to evaluate a number of existing Intervention Values, in order to have an up-to-date scientific basis for these values. This has resulted in the project 'Evaluation of Intervention Values Soil' which is carried out in the framework of the overall-project 'Risk in relation to soil quality'. The main purpose of the evaluation is to derive Intervention Values according to the most recent views on exposure assessment to and toxicity of soil contaminants.
One of the building blocks for Intervention Values is the human-toxicological Maximum Permissible Risk (MPR_{human}) value. Fifty MPR_{human} values earlier derived in 1991 and 1993 have been re-evaluated in 2001 (Baars et al., 2001). The present study comprises the revision of the MPRs of a number of priority compounds of the second, third and fourth series of compounds, and a revision of two compounds which were re-evaluated in 2001. In addition, four compounds are added which have not been evaluated before.

2 General procedure

2.1 Definitions

The MPR_{human} is defined as the amount of a substance (usually a chemical substance) that any human individual can be exposed to daily during full lifetime without significant health risk (see paragraph 2.3 for the more specific definition of cancer risks). It covers both oral and inhalation exposure (and if necessary also dermal exposure), and classical toxic risks as well as carcinogenic risks. The MPR_{human} is generally expressed as either a tolerable daily intake (TDI) or an excess carcinogenic risk via intake (CR_{oral}), both covering exposure by oral ingestion, or a tolerable concentration in air (TCA) or an excess carcinogenic risk via air (CR_{inhal}), both covering exposure by inhalation.
The procedure to derive $MPRs_{human}$ is outlined in detail by Janssen and Speijers (1997). In agreement with this report, and concurring with the earlier re-evaluation (Baars et al., 2001), the approach of the present re-evaluation is a pragmatic one in that use has been made of existing toxicological evaluations by national and international bodies, thus avoiding unwanted duplication of work. Existing evaluations were used in a critical fashion: on a case-by-case basis, their adequacy for use in the present scope was judged, and from that, the need to search additional and/or primary literature was determined.
In the following, the abbreviation 'MPR' is used throughout to indicate the MPR_{human}.

2.2 Threshold versus non-threshold approach

In evaluating the toxicity of chemical substances, distinction must be made between two fundamentally different approaches. Genotoxic carcinogens are assumed to exert their activity also at the smallest dose, i.e., by definition a threshold for genotoxic activity does not exist [1]). Toxic effects other than genotoxic carcinogenicity, however, are assumed to occur via receptor interaction, which implies that a certain threshold needs to be exceeded before a toxic effect will occur (Vermeire et al., 2007).

2.3 Excess lifetime cancer risk

For genotoxic carcinogens, a cancer risk estimate is made based on known tumour incidences for the compound in question. This procedure results in an *excess lifetime cancer risk*. This approach assumes a linear relationship (also at very low doses) between dose and cancer incidence, which implies that the cancer incidence due to exposure to a particular genotoxic chemical is zero only if the dose is zero.
In the framework of the Intervention Values, the MPR is the criterion used for health based risk assessments; for genotoxic carcinogens the MPR has been defined as the excess lifetime cancer risk of 1 out of 10,000 exposed individuals ($1:10^4$; VROM, 1989).

[1]) It should be noted that the correctness of this theory is a matter of debate among scientists. There are clear indications that genotoxic compounds do have a threshold.

2.4 Tolerable daily intake (oral and inhalation)

Applying the threshold approach for all other toxic chemicals, a *tolerable daily intake* (TDI) is derived, representing the estimated amount of the chemical that humans can ingest daily during their entire lifetime without resultant adverse health effects. Analogously, a *tolerable concentration in air* (TCA) is derived for the inhalation route of exposure, representing the air concentration of the chemical that humans can inhale daily during their entire lifetime without resultant adverse health effects.

2.5 Deriving a MPR

Basically, the derivation of the MPR for a particular compound starts with examining the existing toxicology reviews of this compound, i.e., reviews by (inter)national organisations such as RIVM, WHO, EFSA, EU, US-EPA, IARC, ATSDR [2]), etc. These are evaluations that are carried out by (inter)national committees of experts, and generally they can be taken as critical and well-validated data sources. If a data-set is more or less complete, these reviews report studies on the effects of the compound in humans, a variety of toxicological endpoints examined in animal experiments, and include information regarding the dose-effect relationship as well as information regarding the mechanism(s) of the toxic effect(s) observed. This information is critically evaluated, the pivotal toxicological endpoint is defined, and an overall *no observed adverse effect level* (NOAEL) is selected. The NOAEL is the highest dose in a study at which no substance-related adverse health effects were observed, i.e., the first dose below the one at which such effects did occur (which is defined as the *lowest observed adverse effect level* [LOAEL]; Vermeire et al., 2007). In case of a non-genotoxic compound assessment factors are applied to extrapolate from the NOAEL to the MPR (see paragraph 2.7), while for a genotoxic compound a linear extrapolation is applied to arrive at the MPR for cancer risk (Vermeire et al., 2007).
Sometimes a MPR is characterised as *provisional*, this characterization is used if only very limited data for a particular route of exposure are available to derive the MPR.

2.6 The benchmark dose approach

Currently the dose-effect relationship is analysed in a more advanced way by applying the so-called *benchmark dose* (BMD) approach (Vermeire et al., 2007). In fact, it is a statistical analysis of the available data, modelling these data into a mathematical fit, and calculating the confidence limits (e.g. the 95% confidence interval) of this fit. Next, the lowest dose with a significant adverse and critical effect, e.g., a 10% increase of this toxic effect (the BMD_{10}) is calculated, and finally the lower limit of its confidence interval (the BMD *lower confidence limit*, e.g. the 95% confidence limit - $BMDL_{10}$) is taken as the point of departure for deriving the MPR. Applying the BMD approach, in general a "better", i.e., a more precise dose that in the experimental animal results in a certain, well-defined toxic effect is determined.

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[2]) WHO: World Health Organization (e.g., the International Programme on Chemical Safety, the Joint FAO/WHO Meeting on Pesticide Residues and the Joint FAO/WHO Meeting on Food Additives and Contaminants); EFSA: European Food Safety Authority; EU: various Scientific Committees of the European Commission; US-EPA: US Environmental Protection Agency; IARC: International Agency for Research on Cancer; ATSDR: US Agency for Toxic Substances and Disease Registry.

2.7 Assessment factors

In agreement with the international procedures for toxicological risk assessments (Vermeire et al., 2007), *assessment factors* (AFs, formerly called *uncertainty factors* or *safety factors*) are used to derive the MPR from the NOAEL or the BMD. These AFs allow for interspecies (animal to human) variation and for intraspecies variation (variations in susceptibility in the human population). By default, these two types of variation are covered by AFs of 10. However, when there are flaws or omissions in the data package from which the NOAEL is taken, additional AFs or *modifying factors* have to be applied. Thus:

$$\text{MPR} = \frac{\text{NOAEL or BMD}}{AF_1 \times AF_2 \times \ldots}$$

Increasingly, more advanced approaches are coming into use (Vermeire et al., 2007).
Regarding interspecies variation, firstly the toxicokinetic differences between the experimental animal and humans are estimated by allometric scaling, while secondly the toxicodynamic differences are being estimated by considering the mechanism by which the particular toxic effect is expressed. Differences between human individuals (intraspecies variation, such as gender, age, state of health, nutritional status, metabolic polymorphism, etc.) are also being considered in relation to the mechanism by which the particular toxic effect is expressed.
It must be emphasised that the AFs are applied to ensure that the limit value derived is safe for humans, even for sensitive subpopulations within the general population. The size of the AF is not to be interpreted as a simple measure of the reliability of the resulting MPR; it is the factor which by expert judgement is considered necessary to extrapolate from the available toxicological data (mostly animal data) to a MPR, i.e., the daily intake of a chemical which during entire lifetime appears is without appreciable risk on the basis of all currently known facts. Thus, the size of the total AF is not a simple uncertainty score. This does not mean that there is no relation whatsoever between the reliability of the MPR and the size of the AF. Using a higher AF means: making a larger-sized extrapolation (extrapolation further outside the experimentally observed dose-response range). Consequently, MPRs derived using an AF of 1000 (used when no adequate chronic animal NOAEL or BMD is available) will be less accurate than MPRs derived using an AF of 10 (used when an adequate human NOAEL or BMD is available). Lower AFs are possible if more detailed information is available on the toxic response of the chemical in humans. Only in this sense does the total AF reflect the quality of the data-set (see also paragraph 2.9).
In contrast to the derivation of MPRs for toxic compounds, the derivation of MPRs for genotoxic carcinogens does not include the application of AFs, basically because the linear extrapolation to very low doses is thought to be quite conservative. This does imply, however, that the carcinogenic potency of a genotoxic carcinogen is supposed to be the same for humans and experimental animals.

2.8 Route-to-route extrapolation

In the human-toxicological evaluation aimed at deriving MPRs, toxicity data for all routes of interest for a particular compound (i.e., oral, inhalation, and if applicable also dermal) are considered. This full dataset is needed to obtain a complete picture of the toxicological properties of the compound. In practice, however, the available datasets are often limited. Consequently, when oral data are insufficient for deriving a TDI, *route-to-route extrapolation* is done, based on inhalation data. Vice

versa, if inhalation data are lacking, route-to-route extrapolation can be applied using oral data. It must be emphasised, however, that route-to-route extrapolation is a rather unreliable method to derive any limit value (Vermeire et al., 2007).

2.9 Reliability

Depending on the size and quality of the database from which a MPR is derived, the resulting limit value has a certain reliability. In the current re-evaluation the reliability of the resulting MPRs is qualified as *high, medium* or *low*.
Basically these reliability scores are the result of expert judgement of the database from which the limit value is derived. This judgement involves:

- A MPR represents a limit value for lifetime exposure. Accordingly, toxicity studies from which a MPR is derived should thus preferably be chronic studies (exposure of experimental animals during their full or almost full lifetime). Consequently, if chronic studies, and even semi-chronic studies are not available, the resulting MPR will be of low or at best medium reliability. It should be noted, however, that some pivotal effects can only be observed in specific studies regarding, e.g., reproduction or teratogenicity. Moreover, chronic studies are not by definition of better quality than other studies.
- The size of the database. Any specific toxicity of a particular substance is better characterised if observed in different studies, by different investigators, in different animals, with different study designs. Thus, if only studies in one experimental animal species are available, or if only a very small number of studies is available, the resulting MPR will at best be of medium reliability. In this framework it should be noted that more recent studies might be expected to have involved modern research methods and good laboratory practice, but that studies of older date are not by definition less reliable.
- The design of a particular study. It should allow establishing the significance of a particular toxic effect, and its dose-effect relationship. If possible a toxic effect should be supported by histopathological data, microscopic observations, research (in vivo or in vitro) regarding the molecular mechanism of the effect, etc. Thus, poorly designed studies will result in a MPR with low reliability (if the database does not contain other, better designed and more extensive studies).
- In general a MPR is qualified as highly reliable if resulting from the evaluation by an internationally renown committee of experts, particularly because these committees only derive an MPR if a rather complete database is available (cf. paragraph 2.5).
- In addition, the extent of international consensus regarding the nature and the severity of a specific toxic effect of a particular compound indicates the trust (or distrust) of the international expert community in the toxicological characterisation of this substance.

It should be noted that in the present re-evaluation of MPRs the reliability qualification is only of a rough nature, due to the rather pragmatical way by which the MPRs were derived (cf. paragraph 2.1).

3 Results

Table 1 presents the new and the revised MPRs, together with the earlier values. Full details of the evaluations are to be found in the appendices, except for 1,2-dichloroethane (*cis* and *trans*) and methyl-*t*-butylether, which have been reported earlier (Janssen, 2008, and Swartjes et al., 2004, respectively).

Table 1. Human-toxicological Maximum Permissible Risk Levels – re-evaluation 2007-2008

Compound	Earlier MPR			Re-evaluated MPR			
	year	type	value	type	value	remark	reliability
Metals							
Antimony	1995	TDI	0.86	TDI	6	1	medium
Tin	1991	TDI	2000	TDI	200	-	high
Vanadium	1998	pTDI	2	pTDI	2	-	low
	1998	pTCA	1	pTCA	1		low
Other inorganic compounds							
Chloride	-	-	-	-	-	non toxic	high
Sulfate	-	-	-	-	-	non-toxic	high
Organic compounds							
1,2-Dichloroethene (*cis* and *trans*)	2001	TDI	6 / 17	TDI	30	4	medium
	2001	pTCA	30 / 60	TCA	60		medium
Dioxins	2001	pTDI	$1\times10^{-6} – 4\times10^{-6}$	pTDI	2×10^{-6}	-	medium
Ethyl-*t*-butylether	-	-	-	TDI	250	-	medium
	-	-	-	TCA	1,900		medium
Methyl-*t*-butylether	-	-	-	TDI	300	5	medium
	-	-	-	TCA	2,600		high
Organotin	1995	TDI	0.3	TDI	0.25 / 2.3	2	medium
	1995	pTCA	0.02	pTCA	0.02	3	medium

TDIs are expressed in µg/kg bw/day, TCAs are expressed in µg/m^3.
p: provisional
Remarks:
1. For soluble antimony compounds (insoluble antimony compounds are significantly less toxic).
2. The TDI of 0.25 µg/kg bw/day is valid for DBT, TBT, TPT, and combinations of these; the TDI of 2.3 µg/kg bw/day is valid for DOT.
3. For TBT.
4. The TDI of 6 µg/kg bw/day and the pTCA of 30 µg/m^3 as derived in 2001 are valid for *cis*-1,2-dichloroethene, the TDI of 17 µg/kg bw/day and the pTCA of 60 µg/m^3 as derived in 2001 are valid for *trans*-1,2-dichloroethene. The re-evaluation (resulting in a TDI of 30 µg/kg bw/day and a TCA of 60 µg/m^3 for both *cis*- and *trans*-1,2-dichloroethene) has been reported by Janssen, 2008.
5. The evaluation of methyl-*t*-butylether has been reported by Swartjes et al. (2004).

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[3]) Available upon request at SIR-secr@rivm.nl.

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Appendix A1: Antimony

A1.1 INTRODUCTION

Antimony was evaluated within the scope of this project by Janssen et al. in 1995. They derived a TDI of 0.86 µg/kg bw/day for oral intake. This TDI was based on a LOAEL of 0.43 mg antimony/kg bw/day (shortened lifespan and altered blood chemistry) in a lifetime drinking water study with antimony potassium tartrate in rats, applying an uncertainty factor of 500. A TCA was not proposed. For the present update, additional literature was reviewed (published since 1995). This included evaluations by OEHHA (1997), WHO (2003), EFSA (2004) and RIVM (Van Engelen et al., 2006). Antimony occurs mainly in a trivalent or pentavalent state. Natural levels in the environment (soil, water) are at the ppm or ppb level (Van Engelen et al., 2006). Antimony trioxide, the antimony compound which is commercially most significant, is used as a flame retardant synergist, as a fining agent in glass manufacture and as a catalyst in plastics (Kirkland et al., 2007). Antimony potassium tartrate has a historical use as antischistosomal drug (Lynch et al., 1999) or to induce vomiting in poisoning cases (WHO, 2003).
Antimony is released into the environment (predominantly in the form of antimony trioxide) mostly as a result of coal burning or with fly ash when antimony-containing cores are smelted (WHO, 2003).

A1.2 TOXICOLOGY

A1.2.1 Toxicokinetics

Absorption
Approximately 5-20% of antimony, irrespective of its valency, is reported to be absorbed in animals after oral exposure. In four human subjects, an absorption rate of 5% was found after involuntary acute intoxication with antimony potassium tartrate (OEHHA, 1997; WHO, 2003). Antimony absorption from the gastrointestinal tract into the blood is slow (C_{max} is reached after 24 h following a dose of 100 or 1,000 mg/kg bw) and saturable (Kirkland et al., 2007).

Distribution
In animals, absorbed antimony binds to red blood cells and is then distributed to spleen, liver and bone and to some extent into thyroid, skin and hair (OEHHA, 1997; WHO, 2003).

Metabolism
Covalent interactions of antimony with sulfhydryl or phosphate groups are possible. In addition, there is the possibility of valence state inter-conversions in vivo, but reports on this are inconclusive. Special conditions, such as a low pH, may facilitate the change, however, normally the amount of converted antimony will not be significant (OEHHA, 1997; WHO, 2003).

Excretion
In rats, antimony was found conjugated with glutathione and excreted through the bile. Following a single oral dose of 21.1 mg of antimony (as $^{124}SbCl_3$) in lactating cows, 82% of the oral dose was detected in faeces, 1% in urine and less than 0.01% in milk (OEHHA, 1997).

A1.2.2 Toxicity

Inorganic and trivalent forms of antimony are more toxic than organic or pentavalent compounds (Lynch et al., 1999). In addition, antimony toxicity depends on the solubility of the antimony compound: antimony trioxide, which has extreme low water solubility, is practically not toxic (WHO, 2003). Females seem to be more sensitive than males (Janssen et al., 1995) and rats are about 4 times more sensitive to acute exposure to antimony than mice (WHO, 2003).

Essentiality

Antimony is a non-essential element.

Acute and subacute toxicity

The symptoms of acute antimony intoxication resemble those of arsenic intoxication. In humans, ingestion of soluble antimony salts causes strong irritating effects on the gastrointestinal tract and sustained vomiting. In addition, abdominal cramps, diarrhoea and cardiac toxicity were reported. For children, a minimal lethal dose of 300 mg antimony potassium tartrate was reported, for adults this was 1200 mg (WHO, 2003). In experimental animals, the oral LD50 value of antimony potassium tartrate ranges from 15 mg/kg bw in rabbits to 115 mg/kg bw in rats and 600 mg/kg bw in mice (OEHHA, 1997; WHO, 2003).
In a 2 weeks study in rats and mice, antimony (administered as antimony potassium tartrate in drinking water), was tolerated up to doses of 168 (rats) or 273 (mice) mg antimony/kg bw/day (NTP, 1992).

Subchronic and chronic toxicity

Only a few studies are available concerning the (sub)chronic oral toxicity of antimony.
Two studies with antimony potassium tartrate in drinking water administered to rats and mice during lifetime resulted in reduced lifespan, changes in blood biochemistry and a decreased heart weight. A LOAEL of 5 ppm (equivalent to 0.43 mg antimony/kg bw/day, only dose tested) was reported for mice as well as rats (Kanisawa and Schroeder, 1969; Schroeder et al., 1970). However, Lynch et al. (1999) noted several shortcomings in methodology and inconsistent use of control data. For example, comparisons were made between test and control groups from different studies or from different ages. In addition, a high incidence of death due to viral pneumonia was noted in the rat study, which could influence the conclusions on reduced lifespan. Furthermore, no detailed histopathological examination was performed in the mouse study. Therefore, it was concluded that these studies were unsuitable for the derivation of a health-based guidance level (Lynch et al., 1999).
Following 90-day exposure to several doses of antimony potassium tartrate (0, 0.5, 5.0, 50 and 500 ppm antimony) via drinking water in rats, several subtle, histopathological changes in thyroid (reduced follicle size and increased epithelial height) were observed starting at exposure levels of 0.5 ppm. However, thyroid function did not seem to be affected since serum thyroxin levels were normal. In addition, mild and reversible histological changes were observed in the liver (nuclear hyperchromicity), starting at 5 ppm. At the highest dose level, a reduced body weight gain was observed, associated with a decrease in food (12%) and water (35%) intake. Furthermore, signs of mild hepatic cirrhosis were noted (Poon et al., 1998). According to Lynch et al. (1999), the histological changes observed at low dose levels were not associated with signs of overt toxicity, often found without dose-relationship and considered to be the consequence of normal physiological variation. Therefore, a NOAEL of 50 ppm (equivalent to 6 mg antimony/kg bw/day) in the study by Poon et al. was proposed by Lynch et al. (1999), based on a decrease in body weight, food intake and water intake.
The relatively insoluble antimony trioxide has a lower toxicity than antimony potassium tartrate. In a 90 days oral study with rats, antimony trioxide concentrations up to 20,000 mg/kg diet (1407 mg antimony/kg bw/day) did not result in effects of toxicological significance (WHO, 2003).

Genotoxicity and carcinogenicity

Antimony trioxide was found positive in vitro in bacterial mutation assays, a cytogenetic assay with human lymphocytes and a sister chromatid exchange assay. In vivo, chromosomal aberrations were observed, however no clastogenic effects were found (WHO, 2003; EFSA, 2004). For soluble antimony compounds positive results were found in some in vitro studies (trivalent and pentavalent antimony compounds) and also in some in vivo studies (only trivalent antimony compounds) (WHO 2003; De Boeck, 2003)

No oral carcinogenicity of antimony potassium tartrate was found in 2 lifetime studies in rats and mice (Kanisawa and Schroeder, 1969; Schroeder et al., 1970). However, the study design contained several crucial shortcomings and detailed histopathological examination appeared not to have been conducted (Lynch et al., 1999). Antimony trioxide inhalation in rats resulted in lung tumours in combination with direct lung damage due to chronic overload with insoluble particles (WHO, 2003). The data available indicate that these tumours are formed by a non-genotoxic mechanism (Van Engelen, 2006).

A1.3 EVALUATIONS BY OTHER ORGANISATIONS

According to IARC (1989), antimony trioxide is possibly carcinogenic to humans (classified in group 2B) and antimony trisulfide is not classifiable as to its carcinogenicity to humans (classified in group 3).

Previously, US-EPA (1991) derived an RfD of 0.4 µg antimony/kg bw/day. This value was based on a reduced lifespan and altered plasma levels of glucose and cholesterol in a lifetime rat study with a LOAEL of 0.35 mg antimony/kg bw/day (5 ppm; Schroeder et al., 1970) and applying an uncertainty factor of 1000, for intra- and interspecies variation and the conversion of LOAEL to NOAEL.

OEHHA (1997) also used the rat study by Schroeder et al. as basis for the derivation of a drinking-water guideline. They applied an uncertainty factor of 300 (100 for intra- and interspecies variation and a factor 3 for LOAEL to NOAEL conversion and a non-severe endpoint) to the LOAEL (put at 0.43 mg/kg bw/day), implying a TDI of 1.4 µg antimony/kg bw/day.

WHO (2003) took the NOAEL of 6 mg antimony/kg bw/day (administered as antimony potassium tartrate) of the subchronic drinking water study in rats (Poon et al., 1998), suggested by Lynch et al. (1999) as most appropriate starting point for the derivation of a TDI. Applying an uncertainty factor of 1000 (a factor 10 for intra- and interspecies variation and the use of a subchronic study, each) resulted in a TDI of 6 µg antimony/kg bw/day. EFSA (2004) adopted this TDI in its evaluation for use of antimony trioxide in food contact materials. RIVM (Van Engelen et al., 2006) also adopted this TDI as most appropriate limit value for the ingestion of antimony.

A1.4 EVALUATION

Since antimony is not considered a genotoxic compound, a TDI can be derived on the basis of a NOAEL and uncertainty factors.

The TDI for antimony of 0.86 µg/kg bw/day that was proposed by Janssen et al. (1995) was based on a LOAEL of 5 ppm (0.43 mg antimony/kg bw/day) from a lifetime study with rats (Schroeder et al., 1970). Following the evaluation of Lynch et al. (1999), this study is not appropriate for the derivation of a health-based guidance level. Based on effects on body weight gain and food and water intake in the 90-day oral study with potassium antimony tartrate in rats by Poon et al. (1998), a NOAEL of 6 mg antimony/kg bw/day, as proposed by Lynch et al. (1999), was used for the derivation of a TDI. Applying an uncertainty factor of 1000 (100 for intra- and interspecies variation and 10 for the use of a subchronic study), a TDI of 6 µg antimony/kg bw/day could be derived.

This TDI especially accounts for soluble antimony compounds. One should keep in mind that insoluble compounds, such as antimony trioxide, are significantly less toxic.

A1.5 BACKGROUND EXPOSURE

Food, including vegetables grown on antimony-contaminated soils, is the most important source of antimony exposure for the general population. Oral uptake of antimony via food and drinking water is low. Dietary data from the UK, Sweden, Germany, France, Brazil, Turkey and the USA showed average daily intakes for adults ranging from 1.1 to 29 µg/day (EU-RAR, 2004). Antimony uptake from air is significantly less, with estimated amounts between 60 and 460 ng/day per person in urban populations (WHO, 2003).

A1.6 CONCLUSION

Compound	TDI	TCA	Background exposure
Antimony	6	-	0.4

TDI: tolerable daily intake (oral exposure); µg antimony/kg bw/day.
Background exposure: µg antimony/kg bw/day (maximum of given range, rounded).
A TCA for inhalation exposure of antimony is not derived (inhalation exposure of antimony is not relevant).

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Appendix A2: Tin and inorganic tin compounds

A2.1 INTRODUCTION

Tin was evaluated within the scope of this project by Vermeire et al. in 1991. They derived a TDI of 2 mg tin/kg bw/day for oral intake. This value (derived from the PTWI of 14 mg tin/kg bw/day) was based on a NOAEL of 20 mg tin/kg bw/day in a 2-year feeding study with stannous chloride ($SnCl_2$) in the rat, with an uncertainty factor of 10. A TCA was not suggested.
For an update of the TDI for tin, additional literature was reviewed (published since 1991), including evaluations of EFSA (2005), ATSDR (2005) and JECFA (2006).
Tin is a silver-white metal, which can occur in a divalent (Sn(II)) and tetravalent (Sn(IV)) oxidation state. Natural occurrence of tin in the metallic state is rare. Tin is thought to be relatively immobile in soil. Concentrations in soil vary between 2 and 200 mg/kg, but may be higher in areas of high tin deposits (ATSDR, 2005). Background concentrations in soils of Dutch nature reserves range from 0.6-28.1 mg/kg (Van Vlaardingen et al., 2005).
Tin is used in the lineage of cans and containers. It is also present in tin alloys and some soldering materials. Inorganic tin compounds are used in the glass industry, as catalysts, in food additives and as stabilizers in perfumes and soaps. Contamination will occur mostly from production and use of tin and tin compounds.

A2.2 TOXICOLOGY

A2.2.1 Toxicokinetics

Absorption
Gastrointestinal absorption of inorganic tin compounds is reported to be low. In animals and humans, less than 5% of the oral dose is absorbed. In humans, the gastrointestinal absorption of tin decreases with increasing doses.
Quantitative studies regarding the dermal or inhalatory absorption of tin are not present.

Distribution
The absorbed fraction of tin is widely distributed in the body. After oral administration of inorganic tin compounds, the major sites of deposition in rats and mice are bone, kidney and liver. Limited data suggest that tin can also accumulate in the rat brain after prolonged exposure to stannous chloride.

Metabolism
Nothing is known about the in vivo metabolism of tin or tin compounds.

Excretion
Due to the poor absorption of inorganic tin after oral exposure, tin is to a large extend directly excreted in the faeces in both animals and humans. This faecal excretion increases with increasing exposure. Only minor amounts are excreted in urine after oral exposure to high doses of tin or inorganic tin compounds. For absorbed tin however, urinary excretion is the major elimination pathway.

Biomarkers
According to ATSDR (2005), models for the quantitative estimation of exposure to tin or inorganic tin compounds are not developed yet.

A2.2.2 Toxicity

Essentiality
There is no evidence that tin is nutritionally essential for humans.

Acute and subacute toxicity
Data about the acute toxic effects of tin or inorganic tin compounds are scarce. In humans, acute gastro-intestinal effects are reported following ingestion of canned foods with a high tin content (dose range 750-1000 mg tin/kg bw; ATSDR, 2005). In controlled clinical studies on the acute effects of tin migrated from packaging, a threshold concentration for adverse effects of < 730 mg/kg was suggested (EFSA, 2005).

Subchronic and chronic toxicity
Intermediate oral exposure to various inorganic tin compounds for 4-13 weeks in rats resulted in haematological effects, decreased body weight gain and histopathological changes in liver and kidney at doses ≥ 66 mg/kg bw/day. High doses of tin compounds can also result in abdominal distension and pancreatic atrophy. In addition, limited hepatic changes were observed after chronic oral exposure of rats and mice to 0.7 mg/kg bw/day $SnCl_2$, however, in another study these effects were not dose-related. Both ATSDR (2005) and EFSA (2005) concluded to a NOAEL of 32 mg/kg/day for haematological effects, starting at week 4, based on a 13-weeks oral study, where rats were exposed to 0, 9.5, 32, 95, and 315 mg tin/kg bw/day (as stannous chloride) in their diet (De Groot et al., 1973, evaluated by EFSA, 2005 and ATSDR, 2005).
There is only a limited amount of data on dermal or inhalation exposure to tin or tin compounds. Chronic inhalation of Sn(IV) dust in humans can cause a benign form of pneumoconiosis, without impairment of pulmonary function. Tin metal is not irritating to the skin, but inorganic tin salts have been reported to produce mild irritation to skin and eyes in humans (ATSDR, 2005).

Genotoxicity and carcinogenicity
Several studies indicated that Sn(II) ($SnCl_2$), but not Sn(IV), is a genotoxic agent in vitro, probably due to the generation of reactive oxygen species. In vivo however, $SnCl_2$ and SnF_2 were not able to induce micronuclei in bone marrow cells of mice after intraperitoneal injections of doses up to 210 or 39.5 mg/kg bw, respectively (EFSA, 2005). According to ATSDR (2005) and EFSA (2005), no carcinogenic effects of orally ingested inorganic tin in humans or animals were reported.

A2.3 EVALUATIONS BY OTHER ORGANISATIONS

ATSDR (2005) proposed an MRL of 0.3 mg tin/kg bw/day for intermediate-duration oral exposure (15–364 days) to inorganic tin. This value was based on a NOAEL of 32 mg tin/kg bw/day (as stannous chloride) for hematological effects in Wistar rats fed the test material in the diet for 13 weeks (study by De Groot et al., 1973) and an uncertainty factor of 100 (10 for animal to human extrapolation and 10 for human variability). ATSDR (2005) did not derive an inhalation MRL for inorganic tin compounds. In 2005, the Provisional Tolerable Weekly Intake (PTWI) of 14 mg tin/kg bw/wk, derived in 1988, was maintained by JECFA. However, it was argued that the basis for the PTWI was unclear and was based either on a long-term rat study with a NOAEL of 20 mg tin/kg bw/day (cited by Vermeire et al., 1991), or acute gastric irritancy in man, with a threshold of 200 mg/kg. It would therefore be necessary to

(re)assess the long-term effects of inorganic tin concentrations that do not elicit acute effects. In addition, they concluded that it was inappropriate to derive an acute reference dose for inorganic tin, since the adverse effects of ingested tin depend on the concentration and nature of tin in the product, rather than on the dose ingested on a body-weight basis (JECFA, 2006).
EFSA considered the available data from human or animal studies inadequate to derive a tolerable upper intake level for tin (EFSA, 2005).

A2.4 EVALUATION

Inorganic tin is not considered as a genotoxic or carcinogenic agent in vivo. Therefore, a TDI can be derived based on a NOAEL and the application of uncertainty factors.
The TDI of 2 mg tin/kg bw/day recommended by Vermeire et al. in 1991 was based on the PTWI of JECFA of 14 mg tin/kg bw/wk, established in 1988. Extrapolation factors were not described.
The NOAEL of 20 mg tin/kg bw/day in the rat study that may have been used for the derivation of the PTWI of JECFA was based on a small increase in tin accumulation in bone and a decrease in feed efficiency. Applying the standard uncertainty factor of 100 (10 for inter- and 10 for intraspecies variation) to this NOAEL, a TDI of 0.2 mg tin/kg bw/day can be derived (instead of 2 mg tin/kg bw/day, as recommended in 1988). Recommendation of a TDI of 0.2 mg tin/kg bw/day instead of 2 mg/kg bw/day is strengthened by a NOAEL of 32 mg tin/kg bw/day, observed in an intermediate duration study in rats by De Groot et al. (1973) (ATSDR, 2005; EFSA, 2005). Application of uncertainty factors for inter- and intraspecies variation (10x10) and for exposure duration (2) results in a (rounded) TDI of 0.2 mg tin/kg bw/day.
Consequently, it is recommended that the TDI as derived by Vermeire et al. (1991) is replaced by a new TDI of 0.2 mg tin/kg bw/day.

A2.5 BACKGROUND EXPOSURE

The most important source for exposure to tin is from canned food products. According to Vermeire et al. (1991), the maximum daily intake in the Netherlands is approximately 0.14 mg/kg bw/day. Data from Total Diet Studies in the UK in 1997 cited by EFSA (2005) are in the same range of this value, which is therefore maintained.

A2.6 CONCLUSION

Compound	TDI	TCA	Background exposure
Tin	200	-	140

TDI: tolerable daily intake (oral exposure); µg tin/kg bw/day.
Background exposure: µg tin/kg bw/day.
Due to a lack of reliable data, a TCA for inhalation exposure to tin is not derived.

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Appendix A3: Vanadium

A3.1 INTRODUCTION

Vanadium was evaluated within the scope of this project by Janssen et al. in 1998. They derived a provisional TDI of 2 µg vanadium/kg bw/day for oral intake. This TDI was based on a LOAEL for developmental effects of 2.1 mg vanadium/kg bw/day (administered as 5 mg sodium metavanadate/kg bw/day [5])) in a reproduction study in rats and applying an uncertainty factor of 1000. A TCA of 1 µg vanadium/m^3 was adopted from WHO, based on a LOAEL for respiratory effects of 20 µg vanadium/m^3 (inhaled as vanadium pentoxide [6])) from occupational studies and a 'protection factor' of 20 (WHO, 1987).
For the present update, additional literature was reviewed (published since 1998). This included reports by WHO (2000 and 2001), NTP (2002), EFSA (2004) and IARC (2006).
Vanadium is widely distributed in the earth's crust. In the environment, it occurs in varying oxidation states (3+, 4+ and 5+ being the most common) but not as elemental vanadium. In tissues of organism, vanadium predominantly occurs in 3+ and 4+ states, due to reduction, while in plasma the 5+ state is most common. Vanadium is used in alloys with steel and as an oxidation catalyst in chemical industries. The estimated total global emission of vanadium into the atmosphere ranges from 71,000 to 210,000 tons per year (NTP, 2002).

A3.2 Toxicology

According to Janssen et al. (1998), the available toxicological data did not allow a differential evaluation of the toxic effects of the different oxidation states of vanadium. One should keep in mind, however, that acute vanadium toxicity increases with increasing valency (WHO, 2000) and that vanadium pentoxide appears to be the most acutely toxic vanadium compound (NTP, 2002). In addition, it was reported that rats and mice are more tolerant to vanadium than larger experimental animals (EFSA, 2004).

A3.2.1 Toxicokinetics

Absorption
Absorption of vanadium in the lungs following inhalation exposure is about 25% and depends on the size of the particles and the solubility of the compound (Janssen et al., 1998). The available data indicate that, in animals as well as in humans, only less than 5% of ingested vanadium is absorbed by the gastrointestinal tract. Also dermal exposure was reported to result in poor absorption (Janssen et al., 1998; EFSA, 2004; IARC, 2006).

Distribution
Following oral uptake in rats, vanadium is transported in the serum bound to transferrin and is distributed widely throughout the body. Highest amounts were located in the bone, kidneys, liver, spleen and testes. Particularly in bone, retention of vanadium was reported (WHO, 2000; NTP, 2002;

[5]) $NaVO_3$
[6]) V_2O_5

EFSA, 2004). Limited data indicate that also in humans, vanadium binds to transferrin in plasma (NTP, 2002).

Metabolism
It was shown that pentavalent vanadium is reduced in erythrocytes to tetravalent vanadium, a process that depends on glutathione (WHO, 2000).

Excretion
After ingestion, high amounts of (unabsorbed) vanadium are excreted via the faeces. Absorbed vanadium is predominantly excreted via urine. In rats and mice, vanadium is eliminated from plasma in three phases (plasma half times of 15 minutes, 14 hours and 8.5 days (EFSA, 2004)). In humans, initial clearance via urine is rapid, followed by a slower phase. About 60% of absorbed vanadium is excreted by the kidneys within 24 hours (NTP, 2002).

Biomarkers
The determination of vanadium in 'end-of-shift' urine has been used widely to monitor occupational exposure to vanadium compounds. Validated methods were described for the measurement of vanadium in urine (WHO, 2001).

A3.2.2 Toxicity

Essentiality
Although vanadium has been considered an essential element in chickens and rats, there is no evidence that vanadium is an essential element for humans. Vanadium deficiency in chickens and rats may result in growth reduction, impairment of reproduction and disturbances in lipid metabolism (WHO, 2000; EFSA, 2004).

Acute and subacute toxicity
Inhalation exposure to vanadium compounds (mostly vanadium pentoxide) in humans results predominantly in effects on the respiratory tract and alterations of pulmonary function. Symptoms include bronchitis, pneumonia, rhinitis, pharyngitis, laryngitis and conjunctivitis. Studies of occupationally exposed persons, as well as controlled human exposure experiments, suggest a LOAEL of 50-60 µg vanadium/m^3 for acute exposure (WHO, 2000; NTP, 2002).
In animals, acute inhalation of vanadium results in pulmonary edema, bronchopneumonia, fibrosis, bronchitis rhinitis, hemorrhagic lung inflammation, tracheitis and emphysema.
A NOAEL of 0.5 mg vanadium pentoxide (~0.3 mg vanadium)/m^3 was reported in Cynomolgus monkeys exposed to 0.5 or 5 mg vanadium pentoxide/m^3 for 1 week. When monkeys were exposed to sodium vanadate, the effects on pulmonary function were similar, but earlier in onset (NTP, 2002).
Administration of ammonium metavanadate [7]) to drinking water of rats for 4 weeks is reported to reduce the Hb concentration and the number of erythrocytes and to increase the percentage of reticulocytes in blood. The LOAEL was 10 mg ammonium metavanadate (~1.5 mg vanadium)/kg bw/day (Zaporowska et al., 1993).
Skin patch testing with 10% vanadium pentoxide in human volunteers did not result in skin irritation. However, eye irritation has been reported in studies with vanadium workers (WHO, 2001).

Subchronic and chronic toxicity
Chronic inhalation of vanadium (as V_2O_5) dust in humans results in similar effects as for acute inhalation, with a LOAEL of 20 µg vanadium/m^3 (WHO, 2000).

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[7]) NH_4VO_3

In rats and mice, repeated exposure to vanadium pentoxide fume results in decreased survival, decreased body weight and morphological changes in liver, heart, lungs and kidneys. In studies of 3-months exposure in both rats and mice adverse effects are observed at concentrations ≥ 2 mg vanadium pentoxide (~1.1 mg vanadium)/m^3, but in 2-year studies (6h/day, 5d/w) 0.5 and 1 mg vanadium pentoxide/m^3 (~0.3 and ~0.6 mg vanadium/m^3, respectively) are reported to be the LOAEL in rats and mice, respectively (WHO, 2000; NTP, 2002).
Patients that were treated orally with ammonium vanadyl tartrate in increasing doses (up to 0.40 mg vanadium/kg bw/day) for 45 to 68 days complained of gastrointestinal effects, including cramps and diarrhoea, while no effects were observed in patients administered 0.08 mg vanadium/kg bw/day. No haematological and biochemical effects were observed in a double blind, placebo controlled trial in male and female weight-training athletes, that were dosed with vanadyl sulphate (0.12 mg vanadium per kg bw per day) for 12 weeks (EFSA, 2004).
Sodium metavanadate added to the drinking water of rats for 3 months resulted in dose related lesions in spleen, lungs and kidneys. The LOAEL in this study was 5 mg sodium metavanadate/L (~ 0.8 mg vanadium/kg bw/day) (Domingo et al., 1985).

Reproductive and developmental toxicity
Oral studies in animals have also been performed for reproduction/developmental endpoints. Repeated intragastric doses of sodium metavanadate before mating (14 days in female and 60 days in male rats) resulted in a decrease in body weight, tail length, and relative organ weight of liver, spleen and kidneys in the pups. Histopathology on adults was not performed. The LOAEL was 5 mg sodium metavanadate (~2 mg vanadium)/kg bw/day (Domingo et al., 1986). Vanadyl sulphate pentahydrate dosed by gavage to mice on gestational day 6-15 at dosages ≥ 37.5 mg vanadyl sulphate pentahydrate (~7.5 mg vanadium)/kg bw/day induced embryotoxic effects (increase in poorly ossified skeletal elements and early resorptions, micrognathia, decrease in foetal weight). Maternal toxicity started at levels of 75 mg vanadyl sulphate pentahydrate (~15 mg vanadium)/kg bw/day (Paternain et al., 1990). A similar study in mice with sodium orthovanadate resulted in a NOAEL of 7.5 mg sodium orthovanadate (~2 mg vanadium)/kg bw/day for maternal toxicity and 15 mg sodium orthovanadate (~4 mg vanadium)/kg bw/day for developmental toxicity (delayed ossification) (Sanchez et al., 1991).

Genotoxicity and carcinogenicity
In table 1, the results of genotoxicity tests of vanadium compounds are summarized.
Gene mutation tests in various strains of *Escherichia coli* and *Salmonella typhimurium,* and in mammalian cells were generally negative for several vanadium compounds. Ammonium metavanadate produced a weak positive response in *Salmonella typhimurium* and an increase in mutations at the hprt locus in V79 cells (NTP, 2002; EFSA, 2004).
In mammalian cell and human lymphocytes cultures, vanadium pentoxide did not induce sister chromatid exchanges (SCE) or structural chromosomal aberrations (SCA). However, SCE rates were increased in human lymphocytes in vitro by sodium ortho- and metavanadate, ammonium metavanadate and vanadyl sulphate. Data on the in vitro capacity of vanadium compounds to induce SCAs are inconclusive. Whereas results in human lymphocytes were negative for all compounds tested, SCA tests with ammonium metavanadate and vanadyl sulphate in CHO cells were positive. In in vitro experiments increases in the incidence of micronuclei were observed irrespective of the vanadium compound tested (NTP, 2002; EFSA, 2004).
Intragastric administration of vanadyl sulphate, sodium orthovanadate and ammonium metavanadate induced micronuclei and hyperploidy in CD1 mice, but only vanadyl sulphate induced SCAs (Ciranni et al., 1995). Also following oral administration via drinking water in CD1 mice, sodium orthovanadate did induce, at high doses, micronuclei and primary DNA lesions (Leopardi et al., 2005). However, in a recent study the potential of vanadyl sulphate to induce micronuclei could not be confirmed after oral

administration via drinking water in CD1 mice (Villani et al., 2007). No evidence was found for the in vivo induction of SCEs or micronuclei by vanadium pentoxide (NTP, 2002).

Table A3.1 Summary of mutagenic activity of vanadium compounds

	V_2O_5	NH_4VO_3	$NaVO_3$	Na_3VO_4	$VOSO_4$
Bacterial					
Gene mutation	– (E coli) – (Salm typh) + (Bac subt)	– (E coli) – (Salm typh) + (Salm typh) + (Bac subt)			
Mammalian					
Gene mutation	– (V79, no act)	+ (V79, no act) – (V79, act)			– (V79, no act) – (V79, act)
SCE	– (hum lymph) – (V79)	+ (hum lymph) + (CHO)	+ (hum lymph)	+ (hum lymph)	+ (hum lymph) + (CHO)
SCA	– (hum lymph)	– (hum lymph) + (CHO)	– (hum lymph)	– (hum lymph)	– (hum lymph) + (CHO)
Micronuclei	+ (V79) – (Syr HE)	+ (hum lymph)	+ (hum lymph)	+ (hum lymph)	+ (hum lymph)
Aneuploidy		+ (S cerev)			+ (S cerev)
Hypoploidy		+ (hum lymph)	+ (hum lymph)	+ (hum lymph)	+ (hum lymph)
Hyperploidy		– (hum lymph)	– (hum lymph)	– (hum lymph)	
Endoreduplication	+ (V79)				
In vivo					
Gene mutation					+ (Drosophila)
SCE	– (CD1 mice)				
SCA		– (CD1 mice)		– (CD1 mice)	+ (CD1 mice)
Micronuclei	– (B6C3F1 mice)	+ (CD1 mice)		+ (CD1 mice)	+ (CD1 mice) – (CD1 mice)
Hypoploidy		+ (CD1 mice)		+ (CD1 mice)	+ (CD1 mice)
Hyperploidy		+ (CD1 mice)		+ (CD1 mice) + (ICR mice)	+ (CD1 mice)

Pentavalent and tetravalent vanadium compounds did produce aneuploidy, polyploidy, endo-reduplication and other aneugenic-related effects, both in in vitro and in in vivo experiments. The production of micronuclei seems to be the result of aneuploidy instead of clastogenicity. Therefore, the genotoxicity data present at the moment suggest that threshold-based aneuploidy-inducing events rather than structural chromosomal damage are the cause of the DNA damaging activity of vanadium compounds (NTP, 2002; EFSA, 2004).
Lifetime studies with vanadyl sulphate in drinking water in rats and mice did not result in an increase in tumour incidence. However, due to strong limitations in study design, the results should be considered inconclusive (EFSA, 2004). In 2-year studies, performed by NTP, inhalatory exposure to vanadium pentoxide in rats and mice resulted in various nonneoplastic lesions in the respiratory tract. Furthermore, there was an increase in incidences of lung alveolar/bronchiolar adenomas and sarcomas in male rats and in alveolar/bronchiolar adenomas in females (both exceeding the database range, but not significantly and not dose relatedly). In mice, the occurrence of alveolar/bronchiolar neoplasms was significantly increased in all dose groups (1, 2 or 4 mg vanadium pentoxide/m^3 for 6h/d, 5d/w) in males and females (NTP, 2002).

An increase in K-*ras* mutations in alveolar/bronchiolar carcinomas that is observed following vanadium pentoxide exposure (75% compared to 30% in spontaneously occurring alveolar/bronchiolar carcinomas) in addition to a loss of heterozygosity at chromosome 6 in the region of the K-*ras* suppressor gene in many of these tumours suggests a possible mechanism for the carcinogenicity of vanadium pentoxide (NTP, 2002). However, the K-*ras* mutations can also be the result of indirect mechanisms.

A3.3 EVALUATIONS BY OTHER ORGANISATIONS

Based on chronic upper respiratory tract symptoms in occupational studies with a LOAEL of 20 µg vanadium/m^3 (inhaled as V_2O_5) the WHO concluded that exposure to vanadium levels below 1 µg/m^3 (24 hours average) would not likely have adverse health effects. The protection factor of 20 was based on the fact that only minimal effects were observed at 20 µg/m^3, and because a susceptible sub-population was not identified (WHO, 2000).
In 2001, WHO concluded that, although the mechanism for the mutagenic effects of vanadium compounds may be aneugenicity, the available data are insufficient to clearly identify a threshold level for any route of exposure relevant to humans, below which there would be no concern for potential genotoxic activity. Therefore, WHO recommended that the exposure levels to vanadium should be kept as low as possible (WHO, 2001).
IARC concluded in 2006 that vanadium pentoxide is mutagenic in vitro and possibly also in vivo in mice. According to IARC, there is inadequate evidence in humans, but sufficient evidence in experimental animals for the carcinogenicity of vanadium pentoxide. Therefore, they placed vanadium pentoxide in group 2B, meaning that vanadium pentoxide is possibly carcinogenic in humans (IARC, 2006).
Based on several chronic studies in rats and mice with inhalation exposure to vanadium pentoxide, NTP concluded that there is 'some evidence of carcinogenic activity' in male rats, and 'equivocal evidence of carcinogenic activity' in female rats, in addition to 'clear evidence of carcinogenic activity' in male and female mice (NTP, 2002).
According to EFSA, the relevance of the NTP inhalation studies in rats and mice for oral ingestion of vanadium is unclear. In addition to strong limitations of the available drinking water studies, this makes the evaluation of the carcinogenic potential of vanadium by the oral route not possible. It was concluded that it is not possible to derive a tolerable upper intake level for vanadium, due to insufficient available data (EFSA, 2004).

A3.4 EVALUATION

The relevance of the carcinogenic effects as observed for vanadium pentoxide in mice after inhalation for the carcinogenic properties of other vanadium compounds is unclear. Furthermore, also the relevance of these effects for oral ingestion of vanadium compounds is unclear, since only local adenomas and or sarcomas in the lung were induced.
Available genotoxicity data are limited, but suggest that threshold-based aneuploidy-inducing events underlie the observed DNA damaging activity of vanadium compounds. Overall, based on the data currently available, the threshold approach can be applied in the derivation of a TDI and TCA.
Inhalation toxicity of vanadium compounds has only been tested using vanadium pentoxide, therefore, a TCA could only be derived for this compound. The results of the chronic rat and mice studies with vanadium pentoxide from NTP (2002) indicate a LOAEL of 0.5 and 1 mg vanadium pentoxide/m^3, respectively. Applying an uncertainty factor of 1000 (10 each for LOAEL to NOAEL, inter- and

intraspecies variation) would result in a TCA of 0.5-1 µg vanadium pentoxide/m^3. This is only marginally different from the TCA (1 µg vanadium/m^3; ~2 µg vanadium pentoxide/m^3) adopted from WHO (1987), which was based on human studies. Therefore, the TCA of 1 µg vanadium/m^3 is maintained. Since vanadium pentoxide probably is the most toxic vanadium compound (NTP, 2002), this TCA can also be applied as provisional TCA for other vanadium compounds.
Since no relevant new data were available concerning the effects of ingestion of sodium metavanadate or other vanadium compounds, the provisional TDI of 2 µg vanadium/kg bw/day (~5 µg sodium metavanadate/kg bw/day), based on a LOAEL of 2.1 mg vanadium/kg bw/day (administered as 5 mg Na VO_3/kg bw/day) in a reproduction study in rats by Domingo et al., (1986) (developmental effects) and an uncertainty factor of 1000, is maintained as provisional TDI for sodium metavanadate. The results of reproduction/development studies with sodium orthovanadate (NOAEL 2 mg vanadium/kg bw/day for maternal toxicity) and vanadyl sulphate (LOAEL 7.5 mg vanadium/kg bw/day for embryo-toxic effects) indicate that this provisional TDI can also be applied to other vanadium compounds.

A3.5 BACKGROUND EXPOSURE

In 1998, a background exposure of 0.3 µg/kg bw/day was estimated by Janssen et al. (1998). Since then, no data contradicting this value have been published. However, body builders using vanadium supplements to improve their performance were reported to have a daily intake of up to 18.6 mg vanadium/day (~250 µg/kg bw/day).

A3.6 CONCLUSION

Compound	pTDI	pTCA	Background exposure
Vanadium	2	1	0.3

pTDI: provisional tolerable daily intake (oral exposure); µg vanadium/kg bw/day.
TCA: tolerable concentration in air (inhalation exposure); µg vanadium/m^3.
Background exposure: µg vanadium/kg bw/day.

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Appendix A4: Chloride and sulfate

A4.1 CHLORIDE

Chloride salts are vital for human metabolic processes and essential for maintaining electrical neutrality in the body. Chloride is the main electrolyte in the mammalian body: it represents 70% of the body's total negative ion content. The suggested amount of chloride intake for an adult is 750- 900 mg/day. Chloride toxicity has not been observed in humans, except for individuals with an impaired NaCl metabolism (congestive heart failure). Data on acute, subchronic or chronic chloride toxicity for humans or mammals are not available. There are no indications that chloride should be carcinogenic. WHO does not recommend a health-based guideline value for chloride in drinking water. However, chloride concentrations in excess of 250 mg/L can give rise to detectable taste in water (WHO, 2004). The most frequent chloride substance is sodium chloride (common salt), which is considered by the U.S. Food and Drug Administration as safe for its intended use. This GRAS ('generally recognized as safe') classification, and the universal use of sodium chloride since antiquity, affirms its safety.
Acute oral toxic levels of sodium chloride are reported as (Salt Institute, 2007):

Human	TDLo: 12,357 mg/kg (lowest toxic dose)
Mouse	LD_{50}: 4,000 mg/kg
Rat	LD_{50}: 3,000 mg/kg
Rabbit	LDLo: 8,000 mg/kg (lowest lethal dose)

Conclusion

For the purpose of human-toxicological MPRs in the framework of soil contamination, chloride can be considered non-toxic.

A4.2 SULFATE

Sulfates occur naturally in numerous minerals and are extensively used commercially. The highest levels occur in groundwater and are from natural origin. The average daily intake of sulfate from water, air and food is approximately 500 mg, food being the major source.
The sulfate ion is poorly absorbed from the human intestine (WHO, 1984; Daniels, 1988). Sulfate is important in metabolism as a moiety that is conjugated to many metabolites or foreign substances, thereby increasing their water solubility and elimination (Daniels, 1988). Sulfate itself slowly penetrates mammalian cellular membranes and is rapidly eliminated through the kidneys (WHO, 1984). The major acute health effect observed with sulfate ingestion is laxative action (Daniels, 1988; NAS, 1977). US-EPA has identified a LOAEL of 630 mg/L based on diarrhoea in infants receiving formula made with high-sulfate water (US-EPA, 1990).
Sulfates can contribute to an undesirable taste in water. The taste threshold for the sulfate ion in water is 300-400 mg/L (NAS, 1977). WHO does not recommend a health-based guideline value for sulfate in drinking water. However, because of the gastro-intestinal effects resulting from the ingestion of drinking water with a high sulfate level, sulfate concentrations in excess of 500 mg/L should be avoided (WHO, 2004).

Information on the oral subchronic and chronic toxicity of sulfate in humans and animals are unavailable. Likewise, data on the developmental and reproductive toxicity of sulfate in humans and animals are unavailable. Carcinogenicity data were not located.

Conclusion

For the purpose of human-toxicological MPRs in the framework of soil contamination, sulfate can be considered non-toxic.

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Profile compilation: A.J. Baars (22-11-2007)
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Appendix A5: 1,2-Dichloroethene (*cis* and *trans* isomers)

A5.1 EVALUATION

Cis- and *trans*-1,2-dichloroethene were firstly evaluated in 1995 (Janssen et al., 1995) and re-evaluated in 2001 (Baars et al., 2001). In 2008 they were re-evaluated again (Janssen, 2008) in the framework of the programme "International normalisation of substances' of the Ministry of Housing, Spatial Planning and the Environment. This last re-evaluation has been reported by Janssen, 2008, who concluded that on the basis of new toxicological data the difference between *cis*-1,2-dichloroethene and *trans*-1,2-dichloroethene was not longer warranted. The conclusion of this re-evaluation is reprinted below. The author did not report on the background exposure level, but since there are no data justifying a change in the earlier estimate, the background exposure value as reported in the re-evaluation of 2001 is maintained.

A5.2 CONCLUSION

Compound	TDI	TCA	Background exposure
Cis- and *trans*-1,2-dichloroethene	30	60	0.13

TDI: tolerable daily intake (oral exposure); µg/kg bw/day
TCA: tolerable concentration in air (inhalation exposure); µg/m^3
Background exposure: µg vanadium/kg bw/day

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[8]) Available upon request at SIR-secr@rivm.nl.

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Appendix A6: Dioxins (polychlorinated dibenzo-*p*-dioxins, polychlorinated dibenzofurans, and coplanar polychlorinated biphenyls)

A6.1 INTRODUCTION

'Dioxins' is the generic term for a number of chemicals encompassing the polychlorinated dibenzo-*p*-dioxins (PCDDs), the polychlorinated dibenzofurans (PCDFs) and the coplanar polychlorinated biphenyls (coplanar or dioxin-like PCBs).
The possible number of chlorine atoms in a dioxin results in 75 PCDD congeners (7 of which are toxicologically relevant), 135 PCDF congeners (10 of which are toxicologically relevant) and 209 PCB congeners (67 of which are coplanar, i.e., non-ortho or mono-ortho substituted ones, and are thus characterized as 'dioxin-like'-PCBs; 12 of these are toxicologically relevant).
The dioxins were re-evaluated in 2001 by Baars et al. They adopted the by that time valid international evaluation of WHO (Van Leeuwen and Younes, 2000), which resulted in a TDI of 1 - 4 pg/kg bw/day. In 2001 and 2002, the dioxins were re-evaluated by the European Commission's Scientific Committee on Food (SCF, 2001, 2002) and the FAO/WHO Joint Expert Committee on Food Additives and Contaminants (JECFA, 2001). Their considerations are summarised below.

A6.2 TOXICOLOGY

A6.2.1 General

It is generally assumed that the toxicity of dioxins is expressed through a common mechanism of action and all the compounds act through this mechanism, that is, interaction with the cytosolic aryl hydrocarbon receptor protein (Ah receptor). During the last few decades, data from many experimental studies with dioxins are consistent with an additive model. As a result of this generally accepted additivity, the toxic equivalency concept was developed during the mid 1980s. It uses the relative effect potency determined for individual PCDD, PCDF, and dioxin-like PCB compounds for producing toxic or biological effects relative to a reference compound, usually 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) which is considered the most toxic dioxin. The total toxic equivalent (TEQ) is operationally defined by the sum of the products of the concentration of each compound multiplied by its TEF (toxic equivalency factor) value, and is an estimate of the total TCDD-like activity of the mixture (Van den Berg et al., 2006). Thus, in the TEF scheme, a dose of TCDD of, e.g., 1 pg TCDD per kg bw is considered to be equivalent to a toxic equivalence of 1 pg TEQ (properly addressed as 'WHO-TEQ') per kg bw.
The biochemical and toxicological effects of PCDDs, PCDFs and coplanar PCBs are directly related to their concentrations in tissues, and not to the daily dose. The most appropriate measure of dose is therefore the concentration at the target tissue; however, this concentration is seldom known. But the body burden is strongly correlated with the concentrations in tissue and serum, and estimates of body burden are therefore more appropriate measures of dose for interspecies comparisons than is the daily dose.

The long half-lives of PCDDs, PCDFs and coplanar PCBs in humans have several implications for the period of intake that is relevant to the assessment. First, the concentration of toxic equivalents in the body will increase over time as more of the compounds are ingested. Second, after cessation of exposure, the body's concentration of stored toxic equivalents will decline slowly, only half of the accumulated toxic equivalents disappearing over about 7 years, resulting in a pseudo-steady state only after decades. Third, because of this long-term storage in the body and the consequent daily exposure to the body's stored toxic equivalents, intake on a particular day will have a small or even negligible effect on the overall body burden. Hence, the appropriate period for evaluating the mean intake of these compounds is at least a week (SCF, 2000, 2001) or a month (JECFA, 2002).

A6.2.2 Toxicokinetics

Absorption

Experiments in humans and laboratory animals given an oral dose of TCDD showed 50–90% absorption, comparable with the near-complete absorption of PCDDs, PCDFs and PCBs by nursing infants from their mothers' milk.

Distribution

After absorption from the gut, TCDD enters the lymph in the form of chylomicrons and is cleared from the blood within 1 h, to appear mainly (74–81% of an administered dose) in the liver and adipose tissue. The distribution of PCDDs and PCDFs between the blood and organs is governed by lipid partitioning and binding to plasma proteins. After entering liver cells, TCDD either dissolves in the lipid fraction or binds to the Ah receptor or to cytochrome P450 (CYP) proteins.

Metabolism and excretion

In laboratory animals, PCDDs and PCDFs are excreted almost exclusively in the bile, excretion in the urine being a minor route. Whereas the parent compound is found primarily in the organs of rodents, only metabolites of PCDDs and PCDFs occur in bile, indicating hepatic metabolism, including hydroxylation and conjugation, of these compounds. Faecal excretion of unmetabolized PCDDs and PCDFs is also an important route of elimination in humans.

In rodents, the half-life of TCDD ranges from 8–24 days in mice to 16–28 days in rats. Humans eliminate PCDDs and PCDFs more slowly, the estimated mean half-life of TCDD ranging from 5.5 to 11 years. The half-lives of other PCDD congeners and of PCDFs and coplanar PCBs vary widely. These differences in the half-lives of different congeners are reflected in their TEFs.

Biomarkers

A number of biochemical changes, including strong induction of enzymes such as CYP, altered expression of growth factors and enhanced oxidative stress, have been noted in laboratory animals with body burdens of TCDD within a lower range of 3–10 ng/kg bw. These biochemical effects can be considered to be early markers of exposure to PCDDs, PCDFs and coplanar PCBs, or events induced by these compounds in animals and in humans that may or may not result in adverse effects at higher body burdens.

A6.2.3 Toxicity

Acute and subacute toxicity

In laboratory animals, the acute toxicity of TCDD and related PCDDs and PCDFs varies widely between and among species. For example, the median lethal dose in guinea-pigs treated orally was 0.6 mg/kg bw, while that in hamsters was > 5,000 mg/kg bw. Explanations for this variation include differences in Ah receptor functionality, toxicokinetics and body fat content. While data on acute

toxicity are available for various commercial PCB mixtures (median lethal doses usually > 100 mg/kg bw), the data on individual coplanar PCB congeners in mammals are limited.
One of the more common symptoms associated with lethality induced by PCDDs is a generalized delayed wasting syndrome characterized by inhibition of gluconeogenesis, reduced feed intake and loss of body weight. Other toxic effects observed after a single exposure to PCDDs include haemorrhages in a number of organs, thymic atrophy, reduced bone-marrow cellularity and loss of body fat and lean muscle mass.

Genotoxicity and carcinogenicity
The results of several short-term assays for genotoxicity with TCDD, covering various end-points, were negative. Furthermore, TCDD did not bind covalently to DNA from the liver of mice.
TCDD and other PCDDs induced tumours at multiple sites in laboratory animal species of each sex. In a series of assays in vivo and in vitro, TCDD promoted the growth of transformed cells, consistent with observations of cancer promotion in whole animals in vivo. In a long-term study of carcinogenicity with TCDD in rats, the LOAEL for hepatic adenomas in females was 10 ng/kg bw/day, and the NOAEL was 1 ng/kg bw/day. Several studies have shown that TCDD promotes tumours in laboratory animals, in particular liver tumours. Several other PCDDs, PCDFs and coplanar PCBs also promoted liver tumours. In a long-term study in rats in which the incidence of liver tumours was increased over that in controls, the LOAEL of 10 ng/kg bw/day corresponded to a steady-state body burden of 290 ng/kg bw. In order for humans to attain a similar steady-state body burden, they would have to have a daily intake of 150 pg/kg bw.
It can be concluded that TCDD is not a genotoxic carcinogen, but a multi-site carcinogen in experimental animals that has been shown by several lines of evidence to act through a mechanism involving the Ah receptor. This receptor is highly conserved in an evolutionary sense and functions the same way in humans as in experimental animals. The International Agency for Research on Cancer (IARC, 1997) classified TCDD as a human carcinogen (Group 1); other PCDDs and PCDFs were considered not to be classifiable as to their carcinogenicity to humans (Group 3).

Reproductive and developmental toxicity
In a study by Ohsako et al. (2001), pregnant Holtzman rats were given a single oral dose of TCDD at 0–800 ng/kg bw on day 15 of gestation, and the male offspring were examined on days 49 and 120 after birth. No changes were seen in testicular or epididymal weight or in daily sperm production or sperm reserve at any dose. However, the weight of the urogenital complex, including the ventral prostate, was significantly reduced at doses of 200 and 800 ng/kg bw in rats killed on day 120. Moreover, the anogenital distance of male rats receiving doses ≥ 50 ng/kg bw and killed on day 20 was significantly decreased. Administration of TCDD at any dose resulted in a dose-dependent increase in 5α-reductase type 2 mRNA and a decrease in androgen receptor mRNA in the ventral prostate of rats killed at day 49 but not in those killed at day 120, with no adverse sequelae at the lowest dose of 12.5 ng/kg bw. Physiologically-based pharmacokinetic (PBPK) modelling indicates that the equivalent maternal body burden after multiple doses at this NOAEL would be 13–19 ng/kg bw. Likewise, the LOAEL of 50 ng/kg bw corresponds to an equivalent body burden of 51–80 ng/kg bw.
The lowest LOAEL reported for the reproductive system of male offspring was found in an experiment with Wistar rats by Faqi et al. (1998). In this study, the dams were treated subcutaneously before mating and throughout mating, pregnancy and lactation. They received an initial loading dose of [^{14}C]TCDD at 25, 60 or 300 ng/kg bw two weeks before mating, and then a weekly maintenance dose of TCDD at 5, 12 or 60 ng/kg bw. The size of the maintenance doses was determined on the basis of a reported elimination half-life for TCDD of 3 weeks in adult rats. The effects on male reproductive end-points were studied on days 70 and 170 after birth. The number of sperm per cauda epididymis at puberty and in adulthood was lower in the offspring of all treated dams than in those of controls. Daily

sperm production was permanently lower in offspring of treated dams than in those of controls, as was the sperm transit rate, thus increasing the time required by the sperm to pass through the cauda epididymis. Moreover, the offspring of the treated groups showed increased numbers of abnormal sperm when investigated in adulthood. The latency periods to mounting and intromission were significantly greater in offspring of dams at the lowest and highest doses, but not of those at the intermediate dose, than in offspring of controls. In the male offspring of dams at the highest dose, the concentration of serum testosterone was decreased in adulthood, and permanent changes found in the testicular tubuli included pyknotic nuclei and the presence of cell debris in the lumen. The fertility of the male offspring was not affected in any of the treated groups. PBPK modelling showed that a maternal body burden of 25–39 ng/kg bw at steady state would be required to arrive at the fetal body burden which resulted in adverse effects after an initial dose of 25 ng/kg bw and weekly maintenance doses of 5 ng/kg bw (LOAEL).
These studies provide evidence that adverse effects on the reproductive system are induced in male offspring of pregnant rats given TCDD. The studies show reductions in daily sperm production, in the number of sperm in the cauda epididymides and in epididymal weight as well as accelerated eye opening, a reduction in anogenital distance and feminized sexual behaviour in male offspring associated with maternal steady-state body burdens of TCDD of $\geq$ 25 ng/kg bw. Reductions in the weights of the testes and the size of the sex accessory glands, such as the ventral prostate, in male offspring, development of external malformations of the genitalia in female offspring and reduced fertility in males and females required higher maternal body burdens. It should be mentioned that the most sensitive end-points differed between studies. Perhaps this reflects strain differences in sensitivity and even minor differences in the experimental conditions, e.g., the diet.

Observations in humans
In adults, most of the effects other than cancer observed after exposure to PCDDs, PCDFs and coplanar PCBs, such as chloracne, appeared only at doses several orders of magnitude greater than those generally received from background contamination of foods. In Seveso [9]), more female children than expected were born to fathers who had serum TCDD concentrations > 80 pg/g of lipid (16–20 ng/kg bw) at the time of conception.
In most of the epidemiological studies considered for evaluating the carcinogenicity of TCDD, exposure had been primarily to TCDD, with some exposure to mixtures of other PCDDs, as contaminants of phenoxy herbicides and chlorophenols. The studies involved persons with the highest recorded exposure to TCDD, the estimated geometric mean blood lipid concentrations after the last exposure ranging from 1,100 to 2,300 pg/g of lipid in the industrial cohorts; lower average concentrations were found in the population exposed in Seveso.
Low excess risks of the order of 40% were found for all neoplasms combined in all the studies of industrial cohorts in which the exposure assessment was adequate. The risks for cancers at specific sites were increased in some of the studies, but the results were not consistent between studies, and no single cancer site seemed to predominate.
Increasing risks for all neoplasms with time since first exposure were observed in those studies in which latency was evaluated. The follow-up of the Seveso cohort has so far been shorter than that of the industrial cohorts; however, the rate of death from all cancers has not been found to differ significantly from that expected in the general population. Excess risks were seen for cancers at some specific sites among persons in the most heavily contaminated zones at the time of the accident, but there were few cases.

[9]) In an industrial accident in Seveso (Italy) in 1976, several hundred grams up to a few kilograms of TCDD escaped into the atmosphere and settled over an area of approximately 18 km^2. As a result, several thousands of people living nearby the plant were exposed to high amounts of TCDD.

In these well-conducted cohort studies, the intensity of exposure could be ascertained with precision because of the long biological half-life of TCDD in human tissues, and the relative risks increased significantly with increasing exposure. Although the excess cancer risk at the highest exposure was statistically significant, these results must be evaluated with caution, as the overall risks are not high and the strongest evidence is for industrial populations whose exposure was two to three orders of magnitude greater than that of the general population, and who also had heavy exposure to other chemicals; furthermore, lifestyle factors such as smoking were not evaluated. In addition it must be noted that there are few precedents of carcinogens that increase the risk for cancer at all sites combined, with no excess risk for any specific tumour predominating.

A6.3 EVALUATIONS BY OTHER ORGANISATIONS

On the basis of the available toxicological data, both SCF (2000, 2001) and JECFA (2002) concluded that a tolerable intake can be derived for TCDD based on the assumption that there is a threshold for all effects, including cancer. Carcinogenicity due to TCDD was not linked to mutagenicity or DNA binding, and it occurred at higher body burdens in animals than other toxic effects. Hence, the assessment of a tolerable intake based on effects other than cancer would also address any carcinogenic risk.

The lowest LOAEL and NOAEL were provided by the studies of Faqi et al. (1998) and Ohsako et al. (2001), respectively. With the toxicokinetic conversions described above, these two studies indicate maternal body-burden LOAELs and NOAELs for effects on male rat offspring of 25–39 ng/kg bw and 13–19 ng/kg bw, respectively.

In the studies used to estimate body burden on the basis of the distribution of TCDD after multiple dosing, radiolabeled material was used. Therefore, the background concentrations of TCDD and other PCDDs and PCDFs in the tissues of laboratory rats resulting from traces of these compounds in the feed were ignored. Studies aimed to predict the body burdens of rats resulting from the presence of coplanar compounds in laboratory feed indicated that “unexposed” laboratory rats had toxic equivalent body burdens of 3–4 up to 12 ng/kg bw, depending on age. Correcting the body burdens calculated from the studies cited above resulted in estimated total toxic equivalent body burdens at steady state of 16–23 ng/kg bw for the NOAEL and 28–43 ng/kg bw for the LOAEL. By means of PBPK-modelling, it was calculated that these body burdens correspond to equivalent human daily intakes (EHDIs) of 8–10 and 14–20 pg/kg bw/day, respectively.

Use of body burdens to scale doses from studies in laboratory animals to equivalent human doses removes the need for assessment factors to account for differences in toxicokinetics between animals and humans. To account for inter-individual differences in toxicokinetics among humans, however, an assessment factor should be applied. In view of limited data on the toxicokinetics of TCDD in humans, the default factor of 3.2 was considered appropriate (Vermeire et al., 2007).

With regard to the potential differences in toxicodynamics between experimental animals and humans and within the human population, studies of Ah receptor binding affinity and adverse responses directly dependent on Ah receptor activation suggest that humans are less sensitive to TCDD than responsive rodent strains. However, studies of some biochemical or cellular effects, such as CYP1A1 and CYP1A2 induction, suggest a comparable sensitivity. Therefore, for some endpoints it can not be excluded that the most sensitive humans might be as sensitive to the adverse effects of TCDD as experimental animals. Hence, an assessment factor for differences in toxicodynamics between experimental animals and humans and for interindividual variation among humans is not needed. However, if a LOAEL instead of a NOAEL is used for deriving a health-based safety limit, an additional assessment factor is needed. As the LOAEL for the sensitive end-point was considered to be close to a NOAEL and represented marginal effects, the application of a factor of 3 to account for use

of a LOAEL instead of a NOAEL was considered appropriate. This resulted in an overall assessment factor of 9.6 (3 x 3.2). Thus, a total assessment factor of 3.2 should be applied to the EHDI associated with the NOAEL, and a total assessment factor of 9.6 should be applied to the EHDI associated with the LOAEL. This results in values for a provisional tolerable daily intake (pTDI) of 2.5–3.1 based on the NOAEL, and 1.5–2.1 pg/kg bw/day based on the LOAEL.
SCF (2000, 2001) chose the mid-point of these ranges expressed on a weekly basis, and arrived at a provisional tolerable weekly intake (pTWI) of 14 pg/kg bw (per week).
JECFA (2002) chose the mid-point of these ranges expressed on a monthly basis and arrived at a provisional tolerable monthly intake (pTMI) of 70 pg/kg bw (per month).
Furthermore, both organisations concluded that these tolerable intakes should be applied to intake of PCDDs, PCDFs and coplanar PCBs, expressed as TEQs.

A6.4 EVALUATION

RIVM adopts the evaluations by SCF and JECFA as summarised above. For pragmatic reasons a pTDI of 2 pg TEQ per kg bw per day can be used in, e.g., intake calculations, if it is kept in mind that an incidental high intake on a particular day will have a small or even negligible effect on the overall body burden.

A6.5 BACKGROUND EXPOSURE

Background exposure to dioxins is by large the result from intake via food; exposure through other sources is negligible. The daily intake in the late 1970s was high: approximately 9 pg/kg bw/day (Baars et al., 2004; De Mul et al., 2008). Due to measures to reduce the discharge of dioxins in the environment, daily exposures have decreased. Baars et al. (2004) estimated the life-long averaged median intake of dioxins at 1.2 pg/kg bw/day, based on food consumption data collected in 1999. Based on more recent food consumption data (collected in 2004) and applying the recently revised TEF-values (Van den Berg et al., 2006), De Mul et al. (2008) reported the declining trend in median dioxin exposure to continue. They estimated the current background exposure as a life-long averaged median intake of 0.9 pg/kg bw/day, with a 95 percentile of 1.8 pg/kg bw/day.

A6.6 CONCLUSION

Compound	pTDI	TCA	Background exposure
PCDDs, PCDFs, coplanar PCBs [1])	2×10^{-6}	-	0.9×10^{-6} [2])

pTDI: provisional tolerable daily intake (oral exposure); µg WHO-TEQ/kg bw/day
Background exposure: µg WHO-TEQ/kg bw/day.
A TCA for inhalation exposure of dioxins is not derived (inhalation exposure of dioxins is of minor relevance).

[1]) PCDDs: polychlorinated dibenzo-p-dioxins, PCDFs: polychlorinated dibenzofurans; PCBs: polychlorinated biphenyls; amounts expressed in WHO-TEQ.

[2]) Median value 0.9 pg WHO-TEQ/kg bw/day; 95 percentile 1.8 WHO-TEQpg/kg bw/day.

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Appendix A7: Ethyl-*tertiary*-butylether (ETBE)

A7.1 INTRODUCTION

Ethyl-*t*-butylether (ETBE; CAS nr. 637-92-3, 2-ethoxy-2-methylpropane: $(CH_3)_3C\text{-}O\text{-}C_2H_5$) is a synthetic ether, and like methyl-*t*-butylether (MTBE; see Appendix 8)) it is mainly used as a fuel additive: it replaces lead in gasoline, increasing the anti-knock rating. In addition it reduces the emission of aromates, greenhouse gases and dust, while it also decreases the gasoline's vapour pressure. Since ETBE has a lower water-solubility than MTBE, the distribution via groundwater after leakage of accidental ETBE will be less than with MTBE.
At room temperature ETBE is a colourless to slightly yellow liquid (melting point –94 °C, boiling point 73.1 °C, water solubility 23.7 g/L).
As yet, ETBE has not been evaluated by RIVM. Evaluations by other organisations (like WHO, US-EPA, ATSDR) are also not available. Consequently health based safety limits have not been established. However, an extensive toxicological review was published in 2007 (McGregor, 2007).

A7.2 TOXICOLOGY

A7.2.1 Toxicokinetics

Absorption
The inhalation absorption of ETBE in humans was reported to be approximately 26% (Nihlén et al. 1998). Data on oral absorption are lacking, but it can be assumed that ETBE, like MTBE, is rapidly and virtually fully absorbed after oral exposure (ECB, 2006). Data on dermal absorption are not available.

Distribution
ETBE is distributed extensively in the mammalian body. It is moderately soluble in blood, and approximately 15 times more soluble in fat tissues (compared with blood). Its volume of distribution is 6.4 ± 1.4 L/kg bw (Johanson et al., 1995; Nihlén et al., 1998a).

Metabolism
The biotransformation of ETBE is similar in rats and humans, and is comparable to the biotransformation of MTBE. Sex differences are not known.
ETBE is oxidised by cytochrome P450 to *t*-butylalcohol (TBA), liberating acetaldehyde (Bernauer et al., 1998; Nihlén et al., 1998a; Hong et al., 1999; Amberg et al., 2000), which in turn is rapidly converted to acetic acid.
TBA is metabolised to 2-methyl-1,2-propanediol and 2-hydroxyisobutyrate. The latter can be converted to acetone (Bernauer et al., 1998; Dekant et al., 2001), but the main metabolite in urine is 2-hydroxy-isobutyrate. In addition 2-methyl-1,2-propanediol, TBA, TBA-glucuronide, and traces of TBA-sulfate, acetone and parent compound are found in urine, but it must be noted that the main metabolites of ETBE are also produced in the intermediary metabolism (Bernauer et al., 1998; Nihlén et al., 1998a; Amberg et al., 2000; Dekant et al., 2001).

Excretion

In rats the excretion of ETBE and its metabolites is more rapid than in humans. In line with this, following a comparable exposure, blood concentrations in humans are higher than in rats (Amberg et al., 2000).

ETBE is eliminated in several phases. The initial half life in blood in humans is less than 2 h, but the final elimination half life is as high as 24-33 h (Nihlén et al., 1998a; Amberg et al., 2000). Also the elimination of TBA is relatively slow, with a half life in humans of approximately 12 h (Nihlén et al., 1998a).

In humans about 40-70% of inhaled ETBE is found as metabolites in the urine (Amberg et al., 2000; Dekant et al., 2001), the amount excreted via the faeces is negligible (Borghoff and Ashgarian, 1996). The remaining is exhaled, mainly as unchanged ETBE, and 1.4-3.8% as TBA (Nihlén et al., 1998a; Dekant et al., 2001). In rats the clearance of ETBE from blood by exhalation is more rapid (Dekant et al., 2001).

A7.2.2 Toxicity

Acute and subacute toxicity

Animal studies

Like MTBE, ETBE has a low acute toxicity. The oral LD50 in Wistar rats and the dermal LD50 in New Zealand rabbits are above 5000 and 2000 mg/kg bw, respectively. The inhalatory LC50 in Sprague-Dawley rats is higher than 5880 mg/m^3. In none of these studies mortality was observed (MB, 1988a, b; IIT, 1989, 1996).

Human studies

In one human study the effects of ETBE after inhalation were investigated. Eight man were inhalatory exposed to 21.2, 106 or 212 mg/m^3 ETBE during 2 h. Only sensory irritation (eye, mucous membranes, and respiratory tract) and effects on respiratory function were investigated. Exposure to the two highest concentrations resulted in a decreased vital lung capacity and a decreased forced vital lung capacity. However, these decreases were still within the normal human variation and were thus considered not clinically relevant (Nihlén et al., 1998b).

Irritation

Skin

Only with total occlusion dermal ETBE-exposure of rabbits results in some irritating effects, all other exposure schemes were negative (MB, 1988c; CIT, 1992a; Pharmakon, 1994a). In contrast to MTBE, ETBE is thus not irritating to skin.

Eye

An eye irritation study with rabbits resulted in redness and oedema in all animals, which disappeared after 8 days In addition in one animal a reaction of the iris was observed on day 1 (MB, 1992d). In two other rabbit studies moderate conjunctiva reactions were reported, but no effects on iris or cornea (CIT, 1992b; Pharmakon, 1994b).

Hence ETBE is not to moderately irritating to the eye.

Respiratory tract

Animal data on irritation of the respiratory tract are not available.

Sensibilisation

A maximization test with guinea pigs was negative (Pharmakon, 1994c).

Human studies

In a human study investigating the effects of ETBE-inhalation the eight male subjects reported slight irritation of throat and respiratory tract at an exposure to 212 mg/m^3 for 2 h, but objective symptoms of these were not observed. There were no signs of eye irritation (Nihlén et al., 1998b).

Subchronic and chronic toxicity

In mouse and rat inhalation studies ataxia and sedation (both reversible) were seen at concentrations > 2,120 mg/m^3 (White et al., 1995; Dorman et al., 1997; Medinsky et al., 1999). In various inhalation studies with rats increased liver and kidney weights have been reported (White et al., 1995; Medinsky et al., 1999; Gaoua, 2004a). A 90-days inhalation study with mice reported also increased liver and kidney weights, together with increased adrenal and heart weights. In addition centrilobular hypertrophy in the liver and a dose-related increased proliferation of hepatocytes was observed. The NOAEL in this study was 2120 mg/m^3 (Medinsky et al., 1999).

Continued inhalatory exposure to ETBE of male rats resulted in nephropathy and increased proliferation in the proximal tubuli. Because protein droplet accumulation was seen at the same time, it is possible that these effects are the result of α2u-globuline mediated renal toxicity. However, also in female rats a (transient) increase in proliferation of the proximal tubuli was observed. In addition, female rats showed an increased incidence of bone marrow congestion (Medinsky et al., 1999).

In a 4-weeks inhalation study with rats a decreased body temperature of males was reported (White et al., 1995).

In a subchronic inhalation study focussing on the neurotoxic effects of ETBE in the rat no indications for changes in sensomotor or neuromuscular function were found, also the motor activity was not affected (Dorman et al., 1997). Thus ETBE has no irreversible effects on the nervous system.

Taken together it can be concluded that continued inhalatory exposure (28 to 90 days) of rats and mice to ETBE-concentrations up to 2120 mg/m^3 does not lead to relevant clinical-chemical, haematological or pathological abnormalities (White et al., 1995; Dorman et al., 1997; Medinsky et al., 1999).

In continued oral exposure of rats with doses up to 1000 mg/kg bw/day no signs of ataxia or sedation were observed (Gaoua, 2004a, b)

Data with respect to the chronic toxicity and carcinogenicity of ETBE are not available (see below for the only not yet finalized carcinogenicity study).

Genotoxicity and carcinogenicity

ETBE

In various studies no indications of mutagenicity were found: gene mutation tests with *Salmonella typhimurium* strains and CHO cells, chromosome aberration tests with CHO cells in vitro, and in vivo micronucleus tests in mouse bone marrow cells were negative (Zeiger et al., 1992; IPL, 1992a, b; Pharmakon, 1994d; BRRC, 1995a-c).

Data with respect to the carcinogenicity of ETBE are very limited. The only oral carcinogenicity study (which is still in its finalizing stage, although the study dates from 1999) reports an increased incidence of hemangiolymphoreticular neoplasia and tumours of the mouth epithelium and forestomach, but none of these is significant or is related to the dose. In addition a significant number of malignant Schwannomas was observed at the dose of 250 mg/kg bw/day, but not at 1000 mg/kg bw/day (Maltoni et al., 1999). Altogether there are too little data to allow a conclusion regarding the carcinogenicity of ETBE.

Acetaldehyde and TBA

Acetaldehyde causes gene mutations in bacteria and mammalian cells in vitro, and in *Caenorhabditis elegans* and *Drosophila melanogaster*. In a rat study exposure to acetaldehyde resulted in a dose-related increase in the number of nasal tumours. However, in view of the rapid metabolic transformation of acetaldehyde to acetic acid, it is unlikely that acetaldehyde produced in the biotransformation of ETBE will cause any damage (IARC, 1999; IPCS, 1995).

TBA has been tested for mutagenicity in several *Salmonella typhimurium* strains. All results were negative, both without and with metabolic activation. A test for forward mutations with mouse lymphoma cells, however, was positive, but this result could not be reproduced. Chromosome

aberration tests with CHO cells were negative, as was a micronucleus test in mouse erythrocytes in vivo (NTP, 1995, 1997).
Inhalation of acetaldehyde at concentrations > 1,350 mg/m^3 increases the incidence of nasal tumours in Wistar rats (IPCS, 1995). Inhalatory exposure of hamsters results in carcinomas of the larynx in hamsters (IARC, 1999). However, these are not expected to be relevant in exposures to ETBE in view of the rapid biotransformation of acetaldehyde to acetic acid.
Inhalation exposure to TBA is known to cause renal tumours in rats. However, these tumours are not reported in the study of Maltoni et al. (1999). Moreover, they are probably resulting from the α2u-globulin associated nephropathy, and thus not relevant for humans (McGregor, 2007).

Reproductive and developmental toxicity
Reproductive toxicity
In a 2-generation study with daily oral exposure of Wistar rats to ETBE from 10 weeks before mating through lactation no adverse effects on the reproduction in the first and in the second generation were observed. In adults a dose-related decrease of body weights was seen together with an increased salivation. The NOAEL for effects on reproduction was 1000 mg/kg bw/day (Gaoua, 2004a).
Also after two weeks exposure of female Simonson rats to ETBE in drinking water (0.3%, equivalent with approx. 450 mg/kg bw/day) no effects on ovulation, number of ovums or percentage of fertilized ovums were observed (Berger and Horner, 2003).
Developmental toxicity
Oral exposure of Sprague-Dawley rats to 0, 250, 500 and 1000 mg/kg bw/day during gestational days 5 through 19 did not affect any gestational parameters or result in toxic effects in the foetuses. At the highest dosage, however, the dams showed a decrease in body weight. In addition in the adult F0 and F1 generations increased liver and kidney weights were found. The NOAEL for developmental and adult toxicity were 1000 and 250 mg/kg bw/day, respectively (Gaoua, 2004b).

A7.3 EVALUATIONS BY OTHER ORGANISATIONS

ETBE has yet not been evaluated by ATSDR or IARC; US-EPA is in the process of evaluating the compound. ECB (2006) has drafted a classification proposal for ETBE, based on an inhalation NOAEL of 2,120 mg/m^3 for histopathological changes in bone marrow and liver and kidney weight changes in the study of Medinsky et al. (1999). For oral exposure the NOAELs of 1000 and 250 mg/kg bw/day for reproductive effects and adult toxicity, respectively, were taken from the studies of Gaoua (2004a, b).

A7.4 EVALUATION

ETBE and MTBE have similar physico-chemical and toxicokinetic properties. The same holds for the toxic effects following exposure to either compound. Both are not to slightly irritant for eyes and do not result in sensibilisation. There are no indications for mutagenicity. Carcinogenic data for ETBE are lacking. The kidney tumours seen after exposure to MTBE are likely the result of α2u-globuline mediated nephropathy, and thus not relevant for humans. Also the MTBE-induced liver tumours in mice are not likely to be relevant for humans (Swartjes et al., 2004). In view of the similarities of ETBE and MTBE, currently RIVM considers ETBE to be not carcinogenic.
Since human data on ETBE exposure are lacking, data of animal experiments are the base for deriving a MPR. In agreement with ECB (2006), the 90 days inhalation study of Medinsky et al. (1999) is considered the pivotal one. Increased liver and kidney weights and bone marrow congestion are the critical toxic effects. Correction for continuous exposure of the NOAEL of 2,120 mg/m^3 from this

study results in a NOAEL of 2120 x 6/24 x 5/7 = 380 mg/m^3. For the extrapolation of experimental animals to humans an AF of 10 x 10 is applied for inter- and intraspeciesvariation. An additional AF of 2 is applied for extrapolating from a semichronic study to continuous exposure (Vermeire et al., 2007). This AF is justified by the fact that two semichronic inhalation studies both resulted in a NOAEL of 2,120 mg/m^3, and that the chemical and toxicological similarities between ETBE and MTBE together with the finding that also MTBE semichronic and chronic inhalation studies showed a twofold difference in toxic potency (Swartjes et al., 2004). Application of the total AF of 200 results in a TCA for ETBE of 1.9 mg/m^3.
The 2-generation study of Gaoua (2004a) is considered the pivotal one for deriving a TDI. The decreasing body weight in adult rats resulted in a NOAEL of 250 mg/kg bw/day. Since except these reproductive and developmental studies no other chronic oral studies have been reported, firstly a AF of 10 x 10 is applied (for inter- and intraspecies variation), and secondly an additional AF of 10 is used for database limitations. This results in a TDI for ETBE of 0.25 mg/kg bw/day.

A7.5 BACKGROUND EXPOSURE

Data with respect to the background exposure to ETBE could not be located. The use of ETBE potentially resulting in some background exposure of otherwise not exposed humans, however, is its application as a gasoline additive, which is similar to the use of MTBE, and at roughly similar concentrations.
The background exposure to MTBE was estimated by ECB (2002) in a reasonable *worst case* exposure scenario for a person who is exposed to MTBE at the petrol station during and after refuelling his/her car and who lives near to (50 m) a petrol station, and amounts to 70 - 470 µg/day, equivalent to 1 - 7 µg/kg bw/day. This scenario includes also the exposure due to commuting by car and bus. Exposure to MTBE in drinking water produced from groundwater would in a *worst case* scenario add at most approximately 30 µg/day, equivalent to 0.5 µg/kg bw/day.
In view of the similarity in physico-chemical properties of MTBE and ETBE this estimated exposure to MTBE can be assumed to hold also for ETBE, thus resulting in a *worst case* background exposure to ETBE of 1 – 7 µg/kg bw/day (the ETBE exposure from drinking water will probably less than 0.5 µg kg bw/day due to the poorer water solubility of ETBE compared with MTBE).

A7.6 CONCLUSION

Compound	TDI	TCA	Background exposure
Ethyl-*t*-butylether	250	1,900	1 - 7

TDI: tolerable daily intake (oral exposure); µg ETBE/kg bw/day.
TCA: tolerable concentration in air (inhalation exposure); µg ETBE/m^3.
Background exposure: µg ETBE/kg bw/day.

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Profile review: A.J. Baars, P.J.C.M. Janssen

Appendix A8: Methyl-*tertiary*-butylether (MTBE)

A8.1 EVALUATION

Methyl-*t*-butylether (MTBE; CAS nr. 1634-04-4; 2-methoxy-2-methylpropane: $(CH_3)_3C–O–CH_3$) is a synthetic ether that (like ethyl-*t*-butylether; ETBE, see Appendix 7) is mainly used as a fuel additive: it replaces lead in gasoline, increasing the anti-knock rating. Next to this it serves as an intermediate in the production of isobutylene and as a process solvent in the pharmaceutical industry. In clinical practice MTBE is used to dissolve gallstones.
At room temperature MTBE is a colourless liquid (melting point –108.6 °C, boiling point 52.2-52.3 °C, water solubility 42 g/L).
Following a specific request of the Ministry of Housing, Spatial Planning and the Environment, MTBE was evaluated in 2004 (Swartjes et al., 2004). The conclusion of this evaluation is reprinted below.

A8.2 BACKGROUND EXPOSURE

The background exposure was estimated by ECB (2002) in a reasonable *worst case* exposure scenario for a person who is exposed to MTBE at the petrol station during and after refuelling his/her car and who lives near to (50 m) a petrol station, and amounts to 70 - 470 µg/day, equivalent to 1 - 7 µg/kg bw/day. This scenario includes also the exposure due to commuting by car and bus. Exposure to MTBE in drinking water would in a *worst case* scenario add at most approximately 30 µg/day, equivalent to 0.5 µg/kg bw/day.

A8.3 CONCLUSION

Compound	TDI	TCA	Background exposure
Methyl-*t*-butyl ether	300	2,600	4 - 5

TDI: tolerable daily intake (oral exposure); µg MTBE/kg bw/day.
TCA: tolerable concentration in air (inhalation exposure); µg MTBE/m^3.
Background exposure: the mean of the reasonable *worst case* exposure scenarios as estimated by ECB (2002); µg MTBE/kg bw/day.

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Profile review: P.J.C.M. Janssen, W.C. Mennes

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Appendix A9: Organotin compounds

A9.1 INTRODUCTION

Tributyltinoxide (TBTO) and triphenyltin (TPT)-compounds were evaluated within the scope of this project by Janssen et al. in 1995. They derived a TDI of 0.3 µg/kg bw/day for TBTO. This value was based on a NOAEL of 0.025 mg/kg bw/day in a long term toxicity/carcinogenicity study with rats, applying an uncertainty factor of 100. For TBTO a provisional TCA of 0.02 µg/m^3 was derived, based on an (adjusted) NOAEL of 20 µg/m^3 in a 4-weeks study with rats, with an uncertainty factor of 1000. For TPT-compounds, a TDI of 0.5 µg/kg bw/day was proposed. This was based on an NOAEL of 0.1 mg/kg bw/day in a long-term study with rats (critical effect: decrease in white blood cells), apparently applying an uncertainty factor of 200. This value was adopted from JMPR (1991).
For the update, additional literature was reviewed (published since 1995). This included reviews by US-EPA (1997), EFSA (2004) and ATSDR (2005).
Organotin compounds do not occur naturally in the environment. They are used as polyvinyl chloride heat stabilizers, biocides, catalysts, agrochemicals and glass coatings. Also products like shoes and clothing may contain organic tin. Organotin compounds have the tendency to accumulate in the environment and are highly toxic for aquatic organisms. They are released into the environment either directly (from pesticides and antifouling paints) or by leaching from, or disposal of consumer products. The abbreviations of the organotin compounds discussed below are given in footnote [10]).

A9.2 TOXICOLOGY

A9.2.1 Toxicokinetics

Human data concerning the toxicokinetics of organic tin compounds are scarce. Unless otherwise specified, the kinetic data below are derived from rat studies.

Absorption
Data from accidental human exposure to vapours containing TMT indicated that organotin compounds can be absorbed via dermal or inhalatory pathways, but unfortunately quantitative estimates are not available.
Absorption of ingested tin compounds depends on both the organic compound, vehicle and exposure duration. In rat studies, only 8% of a single oral dose (25 mg/kg, ~ 12 mg Sn/kg) of MET was absorbed, whereas 20-55% of TBTO was reported to be absorbed. After a single administration of 2 mg/kg bw TPTOH to rats, 40% was absorbed, while only 12-28% was absorbed within 30 hours after 7 consecutive days of enteral administration of 2 mg/kg bw/day TPTOH to rats (ATSDR, 2005; EFSA, 2004).

[10]) DBT: dibutyltin; DBTCl: dibutyltinchloride; DET: diethyltin; DMT: dimethyltin; DOT: di-n-octyltin; DPT: diphenyltin; MBT: monobutyltin; MET: monoethyltin; TBT: tributyltin; TBTCl: tributyltinchloride; TBTO: tributyltinoxide; TET: triethyltin; TeET: tetraethyltin; TMT: trimethyltin; TPT: triphenyltin; TPTA: triphenyltinacetate; TPTCl: triphenyltinchloride; TPTOH: triphenyltinhydroxide.

Distribution
Rat studies indicated that ingested organotin compounds and their metabolites are rapidly distributed (in varying amounts) to soft tissues, including liver, kidneys and (to a lesser extent) brain. Blood concentrations of organotin compounds are relatively low following ingestion, except for levels of MET in the rat. Dialkylated organotin compounds are more extensively distributed in the rat than trialkylated organotin compounds. Following ingestion, approximately 95% of absorbed TBTO is distributed to the liver in the rat; reported levels in the brain are low. Also TeET is only poorly distributed to the brain. According to EFSA (2004), TBTO may also cross the placenta. Adipose tissue shows a relatively high retention of TBT.

Metabolism
Organotin compounds are rapidly dealkylated or dearylated in laboratory animals, catalyzed by microsomal monooxygenases of the liver. However, the formation of monobutyltin from dibutyltin may also involve nonenzymatic reactions. Only MET is not metabolized by the rat. The major biotransformation product of DET, TET and TeET is ethylene, with ethane as a minor by-product. The alkyl products of ethyltin compounds are conjugated with glutathione and further metabolized to mercapturic acid derivatives. Degradation of TPT derivatives already starts in the gastrointestinal tract before absorption is completed. A volatile product of TPT-metabolism is benzene. According to ATSDR (2005), similar metabolism pathways may be active in humans.

Excretion
Excretion of most orally administered organotin compounds occurs predominantly via the faeces. The amount of tin that is excreted in urine after oral administration of butyltin compounds increases with the number of butyl moieties. Absorbed MET is mainly excreted (unchanged) via urine, whereas a larger part of the absorbed fraction of diethyltin and triethyltin compounds is excreted in the faeces. In the elimination of TPT, biliary excretion also contributes for a small part.

Biomarkers
Models for estimating exposure levels from blood have not been developed. Since absorbed alkyltin compounds are excreted in urine, urinary measurements may provide a means for detecting exposures.

A9.2.2 Toxicity

Acute and subacute toxicity
Case reports indicated that accidental exposure to trialkyltin compounds can result in neurotoxic effects, which are sometimes reported to be permanent. In addition, ingestion of TPT and TBT causes abdominal pain, nausea and vomiting.
The most common effects after acute oral exposure to organotin compounds in animals are immunotoxicity (atrophy of lymphoid organs) and neuropathologic effects. High doses are lethal. Also hepatotoxicity (DBT and TPT), nephrotoxicity (TMT and TBT, but not TPT), and effects on the endocrine system (TBT) were reported.
Acute inhalation of TBTO or TMT results in irritation of the respiratory tract. No reports of acute effects after inhalation of other organotin compounds have been found. Most organotin compounds are dermal irritants, but sensitizing effects of these substances were not reported. TBT and TPT compounds were reported to be extremely irritating to rabbits' eyes (ATSDR, 2005).

Subchronic and chronic toxicity

All reliable data on the toxic effects of repeated exposure to organotin compounds were derived from animal studies. According to ATSDR (2005), TET and TMT are primarily neurotoxic, whereas TBT and TPT are mainly immunotoxic. Also for DBT the critical effect is immunotoxicity. Furthermore, prolonged exposure to DBT and TBT resulted in haematological effects and hepatotoxicity. A reduction in body weight gain was observed after repeated administration of various trialkyltin compounds (TET, TMT, TBT and TPT).

For TBT, several studies (using either TBTO or TBTCl) resulted in a NOAEL of 0.025 mg/kg bw/day. These included a 4-6 and a 15-17 months diet study with TBTO in rats, where the critical effect was a reduced resistance to a *T. spiralis* infection (Vos et al., 1990), a 2 years diet study with TBTO in rats, based on changes in haematological parameters and immunoglobulin levels (Wester et al., 1988, 1990) and a study where pregnant rats were dosed by gavage daily with TBTCl from day 8 of gestation until weaning and pups were dosed by gavage postnatally until day 30-90. In this study a decreased host defence reaction against *Listeria monocytogenes* was observed at doses above 0.025 mg/kg bw/day (Tryphonas et al., 2004). In a 2 years study in rats, a NOAEL of 0.1 mg/kg bw/day was established for TPT, again based on effects of the immune system, *i.e.* reduction in blood lymphocyte and eosinophil numbers (Til et al., 1970). These studies were all evaluated by ATSDR, 2005 and EFSA, 2004.

DBT exposure resulted in similar immunologic effects as TBT, although the effects were more profound and earlier in onset. Based on a 6 weeks feeding study in rats with reduced thymus weight and various parameters for humoral and cellular immune response as endpoints (Seinen et al., 1977a, b), a LOAEL of 2.5 mg/kg bw/day was established for DBT.

Also oral exposure to DOT results in immunotoxicity. In a 2 years rat study, a mixture of octyltin chloride and dioctyltin chloride was tested in the feed. An increased leucocyte count, thymus weight changes and malignant lymphomas were observed, and a NOAEL of 14.5 mg/kg feed (0.72 mg/kg body weight/day) was established (Van Apeldoorn et al., 1989).

Since the evaluation of Janssen et al. (1995) no relevant new information has been published with respect to repeated inhalational exposure to TBT. They reported a NOAEL of 20 µg TBTO/m^3 (adjusted for continuous exposure), based on a 4 weeks study in rats (Prins and Van Velzen, 1983; BUA, 1988). No relevant data were published concerning the adverse effects of inhalatory exposure to other organotin compounds.

Reproductive and developmental toxicity

When administered during gestation, various organotin compounds have shown to induce adverse effects on reproduction and development (DBT, TBT, DPT and TPT, but not MBT). Overall, exposure to organic tin resulted in an increased number of resorptions, an increased percentage of pre- and postimplantation losses, a decreased number of live pups, an increase in anogenital distance, an increase in external malformations (cleft jaw or palate) and a decrease in organ weights of pups. Established LOAELs and NOAELs based on developmental studies are 0.25 mg/kg bw/day for TBT (LOAEL in 2-generation rat study), 0.025 mg/kg bw/day for TBT (NOAEL in a 18 months rat study), 0.4 mg/kg bw/day for TPT (NOAEL in 2-generation rat study) and 0.1 and 0.3 mg/kg bw/day for TPT (NOAEL for maternal and prenatal toxicity, respectively, in a rabbit study; EFSA, 2004).

Genotoxicity and carcinogenicity

DBT does not induce tumours in rats or mice. According to US-EPA (1997), carcinogenicity of TBTO could not be determined (category D), due to limited and inconclusive data.

Two years feeding studies with TPTOH in rats and mice reported tumour induction in both species. In rats, besides a dose-related increase in pituitary adenomas (according to JMPR (1992) not significant), an increased incidence of Leydig cell tumours was observed. In mice, the incidence of hepatocellular adenomas was increased (only at the highest dose; equivalent to 21.76 mg/kg bw/day), which was

consistent with observed nodular hyperplasia of the liver (ATSDR, 2005; EFSA, 2004). According to EFSA (2004), TPTOH was classified as 'category 3 carcinogen' (suspected human carcinogen), based on the increased incidence of Leydig cell tumours, by the EC in 1997 and as 'category B2' (probable human carcinogen) by US-EPA.
Although DBT, DMT and TPT have been found positive in various mutation tests, convincing data of in vivo genotoxicity are lacking. Gene mutations (CHO/HPRG mutation assay) were observed with DBTCl, however, the compound was not mutagenic in the Ames test. TBTO was mutagenic in *S. typhimurium* at cytotoxic concentrations, but no significant genotoxic potential (mutations or SCE) was otherwise observed (EFSA, 2004). Whereas TPTOH-induced chromosomal aberrations were observed in vitro in lymphocytes, in vivo nucleus tests in mice and cytogenetic assays in hamsters were negative. According to JMPR (1992), the TPT-induced chromosomal aberrations are probably related to a toxic effect on T-lymphocytes and not to genotoxic actions (JMPR, 1992). Several studies indicated that TBT does not possess genotoxic properties. Since there is no convincible evidence of in vivo genotoxicity of TPTOH, it is likely that the carcinogenicity of TPTOH is not caused by mutagenic activity, but by hormonal actions (EFSA, 2004).

Toxic mechanism of action
According to ATSDR (2005), the neuronal necrosis observed following TMT exposure is the result of the activation of microglia. This induces the release of cytokines, which causes degeneration of neuronal cells. TMT-induced brain seizures were suggested to be the result of altered neuropeptide expression.
Immunotoxicity of organic tin compounds was thought to be mediated by two main pathways. Firstly, organotin compounds could affect the calcium homeostasis in a variety of cell types. The intracellular calcium concentration is then enhanced by both a disruption of the calcium transport at the cellular membrane and interference with the intracellular calcium storage. This would initiate the induction of genes involved in apoptosis, as well as a suppression of DNA and protein synthesis. Secondly, high concentrations of organotin compounds could inhibit the ATP synthesis in mitochondria, thereby causing a collapse in ion gradients in the cellular membrane. This would induce necrosis and as a result inflammation in the surrounding tissue.
The immunosuppressive effects of organic tin compounds could be explained by the induction of programmed cell death in immunocompetent cells or the suppression of proliferation of immature thymocytes (ATSDR, 2005; EFSA, 2004).

A9.3 EVALUATIONS BY OTHER ORGANISATIONS

For a number of TPT compounds, JMPR (1992) established an ADI of 0.5 µg/kg bw/day (cited in EFSA 2004).
US-EPA (1997) calculated an RfD for TBTO as the lower 95% confidence bound on the benchmark response (10% relative response) for immunotoxic effects in rats dosed orally with TBTO for 18 months (Vos et al., 1990) divided by an uncertainty factor of 100 (for inter- and intraspecies variation). This resulted in a (rounded) RfD of 0.3 µg/kg bw/day.
According to US-EPA (1997), an RfC for TBTO could not be derived, due to inadequate data from inhalation studies and the unavailability of pharmacokinetic studies to conduct route to route extrapolation.
EFSA (2004) established a group tolerable daily intake (TDI) for TBT, DBT, TPT and DOT, because these compounds exert their immunotoxic effects by a similar mode of action and potency. A NOAEL of 0.025 mg/kg bw/day for immunotoxicity from TBTO in chronic feeding studies (Wester et al., 1988, 1990; Vos et al., 1990) and an uncertainty factor of 100 were used to derive a group TDI of 0.25 µg/kg

bw/day. Based on the molecular mass of TBTO, this group TDI is 0.1 µg/kg bw/day when expressed as Sn, or 0.27 µg/kg bw/day when expressed as TBT chloride.
According to ATSDR (2005), relevant MRLs could only be derived for DBTCl and TBTO. No adequate information was available to derive an MRL for TET, TMT and TPT. For DBTCl, an MRL of 5 µg/kg bw/day was proposed for intermediate-duration oral exposure (15–364 days), based on a LOAEL of 5 mg/kg/day for immunological effects in rats (6-weeks study by Seinen et al., 1977a, b) and an uncertainty factor of 1000. For TBTO, an MRL of 0.3 µg/kg/day was derived for both intermediate-duration oral exposure (15–364 days) and chronic-duration oral exposure (≥ 365 days), based on a NOAEL of 0.025 mg/kg/day for immunological effects in a 6- or 18-months study in rats, respectively (both by Vos et al., 1990) and an uncertainty factor of 100. ATSDR (2005) did not derive an inhalation MRL for organotin compounds since the limited amount of available experimental data by this route of exposure lacked enough detail.

A9.4 EVALUATION

Although there are some indications that TPTOH is carcinogenic, it can be argued that the pituitary and testes tumours that were observed in rats are the result of hormonal imbalance (EFSA, 2004). Also the liver tumours observed in mice are probably not relevant for humans, since they were only observed at a top dose equivalent to 21.76 mg TPTOH/kg bw/day (EFSA, 2004). Since there is no convincible evidence of in vivo genotoxicity of TPTOH, it is likely that the carcinogenicity of TPTOH is not caused by mutagenic activity, but by hormonal actions. Consequently, the threshold approach can be applied.
The critical effect of TET and TMT is neurotoxicity. In accordance with ATSDR (2005) however, TDIs for TMT and TET are not derived, due to limited information.
Janssen et al. (1995) established a TDI of 0.5 µg/kg bw/day for TPT (applicable to TPTA, TPTOH, TPTCl, or the sum of these compounds), based on a NOAEL of 0.1 mg/kg bw/day for a decrease in white blood cells in a 2 years feeding study in rats (Til et al., 1970, cited in JMPR, 1971) and a not further specified uncertainty factor of 200. Since 1995, no relevant new data was published.
A more recent study concerning the effects of TBTCl underlines the TDI of 0.3 µg/kg bw/day for TBTO, as derived by Janssen et al. (1995). This study, as the earlier critical studies, reported a NOAEL of 0.025 mg TBTCl/kg bw/day, based on immunotoxicity. The application of a standard uncertainty factor of 100 (for inter- and intraspecies variation) to this NOAEL resulted in a (rounded) TDI of 0.3 µg/kg bw/day for TBT compounds.
Since it was demonstrated in short-term studies that the effects of TBT on thymus atrophy and liver toxicity are predominantly due to the metabolite DBT, with a lower activity of TBT itself, it can be concluded that DBT is at least as toxic as TBT (EFSA, 2004). Therefore, it can be assumed that the LOAEL of 2.5 mg DBT/kg for immunological effects (from an intermediate-exposure study in rats by Seinen et al., 1977a, b) underestimates the toxic potency of DBT and is therefore not useful to derive a TDI. Since exposure to DBT, TBT and TPT all result in immunotoxicity, exerted via similar mechanisms and potency, a group TDI for these compounds can be used, following the decision of EFSA (2004). The group TDI of EFSA (2004) is based on the NOAEL of 0.025 mg/kg bw/day for immunotoxic effects of TBTO (Vos et al., 1990; Wester et al., 1988, 1990; Tryphonas et al., 2004) and an uncertainty factor of 100 (for intra- and interspecies variation), resulting in a TDI of 0.25 µg/kg bw/day for DBT, TBT and TPT and the sum of these. Although also for DOT the critical effect is immunotoxicity, the effects have been shown to occur at a significantly higher concentration when compared to TBT (NOAEL of 0.72 mg/kg body weight/day vs. 0.025 mg/kg bw/day). In 2000, RIVM used the NOAEL of 0.72 mg/kg body weight/day (derived from a chronic rat experiment) to derive a TDI of 2.3 µg DOT/kg body weight (Janssen et al., 2000). This value is adopted here.

The provisional TCA of 0.02 μg/m^3 for TBTO, derived by Janssen et al. (1995), is retained due to the lack of new relevant data concerning the effects of inhalation exposure to TBT compounds. Due to a lack of available information, it is not possible to derive a TCA for other organotin compounds, although it cannot be excluded that inhalatory exposure to other compounds is not relevant.

A9.5 BACKGROUND EXPOSURE

According to Janssen et al. (1995), the estimated upper range of dietary intake of TBTO was 0.2 μg/kg bw/day. Background levels of TPT are unknown.
In particular fish and other seafood are important sources of exposure of the general population to organic tin compounds. According to EFSA (2004), calculations based on the Norwegian consumption patterns of fish and seafood provided dietary exposure levels of 0.078, 0.046 and 0.047 μg/kg bw/day for TBT, DBT and TPT, respectively. These values were based on the 95th percentile of dietary exposure to the mentioned organotin compounds. Since the Norwegian population consumes on average higher amounts of seafood than the Dutch population, we can assume that the dietary exposure in The Netherlands is lower. In addition, the values derived for the intake of TBT in the European population were in a similar range to those derived in studies that evaluated TBT intake in the USA, Asia and Australia. We therefore adopt the values of the EFSA (2004) presented above (rounded downwards to the nearest decimal) as a reasonable worst case estimation of the upper level values for daily intake by the Dutch population.
Data on the amount of background exposure to other organotin compounds are not available.

A9.6 CONCLUSION

A group TDI was established for DBT, TBT and TPT, because the immunotoxic effects caused by these compounds are elicited by a similar mode of action and potency. Contrary to EFSA (2004), DOT was not included in the group TDI, because DOT has shown to have a significantly lower toxic potential than TBT. In addition, the contribution of DOT to soil pollution is probably relatively small. Because the critical effects of TET and TMT are neurotoxic instead of immunotoxic, these compounds are not included in the group TDI. However, it was not possible to derive a separate TDI for TET or TMT, because too little adequate data were available for these compounds.

Compound	TDI	pTCA	Background exposure
DBT	0.25*	-	0.04
DOT	2.3	-	-
TBT	0.25*	0.02	0.07
TPT	0.25*	-	0.04

* Group TDI for (the sum of) TBT, DBT and TPT.
TDI: tolerable daily intake (oral exposure); μg/kg bw/day.
pTCA: provisional tolerable concentration in air (inhalation exposure); μg/m^3.
Background exposure: μg/kg bw/day.

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