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Human-Toxicological Criteria for Serious Soil Contamination: Compounds evaluated in 1993 & 1994

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NOTICE:

This report is part of the procedure for the derivation of proposals for intervention values for soil clean-up for the 2nd & 3rd series of compounds. Both ecotoxicological and human-toxicological data enter into this procedure. The procedure consists of the following three steps to be taken for each compound:
1. Derivation of the ecotoxicological Serious-Soil-Contamination-Concentration (ECOTOX SCC, this is the HC50-value) (see report no 715810008);
2. Derivation of the human-toxicological Maximum Permissible Risk level (MPR-values) (the present report);
3. Derivation of the human-toxicological Serious-Soil-Contamination-Concentration (HUM-TOX SCC) using the CSOIL model and integration of the ECOTOX SCC and HUM-TOX SCC yielding the proposal for the Intervention Value (see report nos. 715810004 & 715810010 for the 2nd & 3rd series of compounds, respectively).

This research was carried out on behalf of the Directorate-General for Environmental Protection, Directorate for Soil, in the framework of RIVM-project no. 950011 (from 1-1-1995 onwards: RIVM-project no. 715810).

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Summary

This report contains the human-toxicological work done at the Toxicology Advisory Centre in the scope of the RIVM project on soil intervention values for soil clean-up in the years 1993 and 1994. The method for derivation of the Maximum Permissible Risk (in Dutch: Maximum Toelaatbaar Risico) as described in the previous RIVM report by Vermeire et al. (1991) was used, with only minor deviations, for a batch of 26 compounds. Within the project these compounds are referred to as the second and third series of chemicals (the compounds dealt with by Vermeire et al. constituting the first series). For each of the compounds in the present report a MPR could be derived. For several of the compounds the values derived are *provisional* only, due to limitations in the available data bases.

Samenvatting

Dit rapport geeft een overzicht van het humaantoxicologische werk uitgevoerd bij het Adviescentrum Toxicologie in de jaren 1993 en 1994 in het kader van het RIVM-project betreffende interventiewaarden t.b.v. bodemsanering. De methode voor afleiding van het Maximum Toelaatbare Risico (MTR), zoals beschreven in het eerdere RIVM-rapport van Vermeire et al. (1991) werd, met slechts geringe wijzigingen, toegepast voor een set van 26 stoffen. Binnen het project worden deze stoffen aangeduid als de tweede en derde serie van stoffen (de in het rapport van Vermeire et al. behandelde stoffen vormen de eerste serie). Voor elk van de in het huidige rapport opgenomen stoffen kon een MTR worden afgeleid. Voor een aantal van de stoffen is de afgeleide waarde een *voorlopige* vanwege beperkingen in de voor deze stoffen beschikbare datasets.

1. INTRODUCTION

In the framework of the periodical revision of the Soil Protection Guidelines in the Netherlands, and the incorporation of the Interim Soil Clean-Up Act in the Soil Protection Act of the Netherlands, toxicologically based intervention values (formerly called C-values) have been derived. This involves the use of ecotoxicological criteria and of human-toxicological criteria. The application of these criteria yields two seperate soil concentrations from which the final soil intervention value is selected or derived. This approach has been developed in the past few years and is described in a number of RIVM-reports. These reports are listed in section 5. The present report deals with the human-toxicological criteria for compounds reviewed in the years 1993 and 1994. Within the scope of the project these compounds are referred to as the second and third series of compounds. The evaluation procedure used for deriving the human-toxicological criteria has been described in the RIVM-report dealing with the first series of compounds, Vermeire et al. (1991). Apart from minor deviations (explained in section 2 hereafter) the same procedure was used for the present batches of compounds.

As explained in the Vermeire et al.-report, in the toxicological evaluation it is determined whether for a given compound a threshold approach or a non-threshold approach should be used. For genotoxic carcinogens a non-threshold approach is warranted. For other compounds (non-genotoxic carcinogens, non-carcinogens) a threshold approach can be used. Via a threshold approach a TDI or ADI can be derived, representing for the compound in question, the estimated daily intake level that can be ingested by humans during their entire lifetime without resultant adverse health effects[1]. For compounds evaluated with a non-threshold approach, the genotoxic carcinogens, such a level cannot be derived (since no threshold for the adverse action is assumed to exist). For these compounds a cancer risk estimate is made based on known tumour incidences for the compound in question; this procedure yields an *excess lifetime cancer risk*. In the present scope (derivation of intervention values for soil clean-up within the Soil Protection Act), the human-toxicological criterium to be used is the *Maximum Permissible Risk*[2] (MPR) level. This approach was introduced in the brochure *Premises for Risk Management*[3] of the Ministry of Housing, Spatial Planning & Environment of the Netherlands (VROM, 1988). In the latter document the MPR has been defined as the TDI or ADI for compounds evaluated using the threshold approach and, for genotoxic carcinogens (non-threshold evaluation), as the exposure level with an excess lifetime cancer risk of 10^{-4}. Thus, in point of terminology the MTR is equivalent with either TDI/ADI or the 1 in 10^4 cancer risk level.

The present report is part of the work done in the scope of the RIVM-project on soil intervention values (project no. 715810; formerly under project no. 950011). A companion report giving the *eco*toxicological criteria for the second and third series of compounds is the RIVM-report by Crommentuyn et al. (1995). The derivation of the final intervention values for clean-up of soil and

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[1]The difference between TDI and ADI is that the Tolerable Daily Intake is allocated for comtaminants whereas the term Acceptable Daily Intake is reserved for compounds that are deliberately added to foods or during the production process of foods.

[2]In Dutch: Maximum Toelaatbaar Risico, abbreviated as MTR.

[3]Title in Dutch: "Omgaan met Risico's".

groundwater (integration values) from the ecotoxicological criteria and the human-toxicological criteria is reported in the RIVM-reports by van de Berg et al. (1994)[4] and Kreule et al. (1995) for the second and third series, respectively. For an overview of the RIVM-reports published on the subject of soil intervention values see section 5.

The procedure followed for the derivation of the proposed intervention values for soil and groundwater is depicted in the following diagram. As already stated, the different items in the diagram have been reported as separate documents. The shaded box in the diagram is the part covered in the present report.

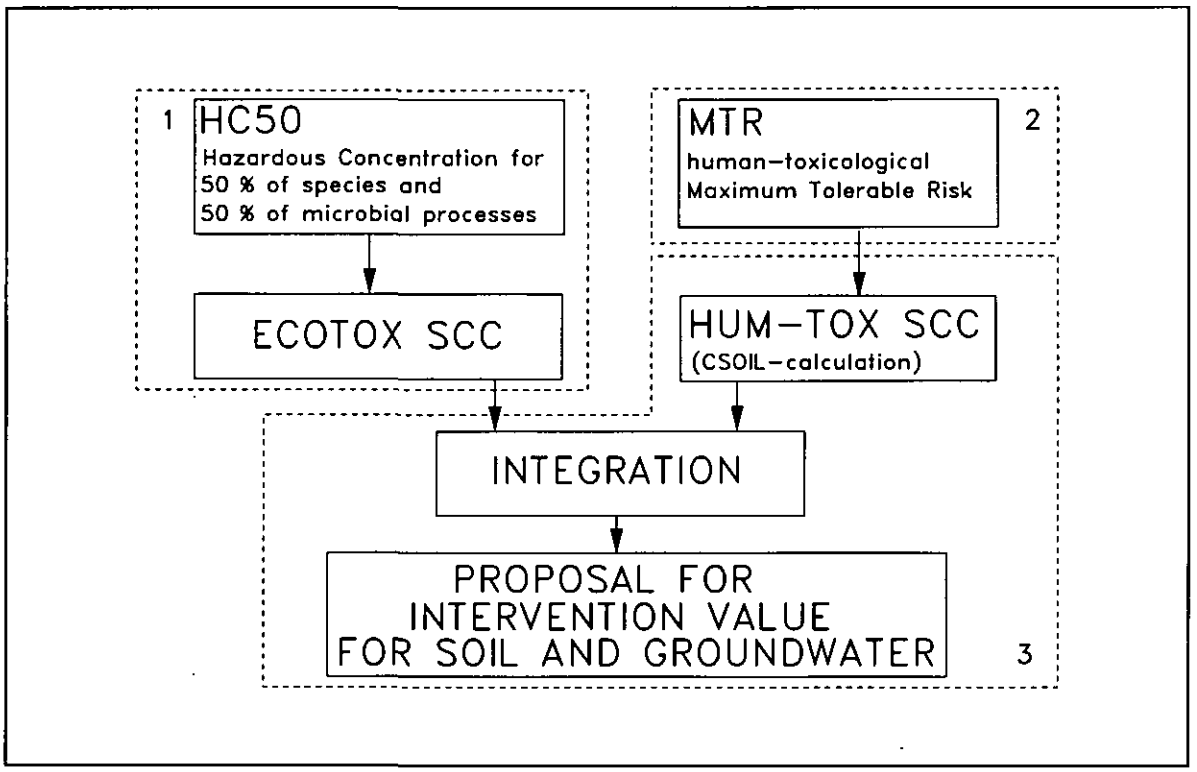

Figure 1. Diagram of pathways leading to the derivation of proposals for intervention values for soil and groundwater

1. the report of Crommentuyn et al. (1995): RIVM report no. 715810008;
2. the present report;
3. - the report of Kreule et al. (1995): RIVM report no. 715810010 (third series of compounds);
   - the report of van den Berg et al. (1994): RIVM report no. 715810004 (second series of compounds).

[4]This report in part overlaps the present report: the human-toxicological criteria for the 2nd series of compounds, as reported in the present report, have also been reported as part of the report by van den Berg et al. (1994). For ease of reference and in order to maintain the human-toxicological work as a recognizable, and in itself complete, unit within the soil intervention project, this duplication has been decided upon.

2. METHOD

For each of the compounds dealt with in the present report a *toxicity profile* for human health evaluation, was prepared. The profiles give a concise summary of the available toxicity data; the presented data are limited to those directly relevant for derivation of the TDI/ADI or cancer risks. In addition some information on background exposure is given in the profiles. The method used to prepare the toxicity profiles concurs with the approach described in the earlier RIVM-report of Vermeire et al. (1991). For a detailed discussion of concepts and procedures the reader is referred to that document. The concepts and procedures used will be restated and updated in a separate guidance document, to be prepared in the near future.

In the present profiles the information under *Miscellaneous data* has been added (such data were not included in the previous profiles as given in the Vermeire et al.-report). The miscellaneous data comprise absorption factors (dermal, inhalational and, where relevant, oral) and existing guideline values in The Netherlands.

In the Vermeire et al.-report the use of a parameter N (a multiplication factor to be applied to the TDI or maximum tolerated cancer risks as derived in the profiles) was proposed. In accordance with the comments given in TCB (1992) this parameter is no longer used in the present report. A further, minor deviation from the method as described in the report by Vermeire et al., is the oral/inhalational biovailability (≈absorption) ratio of 100/75 that is used for route-to-route calculation of tolerable intakes. Use of this ratio instead of 100/100 as formerly used, conforms to the evaluation system USES recently developed in the Netherlands (RIVM, VROM, WVC, 1994). The use of the 100/75 ratio instead of a 100/100 ratio, results in a higher TCA value (higher by factor 100/75) where extrapolation is from TDI (oral) to TCA (inhalational) and a lower TDI (by factor 75/100) where extrapolation is from TCA to TDI. Note that all TDI or TCA values derived using route-to-route extrapolation should be regarded as provisional values (abbreviated as PTDI and PTCA) since this kind of extrapolation involves considerable uncertainty.

Like the Vermeire et al.-report the present report relies, wherever possible, on work done in the past. Full literature searches for original publications were performed for 1-butylacetate, methyl tert-butyl ether, dodecylbenzene and the *aromatic solvents* only, no adequate review documents being available for these compounds. The results of these searches were used selectively: no comprehensive evaluation of *all* available original publications was carried out but only the key publications were selected for inclusion in the profile. For 1,1-dichloroethane, 1,2-dichloroethene and 1,1,1-trichloroethane a limited search was done for original publications supplementary to the data in the review documents available for these 3 compounds. For the remaining 19 compounds adequate review documents (RIVM-Basisdocumenten, evaluations by IPCS, WHO or US-EPA) were available to serve as the basis for the profile. In all cases where review documents were used, wherever necessary, the orginal publications of studies given in these reviews were consulted and evaluated anew. The tolerable intake levels as derived in the review are accepted here (including the safety factors used[5]) unless deviations were warranted because of different evaluation of crucial experimental data. Where *additional* new tolerable intakes or concentrations were derived

[5]Note that these factors may differ from the standard factors to be used according to the method described in the report of Vermeire *et al* (1991).

from studies included the review used (so the study results are given but no tolerable intake or concentration was derived in the review), the orginal publication was used as a check.

The available data bases for the compounds frequently were incomplete, there being a lack of information on one or more toxicological endpoints in such cases. For compounds with a very limited data base the TDIs and/or TCAs derived, are *provisional* (PTDI, PTCA).

3. RESULTS

The human-toxicological criteria (Maximum Permissible Risk levels) derived for the present group of compounds are listed in Table 1 below (see page 6). For brevity and ease of survey, remarks on the citeria of individual compounds have been added as notes to the table. On the individual compounds the following additional remarks of a more general nature can be made (for further details see the appendices).

Antimony is a non-essential element that resembles arsenic both chemically and biologically. The experimental evidence on carcinogenicity and genotoxicity indicates effects comparable to those observed for arsenic. Based on an indirect mechanism of genotoxic action (for which a threshold is assumed to exist), a TDI was derived. For **beryllium** oral toxicity is lower than toxicity for other routes (this is probably due to lower absorption after oral intake). For evaluation of the oral toxicity a threshold approach was considered appropriate. For the inhalational route the evaluation is based on the carcinogenic effect using the quantitative risk estimation from the US-EPA. For **boron** there are no data indicating that it is carcinogenic or genotoxic. In the derivation of a TDI the approach as chosen by the WHO in 1992 (revision of Drinking-Water Guidelines) was adopted.

The TDI for **nitrate**, based on a study in rats, is derived for infants/children as a sensitive group in the population. Currently, additional experiments on nitrite and nitrate are being conducted in the Netherlands (CIVO/TNO and the RIVM) in experimental animals and humans. The results of these studies may necessitate adjustment of the TDI.
For **dioxins**, in accordance with the RIVM Criteria Document by Liem et al. (1993), the TDI as allocated on the 1992 WHO/EURO Consultation is adopted.

For the pesticides in the 2nd series of compounds, evaluations by the Joint Meeting on Pesticide Residues (JMPR) of the WHO/FAO are available. For **azinphos-methyl**, **chlordane** and **heptachlor & -epoxide** the JMPR ADI's are used for the oral route. Actuated by qualitative indications for each of these pesicides that, when present as soil contaminant, humans may be exposed inhalationally, provisional TCA-values (PTCA's) have also been derived for these compounds. For **endosulfan** and **triphenyltin-compounds** also, the JMPR ADI's have been adopted. For **tributyltinoxide** (TBTO) for the oral route the exsisting TDI of the WHO (Drinking-Water Guidelines) was selected; for the inhalational route a new provisional TCA was derived from a short-term study in rats.

The TDI for **silver** is based on the cosmetic effect of silver on the skin called *argyria*, as observed in a group of syphilis patients. Since argyria is not an *adverse* health effect and data for a sensitive subpopulation were used, a low safety factor factor of 3 is sufficient.
On **dodecylbenzene** only few data are available but a TDI was calculated nevertheless. Given the

relatively large data set on the ***high boiling aromatic solvents*** as the mixture, the limited data available for the individual compounds therein, have not been included in the profile.

For **1,1-dichloroethane** the available data base is very limited, allowing derivation of provisional values only. For **1,2-dichloroethene** separate tolerable intakes were derived for the cis and the trans isomers, the cis-isomer showing no-threshold genoxicity *in vivo* where the trans-isomer did not. For each of these three volatile compounds, 1,1-dichloroethane, 1,2-dichloroethene and **1,1,1-trichloroethane**, the data for either the oral route or the inhalational route were too limited to allow derivation of a TDI or TCA and route-to-route extrapolation had to be used. As already stated above (section 2) this procedure yields provisional values only.

For **formaldehyde** a new TCA (for long-term exposure) was derived (to be distinguished from the acute health-based recommendations as derived by the Dutch Health Council (Gezondheidsraad) in 1984). The few data available on background exposure to **methanol** indicate that for the general population the TDI may be reached or even exceeded as a result of normal dietary intake. Drawing firm conclusions on this point, however, requires additional data on prevalent concentrations in the Netherlands and on the chemical form in which the methanol moiety is present in foods (since this may influence biovailability), and in the body. In the absence of such data a possible approach in the calculation of a soil intervention value is allocating a limited part of the TDI (for instance 10%) to uptake resulting from soil pollution.
The available information on **1-butanol** and **1-butylacetate** is limited but TDI's and (where relevant) TCA's could nevertheless be established. Background exposure to **methyl t-butyl-ether** is unknown; if in the Netherlands the compound is used as petrol octane improver (as it is done in the USA), this would lead to substantial background exposure via air. If such use is indeed practiced in the Netherlands, concentration measurements are required to determine exposure.

For **acrylonitrile** a non-threshold approach is warranted based on genotoxicity/carcinogenicity data. A parallel threshold evaluation based on other toxicity endpoints (than carcinogenicity) was carried out to check if such an evaluation did not yield lower safe levels than $1:10^4$ excess lifetime carcinogenicity risk level. This proved not to be the case.
For **ethylene glycol** the TDI was derived with presence of oxalate crystals in urine as the most sensitive effect (present at 200 mg/kg bw/day). Contrary to the conclusion in the review of the US-EPA, where 200 mg/kg bw/day is taken to be the NOAEL, the presence of oxalate crystals is considered a relevant effect when jugded in the light of the pronounced oxalate nephrosis noted at 1000 mg/kg bw/day. For ethylene glycol and **diethylene glycol** a combined TDI was derived because of their close structural relation and the fact that increased excretion of oxalate in urine is the most sensitive effect for both compounds.

Table 1 on the following page lists the human-toxicological criteria (MPR-values) as given in the toxicological profiles in appendix 1 through 26. Points to be noted on the MPR-values for individual compounds are given as notes to the table.

Table 1. Human-toxicological criteria (MPR[a]) for 26 compounds for derivation of soil intervention values

compound[b]	TDI/ADI[c] (µg/kg bw)	safety factor	TCA[d] (µg/m³)	safety factor	background exposure[e] (µg/kg bw/day)
2nd series of compounds (1993)					
I. Metals					
antimony (1)[b]	0.86	1000	f	-	0.3
beryllium (2)	0.5	1000	0.04[g]	-	0.3
boron (3)	90	100	f	-	60
II. Inorganic compounds					
nitrate (4)	3400[h]	100	f	-	i
V. Chlorinated hydrocarbons					
dioxins (5)	1×10^{-5}	100	f	-	0.6×10^{-5}
VI. Pesticides					
azinphos-methyl (6)	5	100	0.2(PTCA)	1000	unknown
endosulfan (7)	6	100	f	-	unknown
chlordane (8)	0.5	100	0.02(PTCA)	1000	unknown
heptachlor & -epoxide (9)	0.1	200	0.5(PTCA)[j]	200	0.001
tributyltinoxide[k] (10)	0.3	100	0.02(PTCA)	1000	0.2
triphenyltin-compounds (11)	0.5	500	f	-	unknown
VII. Miscellaneous compounds					
methylethylketone (12)	190(PTDI)[j]	1000	875	1000	unknown
3rd series of compounds (1994)					
I. Metals					
silver (13)	5	3	f	-	0.06-1.3
III. Aromatic compounds					
dodecylbenzene (14)	5	1000	f	-	0
aromatic solvents[m] (15)	170(PTDI)[j]	-	800	100	0
V. Chlorinated hydrocarbons					
1,1-dichloroethane (16)	80(PTDI)[j]	-	370(PTCA)	1000	0.05
cis-1,2-dichloroethene (17)	6	5000	30(PTCA)[j]	-	0.15
trans-1,2-dichloroethene (17)	17	1000	80(PTCA)[j]	-	0.15
1,1,1-trichloroethane (18)	80(PTDI)[j]	-	380	1000	0.7
VII. Miscellaneous compounds					
formaldehyde (19)	150	100	1.2	100	unknown
methanol (20)	500	1000	1100	100	500
1-butanol (21)	125	1000	550(PTCA)[j]	-	unknown
1-butylacetate (22)	200(PTDI)[j]	-	1000	100	1
methyl t-butyl ether (23)	900	1000	500	1000	unknown
acrylonitrile (24)	0.1[g]	-	10[g]	-	0.028
mono-ethylene glycol (25)	400[n]	100	f	-	0
di-ethylene glycol (26)	400[n]	100	f	-	0

[a] MPR means Maximum Permissible Concentration (in Dutch: Maximum Toelaatbaar Risico). See the remarks in the text of section 1 on how the MPR has been defined by the Dutch Ministry of Housing, Spatial Planning & Environment (VROM).

[b] The number placed in brackets behind the compound name refers to the appendix number (the profile for antimony is appendix 1, the profile for beryllium is appendix 2, etc.).

[c] Tolerable Daily Intake or Acceptable Daily Intake; where only provisional values are available this is explicitly stated in the table (abbreviation PTDI added).

[d] Tolerable Concentration in Air (guideline value for long-term exposure); where only provisional values are available this is explicitly stated in the table (abbreviation PTCA added).

[e] Values given should be considered as rough estimates of prevalent exposures (mostly of the upper range of prevalent exposures; for derivation see the appendices).

[f] Route not considered relevant in present context.

[g] Based on carcinogenicity as endpoint; excess lifetime risk 1 in 10^4 (Maximum Permissible Risk).

[b] Value derived for infants/children as sensitive group.

[i] No generally applicable estimate possible.

[j] Derived via route-to-route calculation.

[k] Dermal route: lowest reported concentration producing contact-dermatitis in humans is 10 mg/litre; the concentration-without-effect is unknown. These data may be used for evaluating dermal contact with TBTO-solutions: in the µg/litre-range no problem may be expected but in the mg/litre-range occurrence of an adverse reaction cannot be ruled out.

[m] short for: high-boiling aromatic solvents; these mixtures are also often referred to as: aromatic nafta.

[n] Combined value for mono- and di-ethylene glycol (applies to sum of concentrations when both compounds are present).

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Vermeire, T.G., Apeldoorn, M.E. van, Fouw, J.C. de & Janssen, P.J.C.M. (1991) Voorstel voor de humaantoxicologische onderbouwing van C-(toetsings)waarden. RIVM-report no. 725201005, dated February 1991. [In Dutch]

VROM (1988) Premises for Risk Management - Annex to the Dutch Environmental Policy Plan. Lower House Session 1988-1989, 21 137, no. 5 (title in Dutch: Omgaan met Risico's - Annex bij het Nationaal Milieubeleidsplan. Leidschendam, Ministerie van Volkshuisvesting, Ruimtelijke Ordening & Milieubeheer.) [In Dutch].

WHO-WQG (1992) WHO Guidelines for Drinking-Water Quality - Volume 2: Health Criteria and Other Supporting Information, Chapter 2: Chemical Aspects. IPCS/EHC/92.60b Unedited Draft.

5. RIVM REPORTS PUBLISHED IN THE SOIL INTERVENTION VALUE PROJECT

Linders, J.B.H.J. (1990) Risicobeoordeling bij de mens bij blootstelling aan stoffen. Uitgangs-punten en veronderstellingen. [In Dutch] RIVM-report no. 725201003, dated August 1990.

Contains: description of calculation formulas to be used for estimation of human exposure via several routes in case of soil contamination; the formulas in this report were used in the compilation of the CSOIL-model as reported in the RIVM-report by van den Berg (1991/1994).

Denneman, C.A.J. & Gestel, C.A.M. van (1990) Bodemverontreiniging en bodemecosystemen: voorstel voor C-(toetsings)waarden op basis van ecotoxicologische risico's. [In Dutch] RIVM-report no. 725201001, dated April 1990.

Contains: ecotoxicolgical criteria for 1st series of chemicals; only data for soil organisms taken into consideration; the separate data for the individual compounds are presented in the appendix to this report.

Denneman, C.A.J. & Gestel, C.A.M. van (1991) Afleiding van C-waarden voor bodemecosystemen op basis van aquatisch ecotoxicologische gegevens. [In Dutch] RIVM-report no. 725201008, dated September 1991.

Contains: for the 1st series of chemicals aquatic ecotoxicological data and QSARs were now also taken into consideration for derivation of C-values for water; from the latter values soil C-values were calculated and compared to the soil C-values previously derived leading to changes for several chemicals.

Vermeire, T.G., Apeldoorn, M.E. van, Fouw, J.C. de & Janssen, P.J.C.M. (1991) Voorstel voor de humaantoxicologische onderbouwing van C-(toetsings)waarden. [In Dutch] RIVM-report no. 725201005, dated February 1991.

Contains: human-toxicological criteria (MPR-values) for 1st series of chemicals, this 1st series consists of 55 compounds or groups of compounds; includes description of the method used to derive the MPR-values.

Berg, R. van den (1995) Blootstelling van de mens aan bodemverontreiniging. Een kwalitatieve en kwantitatieve analyse leidend tot voorstellen voor humaantoxicologische C-toetsingswaarden (beperkt herziene versie). [In Dutch] RIVM-report no. 725201006, March I 1995. **Modified version of the original report from 1991.**

Contains: description of the formulas that form the CSOIL model, the model used to estimate human exposure in case of soil pollution; based on the human-toxicological criteria (MPR-values) for the 1st series of chemicals, CSOIL is used to derive human-toxicological intervention values; appendix 1.11 to this report gives "new" modified human-toxicological intervention values.

Berg, R. van den & Roels, J.M. (1991) Beoordeling van risico's voor mens en milieu bij blootstelling aan bodemverontreiniging. Integratie van deelaspecten. [In Dutch] RIVM-report no. 725201007, dated February 1991.

Contains: for the 1st series of chemicals: integration of ecotoxicological criteria with the results of CSOIL calculations based on the human-toxicological criteria, yielding proposal for soil intervention values; note that several of the then proposed values have been modified at a later stage.

Vermeire, T.G. (1993) Voorstel voor de humaantoxicologische onderbouwing van C-(toetsings)-waarden. Betreft addendum op rapport 725201005. [In Dutch] RIVM-report no. 715801001, dated May 1993.

Contains: re-evaluation of The Maximum Permissible Intake values for 9 (groups of) compounds from the set dealt with in the Vermeire et al.-report from 1991.

Bockting, G.J.M., Swartjes, F.A., Koolenbrander, L.G.M. & Berg, R. van den (1994) Beoordelingssystematiek bodemkwaliteit ten behoeve van bouwvergunningsaanvragen. Deel I. Bodemgebruiksspecifieke beoordelingsmethodiek voor de humane blootstelling. [In Dutch] RIVM-report no. 715810001, dated June 1994.

Contains: methodology for estimating human exposure using calculation formulas from the CSOIL model and measurements in contact media; several standard soil use categories are defined using standard assumptions as to human exposure; this method is part of a system for the evaluation of soil quality in dealing with requests for official building permits to be granted by local authorities.

Swartjes, F.A., Koolenbrander, L.G.M. & Bockting, G.J.M. (1994) Beoordelingssystematiek bodemkwaliteit ten behoeve van bouwvergunningsaanvragen. Deel II. Methodiek ter bepaling van het verspreidingsrisico. [In Dutch] RIVM-report no. 715810002, dated June 1994.

Contains: method for classification of calculated fluxes into 3 classes of increasing risk of contaminant dispersal; this classification provides a pragmatic assessment of the risk of dispersal; this method is part of a system for the evaluation of soil quality in dealing with requests for official building permits to be granted by local authorities.

Crommentuyn, G.H., Plassche, E.J. van de & Canton, J.H. (1994) Guidance document on the derivation of ecotoxicological criteria for serious soil contamination in view of the intervention value for soil clean-up. RIVM-report no. 950011003, dated November 1994.

Contains: description of the methodology used to derive ecotoxicological criteria in a stepwise protocol: data needs, formulas for normalisation & standardisation, data selection & method for calculation of the several HC50-values.

Berg, R. van den, Bockting, G.J.M., Crommentuyn, G.H. & Janssen, P.J.C.M. (1994) Proposals for intervention values for soil clean-up: Second series of chemicals. RIVM-report no. 715810004, dated December 1994.

Contains: physicochemical properties, results of CSOIL calculations, derivation of the serious-soil-contamination-concentrations (scc) using the ecotoxicological and human-toxicological criteria; integration of values yielding proposal for intervention values; this 2nd series consists of 12 chemicals.

Notenboom, J. Eijsackers, H.J.P. & Swartjes, F.A. (1995) Beoordelingssystematiek ten behoeve van bouwvergunningsaanvragen. Deel III. Methodiek ter bepaling van het actuele risico voor het ecosysteem [In Dutch]. RIVM-report no. 715810003, dated January 1995

Contains: method for determination of risks for ecosystems used during the evaluation of soil quality in dealing with requests for official building permits to be granted by local authorities.

Kreule, P., Berg, R. van den, Waitz, M.F.W. & Swartjes, F.A. (1995) Calculation of human-toxicological serious soil contamination concentrations and proposals for intervention values for clean-up of soil and groundwater: Third series of compounds. RIVM-report no. 715810010, dated August 1995.

Contains: physicochemical properties, results of CSOIL calculations, derivation of the serious-soil-contamination-concentrations (scc) using the ecotoxicological and human-toxicological criteria; integration of values yielding proposal for intervention values; this 3rd series consists of 15 compounds.

Appendix 1: ANTIMONY

RELEVANT ROUTE

Exposure route considered to be relevant in present context: oral

TOXICITY

Antimony is a non-essential element and resembles arsenic both chemically and biologically. Trivalent compounds are generally more toxic than pentavalent ones. Females seem to be more susceptible than males (Slooff et al., 1992).

Limited oral studies did not reveal a carcinogenic activity for antimony compounds in laboratory animals. There is *sufficient evidence* (IARC) for carcinogenicity of antimony trioxide after inhalation in experimental animals. The development of lung tumours was clearly accompanied by toxicity in the target organ (lungs). There is only *limited evidence* for carcinogenicity of antimony trisulphide in experimental animals after inhalation. There is *inadequate evidence* for carcinogenicity of antimony trioxide and antimony trisulphide in humans (IARC, 1989; Slooff et al., 1992). IARC (1989) classified antimony trioxide in *Group 2B (possibly carcinogenic to humans)* and antimony trisulfide in *Group 3 (not classifiable as to its carcinogencity to humans).*

The data on genotoxicity reveal that the genotoxic profile of antimony compounds resembles that of arsenic compounds, for which there are indications that the mechanism of genotoxic action is an indirect one. Therefore and because of the correlation between carcinogenicity and toxicity a threshold extrapolation method for risk evaluation is used (Slooff et al., 1992).

With respect to (sub)chronic oral toxicity in animals only a few studies are available. Long-term exposure results primarily in effects on the heart, gastrointestinal disturbances and blood changes. The most appropriate study for risk evaluation is a drinking water study in rats receiving 0 or 5 mg antimony (as potassium antimony tartrate)/litre of drinking water (equivalent to 0.43 mg Sb/kg bw/day) during lifetime. In this study growth rates were not affected but lifespan was shortened 15% and some changes in blood chemistry and a decrease in mean heart weight in males were seen (EPA, 1993; Slooff et al., 1992; WHO-WQG, 1992).
In a similar study mice received 0 or 5 mg antimony (as potassium antimony tartrate)/litre of drinking water for 540 days. Lifespans were significantly reduced in both males and females but the degree of antimony toxicity was less severe in mice than in rats (EPA, 1993; Slooff et al., 1992; WHO-WQG, 1992).

Based on the LOAEL of 0.43 mg/kg bw in the lifetime drinking water study in rats and making use of a safety factor 500 (the standard factor 100 and an extra factor 5 for the use of a LOAEL instead of a NOAEL) a TDI of 0.86 µg/kg bw has been established (Slooff et al., 1992; WHO-WQG, 1992).

Data concerning occupational exposure of humans are of very limited value in the present context because the exposure was via inhalation (a route less relevant in the present context, as stated above) and simultaneous exposure to other compounds occurred in all studies. It is not possible to derive a NOAEL from the occupational data.

Skin lesions are considered of minor importance in case of soil pollution with antimony because immunotoxicity is not involved. It can safely be assumed that the intervention value for antimony in soil, calculated from the TDI, will be below the concentration range within which skin effects have been observed.

BACKGROUND EXPOSURE

Daily dietary intakes of Sb are estimated to be 10 - 20 µg/day (Slooff et al., 1992), corresponding to 0.14 to 0.28 µg/kg bw for a 70 kg adult person (rounded value ≤0.3 µg/kg bw).

MISCELLANEOUS DATA

- Absorption factors: only oral data available
- Guideline values:
· WHO-drinking-water guideline value: 5 µg/litre (WHO, 1992)
· MAC-value (limit for occupational exposure): 0.5 mg Sb/m^3; this value applies for antimony-compounds (SZW, 1992)

CONCLUSION

TDI:	0.86 µg/kg b.w.
Background exposure (maximum of given range):	0.3 µg/kg b.w.

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RIVM-Toxicology Advisory Centre.

Profile compilation by: M.E. van Apeldoorn.
Profile review by: P.J.C.M. Janssen, J.E.M. van Koten-Vermeulen, F.X.R. van Leeuwen & T.G. Vermeire.

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Material Name: Antimony. Update Date: 01-01-92 Effective Date: 01-01-93
Printed February 1993.

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Slooff, W. et al. (1992) Exploratory Report Antimony and Antimony Compounds.
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SZW (1992) Nationale MAC-lijst 1992, Arbeidsinspectie, publikatienummer P 145. Ministerie van Sociale Zaken en Werkgelegenheid)

WHO (1992) WHO Revision of the WHO Guidelines for Drinking-Water Quality - Report of the Final Task Group Meeting, Geneva, Switzerland, 21-25 September 1992; WHO document no. PEP/IPCS/EURO/92.1.

WHO-WQG (1992) WHO Guidelines for Drinking-Water Quality - Volume 2: Health Criteria and Other Supporting Information, Chapter 2: Chemical Aspects - Antimony, IPCS/EHC/92.60b Unedited Draft.

Appendix 2: BERYLLIUM

RELEVANT ROUTE

Exposure route considered to be relevant in this context: oral & dermal contact. Beryllium compounds have low volatility. Because of the low TCA and the severity of the endpoint on which it is based (see below), however, the inhalational route may yet be of relevance due to exposure via inhalation of soil particles containing beryllium compounds.

TOXICITY

In general beryllium compounds administered orally are less toxic in animals than those administered by other routes, probably because beryllium salts are poorly absorbed from the gastrointestinal tract (IPCS, 1990).

Limited long-term oral studies in rats and mice with beryllium salts did not reveal significantly increased tumour incidences (Morgareidge et al., 1977; Schroeder and Mitchener, 1975a; 1975b).

According to IARC (1980) there is *sufficient evidence* for carcinogenicity of beryllium metal and several beryllium compounds in laboratory animals after exposure by inhalation or intratracheal instillation (lung tumours in rats and perhaps monkeys but not in hamsters, guinea-pigs and rabbits) and by intravenous and/or intramedullary injection (osteosarcoma in rabbits but not in rats or guinea-pigs). There is only *limited evidence* for carcinogenicity of beryllium (compounds) in humans (occupational exposure by inhalation). IARC (1987) classified beryllium and beryllium compounds in *Group 2B (probably carcinogenic to humans).* However uncertainty exists on the adequacy of the epidemiological studies that also led to this conclusion (US-EPA, 1993; IARC, 1980).

The results of genotoxicity tests with beryllium compounds are disparate. No gene-mutations were induced in bacteria and yeast cells. In a gene-mutation assay *in vitro*, beryllium chloride induced only a slight effect, which became saturated at high exposure levels (Miyaki et al., 1979). In tests for chromosome aberrations in mammalian cells *in vitro*, both positive and negative results were reported. SCE's were induced in mammalian cells *in vitro* (ATSDR, 1991; IARC, 1987; IPCS, 1990).

Beryllium salts were shown to provoke the formation of complexes between DNA and proteins (IPCS, 1990) and beryllium ions were suggested to bind to DNA polymerizing enzymes (IPCS, 1990).

No UDS in rat hepatocytes was induced by beryllium sulphate and also an *in vivo* micronucleus assay in mice (oral exposure) with beryllium sulphate tetrahydrate showed negative results (ATSDR, 1991; IPCS, 1990).

It can be concluded that beryllium compounds do exhibit genotoxic properties *in vitro*. The mechanism(s) involved in genotoxic effects observed *in vitro* are not elucidated, but may be related to a reaction or interference of beryllium with enzymatic, non-DNA targets such as those involved in the metabolism of phosphate and the biological functions of magnesium. In turn, this indicates that the genotoxic effects of beryllium may be indirect in nature and have thresholds of exposure.

Based on the data given above a threshold extrapolation method for evaluation of the risk for man after oral exposure, is used.

The most appropriate study for extrapolation is a lifetime oral drinking water study with rats

receiving 0 or 5 mg Be/litre of drinking water (corresponding to 0 and 0.54 mg Be/kg bw/day and given as beryllium sulphate) (Schroeder and Mitchener, 1975a). Mortality was 22-35% in both control and treated group at 20 months of age due to a pneumonia epidemic. No treatment related adverse effects on lifespan, body weight gain, serum chemistry, urinalysis, macroscopy or microscopy of liver, kidneys, spleen or heart were seen. No significant increased tumour incidences were observed. In a similar study mice received also 0 or 5 mg Be/litre of drinking water for lifetime (corresponding to 0 and 0.95 mg Be/kg bw/day). In this study also no significant treatment related effects were seen (Schroeder and Mitchener, 1975b).
In a two-year study with Wistar rats receiving 0, 0.25, 2.5 or 25 mg Be/kg bw as beryllium sulphate via the diet a slight depression of weight gain was observed at the highest dose-level. No increased tumour incidences were seen. Only an abstract of this study is available (Morgareidge et al., 1977).

Based on the NOAEL of 5 mg/litre of drinking water in the lifetime rat study (corresponding to 0.54 mg Be/kg bw) and applying a safety factor 1000 (the standard factor 100 and an extra factor of 10 for uncertainties with respect to the genotoxic mechanism) a TDI of 0.5 µg/kg bw can be calculated.

At exposure by inhalation several beryllium compounds showed carcinogenic activity. US-EPA (1993) calculated extra tumour risks of $1 : 10^4$, $1 : 10^5$ and $1 : 10^6$ at lifetime exposure to beryllium at concentrations in the air of 0.04, 0.004 and 0.0004 µg/m^3, respectively (extrapolation method: relative risk). The risk estimate was based on the data from an epidemiologic study in occupationally exposed men of Wagoner et al. (1980) in which the smoking-adjusted, expected lung cancer deaths were found to range from 13.91 to 14.67, in comparison to 20 observed. The effective dose was determined by adjusting for duration of daily (8/24) and annual (240/365) exposure, and the fraction of the lifetime at risk (i.e. time from onset of employment to termination of follow-up).
According to US-EPA (1993) this estimate risk for inhalation is based on an epidemiologic study having several confounding variables. The estimates of exposure levels and duration were also somewhat uncertain. While a quantitative assessment based on several animal studies resulted in a similar estimate of risk (which increases the confidence somewhat), the quality of the available studies was poor.

Depending on individual sensitivity, direct contact with soluble beryllium compounds can cause delayed (contact) dermatitis in man, occasionally associated with conjunctivitis. When beryllium compounds are retained in or beneath the skin, chronic granulomatous ulcerations develop. (IPCS, 1990) The available data do not give information on threshold concentrations for these effects. The skin effects reflect immunotoxicity and for this reason, once sensibilisation has taken place, low exposure concentrations may alrady lead to adverse effects.

BACKGROUND EXPOSURE

Primary sources for exposure are food and drinking-water. Total daily intake was reported to range from 10 to 20 µg/day (ATSDR, 1992). For a 70 kg adult this intake level equals ≤ 0.3 µg/kg bw/day. The exposure via air contributes little to total exposure (in the USA, for instance, 0.0006 µg/person/day). For smokers only minor amounts are inhaled via cigarette smoke (smoking of 20 cigarettes/day gives an exposre of only 1.5 µg/day).

MISCELLANEOUS DATA

- Absorption factors: only oral data available
- Guideline values:
  WHO-drinking-water guideline value: no limit was set due to the lack of suitable oral data (WHO, 1992)
  MAC-value (limit for occupational exposure): 0.002 mg Be/m^3 (SZW, 1992)

CONCLUSION

TDI:	0.5 µg/kg bw/day
Background exposure (maximum of given range):	0.3 µg/kg bw/day
Inhalational excess lifetime tumour risk 1:10^4:	0.04 µg/m^3

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RIVM-Toxicology Advisory Centre.

Profile compilation by: M.E. van Apeldoorn.
Profile review by: P.J.C.M. Janssen, J.E.M. van Koten-Vermeulen, F.X.R. van Leeuwen & T.G. Vermeire.

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Appendix 3: BORON

RELEVANT ROUTE

Most boron compounds are transformed to borates in soil due to the presence of moisture. Borates themselves are not further degraded in soil. Boron alone does not evaporate easily, but it does adsorb to soil particles. No information was found on whether borates evaporate easily or adsorb to soil particles (ATSDR, 1992).
Exposure route considered relevant in present context: oral.

TOXICITY

Elemental boron and other boron compounds are widely used for different purposes, e.g. boron and its carbides are used in composite structural material and borates are used mostly in the production of glass.
The available toxicity data apply to boron and borates only. No mutagenic effects were observed in *in vitro* studies with boric acid, sodium borate and borax [sodium tetraborate(as the decahydrate)]. In long term/carcinogenicity studies no evidence of carcinogenicity was found after the administration of borax and/or boric acid to mice and rats (ATSDR, 1992; NTP, 1987; USEPA, 1992; WHO-WQG, 1992). No IARC-classifiation is available for boron and/or boron compounds. After repeated oral administration to rats and dogs growth inhibition, organ weight changes and testicular athrophy were the most striking effects. In long term studies with mice, rats and dogs testicular athrophy was the most sensitive effect with the dog being the most sensitive species. In a 2-year diet study with dogs (doses 0, 58, 117 or 350 mg B (as borax or boric acid/kg diet) no effects were observed on body weight, food consumption, organ weights, clinical parameters, macroscopy and histopathology. An additional group of dogs was fed a diet containing 1170 mg B (as borax)/kg food for 38 weeks. Severe testicular athrophy and spermatogenic arrest were evident by week 26. The NOAEL in this study was 350 mg B/kg food (equivalent to 8.8 mg B/kg bw/day) (Weir & Fischer, 1972). In a multigeneration study with rats, at 1170 mg B (as borax or boric acid)/kg food males showed lack of spermatozoa in atrophied testes and females showed decreased ovulation ; no effects were observed at 350 mg B/kg food, equivalent to 17.5 mg B/kg bw/day (Weir & Fischer, 1972). A TDI of 0.09 mg/kg bw/day can be calculated by applying an uncertainty factor of 100 to these NOAELs (WHO-WQG, 1992).

BACKGROUND EXPOSURE

The total daily intake in normal human diets has been reported to range from 2.1-4.3 mg B/day in 1965 and in 1972 1.3-4.4 mg B/day; these intakes are equivalent to $\leq$ 0.06 mg/kg bw/day (EPA, 1992; WHO-WQG, 1992).

MISCELLANEOUS DATA

- Absorption factors:
  dermal: humans, intact skin: "poor" (no percentage given)(WHO-WQG, 1992)
  inhalation: no data (WHO-WQG (1992)
- Guideline values: WHO-drinking-water-guideline: 0.3 mg B/litre (WHO, 1992)

CONCLUSION

TDI:	90 µg B/kg bw/day
Background exposure (maximum):	60 µg B/kg bw/day

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Profile compilation by: J.E.M. van Koten-Vermeulen.
Profile review by: M.E. van Apeldoorn, P.J.C.M. Janssen, F.X.R. van Leeuwen & T.G. Vermeire.

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WHO-WQG (1992) WHO Guidelines for Drinking-Water Quality - Volume 2: Health Criteria and Other Supporting Information Chapter 2: Chemical Aspects. Unedited Draft.

Appendix 4: NITRATE

RELEVANT ROUTE

Exposure route considered relevant in present context: oral.

TOXICITY

The principal adverse health effects caused by nitrate arise as a result of bacterial conversion to nitrite, a process that takes place in the oral cavity and/or stomach. Nitrite oxidises blood hemoglobin to methemoglobin, the latter being unable to discharge oxygen and thus interfering with oxygen transport via the blood. In humans clinical methemoglobinemia (with cyanosis as an important symptom) is present at methemoglobin levels in the blood of ≥ 10%.
Human newborns (age ≤ 3 months) are more susceptible to nitrate methemoglobinemia due to the following differences with older persons: increased formation of nitrite in the stomach (due to lower stomach acidity), higher oxidisability of hemoglobin to methemoglobin, absence of the enzyme that catalyses reduction of methemoglobin to hemoglobin.
Apart from methemoglobinemia, nitrite in humans is linked with the possible formation of carcinogenic N-nitroso-compounds (e.g. nitrosamines) in the stomach lumen through reaction with nitrosatable compounds from food. The body of available data on this issue does not allow a meaningful quantitative estimate of the carcinogenic risk to be made. Nevertheless, the data warrant the conclusion that the real effect probably is only small. (Duijvenbooden & Matthijsen, 1989; Gezondheidsraad, 1990)

The derivation of a TDI for nitrate is based on the methemoglobin formation by nitrite. For this effect the long-term NOAEL in the rat is 1000 mg $NaNO_2$/litre drinking-water (equivalent to 100 mg $NaNO_2$/kg bw/day or 67 mg NO_2^-/kg bw/day). Assuming that in human sucklings 20% of the ingested nitrate is converted to nitrite, the latter dose level is equivalent to about 340 mg NO_3^-/kg bw. Using a safety factor of 100 the calculated TDI is 3.4 mg NO_3^-/kg bw. (RIVM, 1992) Other approaches (also based on methemoglobin formation) have yielded similar tolerable intakes. The US-EPA (1991) has established an Oral Reference Dose (RfD) of 1.6 nitrate-N/kg bw/day (7 mg NO_3^-/kg) from epidemiological surveys in humans concerning the occurrence of early clinical signs of methemoglobinemia in infants. For use of nitrate as a food additive, the Scientific Committee Food of the EC derived an ADI for nitrate of 5 mg $NaNO_3$/kg bw (3.6 mg NO_3^-/kg) from a NOAEL of 2500 mg $NaNO_3$/kg bw/day in a chronic study in rats
(SCF, 1992).
Currently, additional experiments on nitrite and nitrate are being conducted in the Netherlands (CIVO/TNO and the RIVM) in experimental animals and humans. The results of these studies may necessitate adjustment of the TDI.

BACKGROUND EXPOSURE

The most recent determination of nitrate intake via the diet in the Netherlands dates back to 1984/85; the results of this 24 h-diet study show a mean intake of 50-54 mg NO_3^-/day (range 2 to 500 mg/day). Primary sources of this dietary exposure (covering about 80% in typical cases) are leafy vegetables high in nitrate concentration (endive, lettuce, spinach, a.o.). (Ellen et al., 1988;

Duijvenbooden & Matthijsen, 1989) Drinking water is an additional source, the contribution of which has increased over the years past; this trend is expected to persist in near-future years. Data from 1984/85 show that for adult persons the estimated nitrate intake via drinking water was ≤ 20 mg/day for 80% of the pumping stations in the Netherlands; for 5% of the pumping stations the estimated daily intake for an adult may be as high as 100 mg NO_3^-. (Duijvenbooden & Matthijsen, 1989)
For infants the following data are relevant. The higher susceptibility of newborns up to age 3 months, already noted above, is important in case of bottle feeding of these babies. Where drinking water contains 50 mg NO_3^-/litre (the EEC drinking water guideline) the estimated exposure is about 25 mg NO_3^-/day (equal to about 8 mg/kg bw /day for a 3 kg baby). There are a few reports, mostly for private wells, of drinking water concentrations equal to or even in excess of the 50 mg/litre limit[6,7]. In ready-to-eat weaning foods, used by infants ≥ 3 months old, an average nitrate concentration of 92 mg/kg has been reported (maximum 570 mg/kg). (Duijvenbooden & Matthijsen, 1989)

Estimating *background* exposure in the current context from the above data is complicated by the fact that nitrate is routed into food and drinking water almost exclusively as a result of soil contamination (use as food additive is only a minor source of exposure). Because soil contamination with nitrate is a widespread phenomenon in the Netherlands it must be assumed that, in addition to the exposure as a result of any possible *local* contamination, there will be an additional exposure, due to soil contamination, but not directly related to that particular site. This entanglement precludes the estimation of background exposure. The above data may nevertheless be of value as providing a general orientation. The data indicate the necessity of a careful analysis of total actual exposure at nitrate contaminated soil sites.

MISCELLANEOUS DATA

- Absorption factors: no quantitative data found in the literature used
- Guideline values (Duijvenbooden & Matthijsen, 1989; WHO, 1992):
  - groundwater (general): see Duijvenbooden & Matthijsen (1989), section 1.2
  - groundwater (intended for use as drinking-water): ≤50 mg NO_3^-/litre
  - surface water (general): see Duijvenbooden & Matthijsen (1989), section 1.2
  - surface water (intended for use as drinking-water): ≤50 mg NO_3^-/litre
  - infant formula's (Dutch Food & Drugs Act[8]): ≤50 mg NO_3^-/kg dry matter
  - meat & meat products (Food & Drugs Act): ≤500 mg KNO_3/kg may be added
  - cheese and cheese spread (Food & Drugs Act): ≤50 mg NO_3^-/kg
  - lettuce (Food & Drugs Act): ≤3000 mg NO_3^-/kg (summer)

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[6] The Gezondheidsraad (Dutch Health Council) has addressed this problem using the available human epidemiological evidence. While concluding that bottle babies are potentially at risk for methemoglobinemia in case of concentrations in drinking water ≥ 50 mg NO_3^-/l, nevertheless it is pointed out that infant methemoglobinemia is likely to occur only when there is, in addition to exogenous nitrate exposure, increased endogenous exposure due to gastrointestinal infection with nitrate-reducing bacteria. Owing to improved hygienic conditions this kind of infections is of rare ocurrence nowadays.

[7] In the cases where the 50 mg/litre limit is found to be exceed at pumping stations for the public drinking-water supply, measures are taken to achieve levels well below 50 mg/litre (J.F.M Versteegh, RIVM-LWD, personal communication).

[8] In Dutch: Warenwet

≤4500 mg NO_3^-/kg (winter)
· spinach (Food & Drugs Act): ≤3500 mg NO_3^-/kg (summer)
≤4500 mg NO_3^-/kg (winter)
· endives (Food & Drugs Act): ≤3000 mgNO_3^-/kg (summer)
≤3500 mg NO_3^-/kg (winter)
· drinking-water for cattle: ≤200 mg NO_3^-/litre (recommended value: ≤100 mg/litre)
· drinking-water for pigs: ≤100 mg NO_3^-/litre (recommended value: ≤25 mg/litre)
· drinking-water for poultry: ≤50 mg NO_3^-/litre (recommended value: ≤25 mg/litre)
· coarse fodder for cattle: for an adult cow NO_3^- intake of ≤50-60 g/day via soilage and ≤25-30 g/day via hay
· drinking-water (Dutch Water Board Decree[9]): ≤50 mg NO_3^-/litre[10]
· drinking-water, WHO drinking-water guideline: 50 mg/litre

CONCLUSION

TDI (derived for infants/children as sensitive group): 3.4 mg NO_3^-/kg bw/day
Background exposure[11]

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Profile compilation by: P.J.C.M. Janssen.
Profile review by: M.E. van Apeldoorn, J.E.M. van Koten-Vermeulen, F.X.R. van Leeuwen & T.G. Vermeire.

[9] In Dutch: Drinkwaterbesluit

[10] Decree according to the EEC Guideline (1980) on the quality of drinking-water intended for human consumption.

[11] No generally applicable estimate possible. For the high risk group of bottle babies of age ≤ 3 months, drinking water may be assumed to be the route determining the extent of exposure; nitrate concentrations in drinking-water depend largely on local soil contamination.

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Appendix 5: DIOXINS (PCDDs & PCDFs)

RELEVANT ROUTE

Exposure route considered relevant in present context: oral, dermal.

TOXICITY

Polychlorinated dibenzo-p-dioxins (PCDDs) and polychlorinated dibenzofurans (PCDFs), have been examined in a large number of toxicological studies. The toxic effects of PCDD/PCDF-mixtures are mainly attributed to the 2,3,7,8-substituted compounds, the most toxic and most studied of which is 2,3,7,8-tetrachlorodibenzo-p-dioxin (2,3,7,8-TCDD). Total toxicity of PCDD/PCDF-mixtures is expressed as equivalents of 2,3,7,8-TCDD. This approach involves multiplication of the concentrations of the individual congeners by a toxic equivalence factor (TEF), expressing the toxicity of the individual congener relative to 2,3,7,8-TCDD (comparison based on short term *in vitro* or *in vivo* animal studies). Several systems of TEF-calculation are available, the differences in which reflect divergences in the assumptions made and in the toxicological data used for comparison. In the Netherlands I-TEF's (International Toxic Equivalence Factors) are used, yielding I-TEQ's (toxic equivalents of 2,3,7,8-TCDD) as the units in which PCDD/PCDF toxicity is expressed. It should be noted that the toxic equivalence concept is of a pragmatic nature and is based on simplistic assumptions. Based on present information it appears that the I-TEF appproach may overestimate the risk. (Liem et al., 1993; Kello & Yrjänheikki, 1992)

The carcinogenicity of 2,3,7,8-TCDD was examined in experimental animals and in epidemiological studies in humans. There is *sufficient evidence* for carcinogenicity in animals and *inadequate evidence* for carcinogenicity in humans; the IARC-classification is *Group 2B* (*possibly carcinogenic to humans*). (IARC, 1987; Liem et al., 1993) On the basis of the results of genotoxicity studies 2,3,7,8-TCDD is considered non-genotoxic. Based on the genotoxicity data combined with data on the mechanism of action *in vivo*, a threshold approach was deemed justified. For pre-carcinogenic liver toxicity, reproductive effects and immunotoxicity tested in the various laboratory animal species a no-effect level of 1000 pg/kg bw/day was identified. Using kinetic data this was calculated to equal 100 pg/kg bw in humans. Through application of a safety factor of 10 a TDI for 2,3,7,8-TCDD of 10 pg/kg bw was derived. (Kello & Yrjänheikki, 1992; Liem et al., 1993) This value can be used for the total mixture of PCDDs/PCDFs via application of the I-TEF concept[12]. Thus, for toxicological evaluation of the mixture a TDI of 10 pg I-TEQ/kg bw is applicable. (Liem et al., 1993).

PCDDs are known to produce chloracne in humans after dermal contact (the effect is however also believed to occur after exposure via other routes). The available data show dioxins to have a high potency to produce this effect but the quantitative dermal concentration-effect relationship has not been established (even an unequivocal indication of a dermal effect-level in humans is lacking). (ATSDR, 1989; IPCS, 1989)

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[12]A possible elaboration of the I-TEF concept is the inclusion therein of polychlorinated biphenyls, a group of compounds with toxicological effects similar to PCDDs and PCDFs. This is a possible future step; as yet the I-TEF concept only covers mixtures of PCDDs and PCDFs.

BACKGROUND EXPOSURE

Food is the major source of exposure for the general population, covering 90-95% of the total amount. A recent study in the Netherlands (results reported in 1991) showed the median daily intake via food for children (age ≤20 years) to be 35 to 70 pg I-TEQ (95%-percentile about 60 to 120 pg); for adults the median intake was 70 pg (95%-percentile about 130 pg). The median figures correspond to ≤3 pg/kg bw for children and 1 pg/kg bw for adults, with 95%-percentiles ≤6 pg/kg bw for the two groups together. (Liem et al., 1993)

MISCELLANEOUS DATA

- Absorption factors:
· dermal bioavailability from soil for TCDD: 2% (Paustenbach et al., 1992)
· inhalational: value used for calculation is 100% (Paustenbach et al., 1992)
- Guideline values (Liem et al., 1993; WHO, 1992):
· $soil_{residential\ areas}$ (to protect human health): 1000 ng I-TEQ/kg d.m. (preliminary value)
· $soil_{grazing\ lands}$: values exceeding 10 ng I-TEQ/kg d.m., considered undesirable
· remediation value for sediments: 100 ng I-TEQ/kg
· air: no limit value proposed; for waste incinerators an emission limit value of 0.1 ng I-TEQ/Nm^3 has become effective on 30 November 1993
· milk & milk products: ≤6 pg I-TEQ/g milk fat

CONCLUSION[13]

TDI:	10×10^{-6} µg I-TEQ/kg bw
Background exposure (95%-percentile):	6×10^{-6} µg I-TEQ/kg bw

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RIVM-Toxicology Advisory Centre.

Profile compilation by: P.J.C.M. Janssen.
Profile review by: M.E. van Apeldoorn, J.E.M. van Koten-Vermeulen, F.X.R. van Leeuwen & T.G. Vermeire.

[13]The special problem of dioxins and breast feeding is not considered to require special attention in the present context (there being, for sucklings, no additional exposure route directly related to soil contamination).

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Appendix 6: AZINPHOS-METHYL

RELEVANT ROUTE

Exposure routes considered relevant in present context: oral and, possibly, inhalational.

TOXICITY

Azinphos-methyl is an organophosphorous cholinesterase inhibitor used as an insecticide.
The toxicological data were evaluated by the JMPR in 1991. The available long-term studies in mice (2 studies) and rats (2 studies) did not show azinphos-methyl to be carcinogenic. The data on genotoxicity are partly contradictory some *in vitro* tests having a positive result, others (with the same endpoints) being negative. *In vivo* studies showed no effect. These results led the JMPR to conclude that it is unlikely that azinphos-methyl is genotoxic to humans. (JMPR, 1991) No IARC-classification is available for the compound.
The 1991 JMPR evaluation resulted in an ADI of 0 - 0.005 mg/kg bw. This ADI was based on a NOAEL of 5 mg/kg diet (equal to 0.48 mg/kg bw/day) from a two-generation reproduction study in rats. The critical effects in this study were decreased fertility and pup viability. Supporting evidence was provided by the following studies: 2-year feeding study in mice (NOAEL 5 mg/kg diet, equal to 0.88 mg/kg bw/day), 2-year feeding study in rats (NOAEL 5 mg/kg diet, equal to 0.86 mg/kg bw/day), 52-weeks study in dogs (NOAEL 25 mg/kg diet (equal to 0.74 mg/kg bw/day) and a 30-days oral study in humans (NOAEL 0.3 mg/kg bw/day). In each of these supporting studies the critical effect was decreased cholinesterase activity in erythrocytes and/or brain. (JMPR, 1991)

Inhalational data are very limited, the only study with repeated dosage being a limited 12-week study in rats with treatment with an aerosol during 6 hours/day, 5 days a week. The NOAEL in this study was 1.24 mg/m^3, with growth retardation as the critical effect. (Kimmerle, 1976; JMPR, 1991) Using a safety factor of 1000 (incorporating an extra factor of 10 for limited duration of the study), from this NOAEL, a provisional TCA (PTCA) of 0.2 µg/m^3 (rounded figure) can be derived (after adjustment of the NOAEL to continuous exposure). This is a povisional value because of the limitations in the underlying data.

BACKGROUND EXPOSURE

Since no direct measurements of daily intake via the total diet (market basket surveys or duplicate 24 h-diet studies) are available, background exposure is unknown.[14]

MISCELLANEOUS DATA

- Absorption factors:
· dermal: in humans ≤60% (JMPR, 1991)
· inhalational: no data found in the literature used

[14]The theoretically possible maximal daily dietary intake would seem to be roughly estimable from the residue tolerances for azinphos-methyl as given in the Bestrijdingsmiddelenwet (Pesticide Act). Because of the great inherent uncertainty of the result of such an approach however, it cannot be taken as a relevant indication of the real dietary exposure. For a discussion of this topic see for instance C.K. Winter, Pesticide Tolerances and their Relevance as Safety Standards, Regulatory Toxicology and Pharmacology, 15, 1992, 137-150.

- Guideline values:
· residue tolerances in mg/kg, as given in the Dutch Pesticide Act (Bestrijdingsmiddelenwet) (1992):

citrus fruits: 2 mg/kg	soya beans: 0.2 mg/kg
grapes: 1 mg/kg	potato: 0.02 mg/kg[15]
kiwi fruit: 4 mg/kg	cotton seed: 0.2 mg/kg
other fruits: 0.5 mg/kg	sunflower seeds: 0.2 mg/kg
vegetables: 0.5 mg/kg	other products: 0 mg/kg (detection limit 0.05 mg/kg)

· MAC-value (limit for occupational exposure): 0.2 mg/m^3 (with the additional remark that uptake via skin occurs (SZW, 1992)

CONCLUSION

ADI:	5 µg/kg bw/day
Background exposure:	unknown
PTCA:	0.2 µg/m^3

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Profile compilation by: P.J.C.M. Janssen.
Profile review by: M.E. van Apeldoorn, J.E.M. van Koten-Vermeulen, F.X.R. van Leeuwen & T.G. Vermeire.

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[15]No detectable residue.

Appendix 7: ENDOSULFAN

RELEVANT ROUTE

Exposure route considered relevant in present context: oral.

TOXICITY

Endosulfan is a pesticide used in countries throughout the world to control pests in fruits, vegetables, tea, cereals and several non-food crops. For application as pesticide *technical* endosulfan, a 70:30 mixture of the α- and β-isomers, is used. The available toxicity data apply to this mixture.

Endosulfan showed no carcinogenic activity in long-term toxicity studies in rats and mice, nor was there evidence of genotoxicity in the available mutagenicity tests (*in vitro & in vivo*). (JMPR, 1989). No IARC-classification is available for the compound.

The 1989 JMPR evaluation of the toxicological data file on endosulfan has yielded an ADI of 0 - 0.006 mg/kg bw. The data file included 2-year feeding studies in mice and rats and a 1-year feeding study in dogs. The principal effects in these tests were: increased mortality (mice only), growth retardation (mice, rats), kidney damage (rats only) and neurotoxicity (dogs only). The ADI was derived using standard safety factor 100 from NOAELs of 15 mg/kg diet in rats (equal to 0.6 mg/kg bw/day) and 10 mg/kg diet in dogs (equal to 0.57 mg/kg bw/day). (JMPR, 1989)

BACKGROUND EXPOSURE

Since no direct measurements of daily intake via the total diet (market basket surveys or duplicate 24 h-diet studies) are available, background exposure is unknown.[16]

MISCELLANEOUS DATA

- Absorption factors:
  - dermal: in rats 25% penetrates through the skin and 55% remains in the skin, in sum 80% is absorbed (JMPR, 1989)
  - inhalational: no data found in the literature used
- Guideline values:
  - residue tolerances (sum of α- & β-endosulfan & endosulfan sulphate) in mg/kg, as given in the Dutch Pesticide Act (Bestrijdingsmiddelenwet) (1992):

fruits: 1 mg/kg	milk: 0.004 mg/kg
winter carrot: 0.2 mg/kg	potato:0.05 mg/kg[17]
carrot: 0.2 mg/kg	cotton seed: 1 mg/kg

[16]The theoretically possible maximal daily dietary intake would seem to be roughly estimable from the residue tolerances for endosulfan as given in the Bestrijdingsmiddelenwet (Pesticide Act). Because of the great inherent uncertainty of the result of such an approach however, it cannot be taken as a relevant indication of the real dietary exposure. For a discussion of this topic see for instance C.K. Winter, Pesticide Tolerances and their Relevance as Safety Standards, Regulatory Toxicology and Pharmacology, 15, 1992, 137-150.

[17]No detectable residue.

other vegetables: 1 mg/kg
maize: 0.2 mg/kg
other cereals & buckwheat: 0.1 mg/kg
other products: 0 (detection limit 0.05 mg/kg)
tea: 30 mg/kg
meat: 0.1 mg/kg

CONCLUSION

ADI:	6 µg/kg bw/day
Background exposure	unknown

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Profile compilation by: P.J.C.M. Janssen.
Profile review by: M.E. van Apeldoorn, J.E.M. van Koten-Vermeulen, F.X.R. van Leeuwen & T.G. Vermeire.

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Appendix 8: CHLORDANE

RELEVANT ROUTE

Exposure routes considered relevant in present context: oral and inhalational.

TOXICITY

Chlordane (*cis-* and *trans-*) was formerly used as an insecticide in the Netherlands and other countries; such use is now prohibited in the EC-countries. The rationale for this prohibition is the high environmental persistence and the selective bioaccumulation in fat (chlordane shares these properties with several other, closely related organochlorine pesticides).

Available data on the possible carcinogenicity of chlordane have been evaluated by the IARC. The conclusion was that there is *sufficient evidence* for the carcinogenicity of chlordane in experimental animals and *inadequate evidence* in humans. Classification is in *Group 2B* (*possibly carcinogenic to humans*). (IARC, 1991) Genotoxicity studies have generally yielded negative results. Chlordane is not considered a genotoxic agent. (IPCS, 1984; JMPR, 1986; ATSDR, 1992). The JMPR evaluated all available toxicological data in 1986 and allocated an ADI of 0 - 0.5 µg/kg bw/day. The data file included 2-year feeding studies in mice, rats and dogs; in all three species liver enlargement with concomitant histopathological lesions were the critical effects. In mice and rats the NOAEL was 1 mg/kg diet (equal to 0.12 mg/kg bw/day in mice and equivalent to 0.05 mg/kg bw/day in rats). In dogs the NOAEL was 3 mg/kg diet (equal to 0.075 mg/kg bw/day). The ADI was calculated from the NOAEL in rats of 0.05 mg/kg bw/day using standard safety factor 100. (JMPR, 1968, 1986)

Inhalational exposure is possible - in WHO-WQG (1992), for instance, it is noted that volatilization of chlordane from soil occurs. Two semichronic inhalation studies, carried out in rats and monkeys respectively, both had treatment concentrations of 0.1, 1 and 10 mg/m^3 (administration 8 h/day, 5 days/week for 13 weeks). In rats effects on the liver were clear-cut at 1 and 10 mg/m^3 (hepatocyte enlargement, weight increase) and marginal at 0.1 mg/m^3 (increased cytchrome P450 only). In monkeys no effects were observed. (Khasawinah et al., 1989) Based on the marginal-effect-level in rats of 0.1 mg/m^3 (equivalent to 23 µg/m^3 after adjustment to continuous exposure), using a safety factor of 1000 (incorporating an extra factor of 10 for limited duration of the study), a provisional TCA (PTCA) of 0.02 µg/m^3 (rounded figure) can be calculated. This is a povisional value because of the limitations in the underlying data.

BACKGROUND EXPOSURE

Dietary exposure probably is the primary route for background exposure. The scanty data suggest the concentrations in air to be negligible (in the vicinity of spray-treated plots however concentrations may expected to be higher). Measurements of the total dietary intake of chlordane have not been made in the Netherlands. In market basket surveys in other countries (USA, Canada) chlordane was mostly found to be absent. (IPCS, 1984) Thus for background exposure in the

Netherlands no figure can be given[18] but the data suggest a low level of exposure.

MISCELLANEOUS DATA

- Absorption factors:
· dermal: absorption from soil in monkeys 4% (ATSDR ,1992)
· inhalational: compound is absorbed but no quantitative data are available (ATSDR ,1992)
- *Guideline values:*
· residue tolerances in mg/kg, as given in the Dutch Pesticide Act (Bestrijdingsmiddelenwet) (1992):

(sum of cis- & trans-chlordane):

melon: 0.1 mg/kg	cucumber: 0.1 mg/kg
pineapple: 0.1 mg/kg	pulses: 0.02 mg/kg
other fruits: 0.02 mg/kg	other vegetables: 0.02 mg/kg
potato: 0.05 mg/kg	vegetable oils: 0.02 mg/kg

other: 0 (detection limit 0.02 mg/kg)

(sum of cis- & trans-chlordane & oxychlordane):

milk: 0.002 mg/kg	other products: 0.05 mg/kg (in the fat)

· MAC-value (limit for occupational exposure): 0.5 mg/m^3 (with the additional remark that uptake via skin occurs (SZW, 1992)
· drinking-water: WHO-drinking water guideline: 0.2 µg/litre (WHO, 1992)

CONCLUSION

ADI:	0.5 µg/kg bw/day
Background exposure:	unknown, but estimated to be low
PTCA:	0.02 µg/m^3

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Profile review by: M.E. van Apeldoorn, J.E.M. van Koten-Vermeulen, F.X.R. van Leeuwen & T.G. Vermeire.

[18]The theoretically possible maximal daily dietary intake would seem to be roughly estimable from the residue tolerances for chlordane as given in the Bestrijdingsmiddelenwet (Pesticide Act). Because of the great inherent uncertainty of the result of such an approach however, it cannot be taken as a relevant indication of the real dietary exposure. For a discussion of this topic see for instance C.K. Winter, Pesticide Tolerances and their Relevance as Safety Standards, Regulatory Toxicology and Pharmacology, 15, 1992, 137-150.

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Appendix 9: HEPTACHLOR & HEPTACHLOR EPOXIDE

RELEVANT ROUTE

Exposure routes considered relevant in present context: oral and inhalational.

TOXICITY

Heptachlor was formerly used as an insecticide in the Netherlands and other countries; such use is now prohibited in the EC-countries. The rationale for this prohibition is the high environmental persistence and the selective bioaccumulation in fat (heptachlor shares these properties with several other, closely related organochlorine pesticides). Heptachlor epoxide, the oxidation product of heptachlor, is the primary degradation product in soil and an important metabolite *in vivo*.

Available data on the possible carcinogenicity of heptachlor and heptachlor epoxide have been evaluated by the IARC. The conclusion was that there is *sufficient evidence* for the carcinogenicity of heptachlor in experimental animals and *inadequate evidence* in humans. Classification is in *Group 2B* (*possibly carcinogenic to humans*). (IARC, 1991) On the basis of the results of genotoxicity studies heptachlor is considered non-genotoxic (JMPR, 1991). After reviewing all available data the JMPR recommended not to use heptachlor as a pesticide in the production of food commodities; an ADI was allocated for assessment of dietary exposures due to past uses and any uses awaiting discontinuation.
An ADI of 0 - 0.1 µg/kg bw/day was based on an oral NOAEL in dogs of 1 mg/kg diet (equivalent to 0.025 mg/kg bw/day). This NOAEL was found both in a 2-year feeding study (critical effect: increased liver weight and concomitant histological changes) and a 2-generation reproduction study (effect: increased mortality in F_2 pups). A safety factor of 200 was used, incorporating an extra factor of 2 (above the usual factor 100) for inadequacies in the data base. (JMPR, 1991) The JMPR has not established a separate ADI for heptachlor epoxide. The JMPR ADI is therefore interpreted as covering the sum of heptachlor and heptachlor epoxide.

Although inhalational exposure is possible - in WHO-WQG (1992), for instance, it is noted that volatilization of heptachlor from soil occurs -, no toxicological studies for this route are available. A provisional TCA (PTCA) can be derived from the oral ADI. Assuming a daily ventilation volume of 20 m^3 for an adult (bw 70 kg) and an oral/inhalational bioavailability ratio of 100/75, the ADI is equivalent with a concentration of 0.5 µg/m^3 (rounded figure). This is a provisional value because it was derived via route-to-route calculation, a procedure involving considerable uncertainty.

BACKGROUND EXPOSURE

The diet is considered the primary route determining background exposure. In 1984 and 1985 duplicate 24 h-diet studies were carried out in the Netherlands, showing maximum daily intakes of < 1 µg/day for both heptachlor and heptachlor epoxide (Greve et al., 1987). In the same years a market basket survey was done; the preliminary results showed a daily intake for heptachlor and hepatachlor epoxide (sum) of 0.07 µg/day (mean value; percentile distribution not reported) (de Vos et al., 1987). For an adult person this equals 0.001 µg/kg bw /day.

For the inhalational exposure route no data are available for the Netherlands. For the USA 0.5 ng/m^3 is given as a typical concentration in air (IPCS, 1984). Thus, the scant data suggest that inhalational background exposure is very low.

MISCELLANEOUS DATA

- Absorption factors: no data found in the literature used
- Guideline values:

· residue tolerances (sum of heptachlor & -epoxide) in mg/kg, as given in the Dutch Pesticide Act (Bestrijdingsmiddelenwet) (1992):

citrus fruits: 0.01 mg/kg[19]
pineapple: 0.01 mg/kg[19]
tomato: 0.02 mg/kg
other vegetables: 0.05 mg/kg
soya beans: 0.02 mg/kg
potato: 0.05 mg/kg
game & fowls: 0.2 mg/kg (in the fat)
other: 0 (limit of detection 0.01 mg/kg)
cotton seed: 0.02 mg/kg
vegetable oils & fats: 0.02 mg/kg
egg: 1 mg/kg (in het vet)
milk: 0.004 mg/kg
meat: 0.2 mg/kg (in the fat)
poultry meat: 0.2 (in the fat)

· MAC-value (limit for occupational exposure): 0.5 mg/m^3 (with the additional remark that uptake via skin occurs (SZW, 1992)

· drinking-water: WHO-drinking water guideline: 0.3 µg/liter (heptachlor + heptachlorepoxide)(WHO, 1992)

CONCLUSION

ADI[20]:	0.1 µg/kg bw/day
Background exposure (mean):	0.001 µg/kg bw/day
PTCA (extrapolated from the TDI):	0.5 µg/m^3

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Profile compilation by: P.J.C.M. Janssen.
Profile review by: M.E. van Apeldoorn, J.E.M. van Koten-Vermeulen, F.X.R. van Leeuwen & T.G. Vermeire.

[19]No demonstrable residue.

[20]ADI for the sum of heptachlor and heptachlor epoxide.

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Appendix 10: TRIBUTYLTIN OXIDE (TBTO)

RELEVANT ROUTES

Exposure routes considered relevant in present context: oral, dermal, inhalational.

TOXICITY

TBTO is used as a biocide in antifouling paints (for boats) and as a wood preservative. The use in antifouling paints has been banned in the Netherlands, the UK and France; an EEC ban has been proposed. These actions were taken in view of the bioaccumulation in the environment and the high toxicity for aquatic organisms.

In a long-term toxicity/carcinogenicity study in rats, TBTO had no carcinogenic effect (Wester et al., 1988). The results of the mutagenicity studies did not show the compound to be genotoxic (WHO-WQG, 1992). No IARC-classification is available for TBTO. Based on these results a threshold approach is considered appropriate for derivation of the tolerable intake.
The long-term rat study had dietary dose levels of 0.5, 5 and 50 mg/kg diet. The principal toxic effects in this study were: histopathological changes in kidney, thyroid and bile duct, changes in immunoglobulin concentrations and numbers of lymphocytes in the blood and suppression of resistance to the nematode *Trichinella spiralis*. These effects were observed primarily in the high-dose group and were often only marginal at the medium-dose level. The suppression of host resistance however, was seen to a dose-related and significant degree both at the high-dose and the medium-dose level. The NOAEL from this study is 0.5 mg/kg diet (equivalent to 0.025 mg/kg bw/day). (WHO-WQG, 1992) In oral teratogenicity studies in mice and rats a teratogenic response (increased incidence of cleft palate) in combination with maternal toxicity occurred at dose levels of ≥11.7 mg/kg bw/day; the NOAEL in these studies was 5 or 6 mg/kg bw/day (BUA, 1988; WHO-WQG, 1992).
In WHO-WQG (1992) a TDI of 0.3 µg/kg bw (rounded figure) was derived by application of the standard safety factor of 100 to the long-term NOAEL of 0.025 mg/kg bw.

In experimental animals TBTO produced irritation of the skin and eyes. These effects were seen at concentrations of ≥0.5% (skin) and ≥0.15% (eyes); the results of these irritation studies do not allow derivation of concentrations-without-effect. (BUA, 1988; IPCS, 1990) In humans TBTO has been shown to produce severe dermatitis after direct contact with the skin. The reaction is delayed, being noticable not before a few hours after onset of contact. The concentration-response relationship for this effect is not known exactly. The lowest reported concentration producing a response is 0.01 g TBTO/litre (the concentration-without-effect has not been determined unequivocally). (IPCS, 1990)

For the inhalational route in humans there are qualitative data (exposure concentrations unknown) showing that TBTO may produce irritation of the upper respiratory tract and chest pain in humans (IPCS, 1990). Inhalational data concerning repeated dosage are limited to a 4-weeks study in rats with exposure for 4 hours/day, 5 days per week. This study yielded a NOAEL of 0.16 mg TBTO/m^3 (as vapour). (Prins & van Velzen, 1983; BUA, 1988) This NOAEL adjusted to continuous exposure (24 hours/day, 7 days/week) is 20 µg/m^3. From the latter concentration a provisional TCA (PTCA) of 0.02 µg/m^3 can be calculated by application of safety factor 1000 (an extra factor of 10 for limited

duration of the study). This is a povisional value because of the limitations in the underlying data.

BACKGROUND EXPOSURE

No direct measurements of daily intake via the total diet (market basket surveys or duplicate 24 h-diet studies) are available. Most likely the primary source of dietary exposure is consumption of TBTO-contaminated fish and shellfish. The only indication of concentrations in fish in the Netherlands is the range of <0.025-0.26 mg/kg (year 1988) given in IPCS (1990) for "various fish species" (not specified). Using 50 grams/day as the daily fish consumption rate[21], the upper limit of the reported range of concentrations gives a TBTO intake via fish of 13 µg/day (equal to about 0.2 µg/kg bw/day for an adult). This figure should be taken as a rough estimate of the upper range of background exposures via the diet.

No data on concentrations in outdoor air are available; most likely these levels are so low that they are negligible relative to dietary exposure. In indoor air concentrations may be higher due to use of TBTO as wood preservative; representative concentration-measurements, however, are lacking. (BUA, 1988)

MISCELLANEOUS DATA

- Absorption factors:
· dermal: absorption percentage for monkeys 10-15%
· inhalational: compound is absorbed"well" but no quantitative data are available (BUA,1988; IPCS, 1990)
- Guideline values:
· MAC-value (limit for occupational exposure): 0.1 mg Sn/m^3; this value applies for organotin-compounds (the MAC-value expressed as TBTO: 0.25 mg/m^3)(SZW, 1992)
· drinking-water: WHO-drinking Water Guideline: 2 µg/litre (WHO, 1992)

CONCLUSION

TDI:	0.3 µg/kg bw/day
Background exposure (rough estimate of upper range):	0.2 µg/kg bw/day
PTCA:	0.02 µg/m^3
LRCCD[22]:	10 mg/litre

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[21]Estimate based on the 95%-percentile upper limits of 30 to 67 grams/day for various population groups in the USA (Reference: US-EPA, 1989 - Exposure factors handbook; EPA report no. EPA 600 8-89 043, dated July 1989).

[22]Lowest Reported Concentration producing Contact Dermatitis; the concentration-without-effect is unknown. This LRCCD may be used for evaluating dermal contact with TBTO-solutions: in the µg/litre-range no problem may be expected but in the mg/litre-range occurrence of an adverse reaction cannot be ruled out.

Profile compilation by: P.J.C.M. Janssen.
Profile review by: M.E. van Apeldoorn, J.E.M. van Koten-Vermeulen, F.X.R. van Leeuwen & T.G. Vermeire.

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Appendix 11: TRIPHENYLTIN compounds

RELEVANT ROUTE

Exposure routes considered relevant in present context: oral.

TOXICITY

Triphenyltin (or fentin-)compounds, i.e. triphenyltinacetate (TPTA), triphenyltinchloride (TPTCl) and triphenyltinhydroxide (TPTH), are used as non systemic fungicides.

The toxicological data have been evaluated by the JMPR in 1991. No IARC classification is available for triphenyltin compounds.

Most *in vitro* and *in vivo* genotoxicity tests were negative. However, 2 human lymphocyte chromosomal aberration assays and 2 mouse lymphoma mutation assays were positive. Since 2 *in vivo* studies for chromosomal aberrations were negative, it would appear that any genotoxic properties are of low potency. No carcinogenic activity was observed in two long-term/carcinocinicity studies in mice and one in rats. In a third long-term/carcinogenicity study in mice increased nodular hyperplasia and hepatocellular adenomas and carcinoma occurred. In a second long-term/carcinogenicity study in rats (1989) the incidence of pituitary adenomas was increased in females and the incidence of Leydig cell tumours was increased in both males and females. These changes were accompanied by non-neoplastic lesions in the pituitary and the testes. Based on these data and the results of the available genotoxicity assays, the JMPR concluded that fentin is not a genotoxic carcinogen (JMPR, 1991).

In 1970 the JMPR established an ADI of 0-0.0005 mg/kg bw, based upon a NOAEL of 0.1 mg/kg bw/day in a long-term study in rats (critical effect: decrease in white blood cells); this ADI is applicable to TPTA, TPTH and TPTCl each and to the sum of the three compounds. In the 1989 long-term rat study increased mortality was observed at the lowest dose (0.3 mg/kg bw/day). Applying an uncertainty factor of 500 to this LOAEL would result in approximately the same ADI as the one previously established in 1970. Therefore the JMPR retained in 1991 the ADI of 0-0.0005. This ADI is supported by NOAELs derived from other recent studies, including the NOAEL of 5 ppm in the diet (equal to 0.4 mg/kg bw/day) in the 2-generation reproduction study in rats, the NOAELs in short-term studies in rats (0.3 mg/kg bw/day) and dogs (6 ppm equal to 0.2 mg/kg bw/day) and in a teratology study in rabbits (0.1 mg/kg bw/day for maternal toxicity) (JMPR, 1991).

BACKGROUND EXPOSURE

Human exposure is possible as a result of skin contact with contaminated swimming-water, ingestion of crops containing residues, consumption of contaminated fish and inhalation of air containing fentin (RIZA, 1992). However no measurements of daily intake via the total diet (market basket surveys or duplicate 24 h-diet studies) or of concentrations in ambient air are available. Thus, background exposure is unknown[23].

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[23]The theoretically possible maximal daily dietary intake would seem to be roughly estimable from the residue tolerances for triphenyltin compounds as given in the Dutch Pesticide Act (Bestrijdingsmiddelenwet). Because the great inherent uncertainty of the result of such an approach however, it cannot be taken as a relevant indication of the real dietary exposure.For a discussion of this topic see for instance C.K.Winter, Pesticide Tolerances and their Relevance as Safety Standards, Reg. Toxicol. Pharmacol., 15, 1992, 137-150.

MISCELLANEOUS DATA

-Absorption factors:

- dermal: absorption max. 55% (of which max. 30% penetrated and 20% remained in skin) (JMPR, 1991)
- inhalation: no data found
- Guideline values: residue tolerances (maximal residue as TBHP) in mg/kg, as given in the Dutch Pesticide Act (Bestrijdingsmiddelenwet) (1992):

peca nut: 0.1[24]	celeriac: 0.1
winter carrot: 0.1	carrot: 0.1
celery: 1	rice (not husked): 0.1[24]
potato: 0.1	ground nut: 0.05[24]
tropical seeds: 0.1	other: 0[24] (detection limit 0.1 mg/kg

CONCLUSION

ADI:	0.5 µg/kg bw/day
Background exposure:	unknown

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[24]No detectable residue.

Appendix 12: METHYLETHYLKETONE (MEK)

RELEVANT ROUTE

Exposure routes considered to be relevant in this context: inhalational, oral.

TOXICITY

No adequate data with respect to the carcinogenic potential of MEK by the oral or inhalation route are available. In one long-term dermal study in which MEK was used as solvent (dissolved in water) and was applied twice a week to the clipped skin of mice for a year, no increased number of skin tumours was observed. MEK did not induce gene-mutations in prokaryotic or eukaryotic cells in vitro. In *Saccharomyces cerevisiae* aneuploidy was induced. In *in vitro* and *in vivo* assays detecting chromosomal aberrations or UDS, MEK showed negative results. MEK did not induce cell transformation (ATSDR, 1992; US-EPA, 1993; IPCS, 1990; RA 16/90, 1991). MEK was not evaluated by IARC.

Based on the data given above it is assumed that MEK does not possess genotoxic activity. Therefore a threshold extrapolation method for evaluation of the risk for man is used.

No long-term oral or inhalation studies with MEK are available. In most subchronic toxicity studies with MEK the route of administration was by inhalation. As many other organic solvents MEK causes reversible depression of CNS activity at exposure to high concentrations. At repeated exposure to levels up to and including 17700 mg/m^3 rats did not reveal neurological symptoms and/or neuropathological effects. However MEK markedly potentiates the neurotoxicity of ethanol, n-hexane, methyl-n-butyl ketone and ethyl-n-butyl ketone (ATSDR, 1992; IPCS, 1990; RA 16/90, 1991).

Appropriate studies for establishing a NOAEL for MEK are the teratogenicity studies in mice and rats. In a study with pregnant rats, exposed for 7 h/day, during day 6-15 of gestation, to 0, 3320 or 7720 mg MEK/m^3, significant increases in skeletal (sternebral) malformations and soft tissue anomalies were seen at 7720 mg/m^3, as well as four grossly malformed fetuses. No maternal toxicity was seen. The total number of litters with anomalous skeletons was increased significantly at 3320 mg/m^3, but not at 7720 mg/m^3 (Schwetz et al., 1974). Deacon et al. (1981) exposed pregnant rats 7 h/day, during day 6-15 of gestation, to concentrations of 0, 1215, 2955 and 8861 mg/m^3 and did not observe increased incidences of external or soft-tissue alterations among the fetuses. A significantly increased incidence of extra lumbar ribs and delayed ossification of the cervical centra were seen at 8861 mg/m^3. At the same exposure level decreased maternal weight gain and increased water consumption indicated some maternal effect. At the two lower exposure levels no effects in dams or fetuses were seen.

In a study with pregnant mice exposed to 0, 1174, 2987 or 8906 mg MEK/m^3 7 h/day, during day 6-15 of pregnancy, mild developmental effects (decreased fetal body weight and misaligned sternebrae) were seen at 8906 mg/m^3. At the same exposure level an equivocal maternal effect was observed (increased relative liver and kidney weight). At exposure levels
$\leq$ 2987 mg/m^3 no effects were seen (Mast et al., 1989; Schwetz et al., 1991).

In humans exposed to 300 mg/m^3 slight nose and throat irritation was seen and exposure to 900

mg/m^3 became objectionable (ATSDR, 1992). The threshold odour concentration in the air is 5.8-250 mg/m^3 for detection and 16-163 mg/m^3 for recognition (RA 16/90; 1991).
In occupational studies it was found that simultaneous inhalational exposure to MEK and other industrial solvents (a.o. n-hexane, xylenes, toluene) can produce neurotoxicity. It is not possible to derive a NOAEL for MEK from these data. From the contradictory results of two short-term behavioural studies in humans no conclusion concerning the inhalational NOAEL in humans can be drawn. (IPCS, 1990)

Based on the data given above, 3000 mg MEK/m^3 7 h/day can be considered as a NOAEL for mice and rats. The exposure level for 7 h/day corresponds with 875 mg/m^3 for continuous exposure (24 h/day). Applying a safety factor 1000 (standard factor 100 multiplied by an extra factor 10 for the incomplete data base including the lack of chronic and reproductive studies), results in a TCA of 0.875 mg/m^3.
As no appropriate oral studies with MEK are available a provisional TDI (PTDI) has to be extrapolated from the figure for the TCA. Assuming a daily ventilation volume for man of 20 m^3 and asssuming that bioavailability (≈absorption) after oral and inhalational exposure is 100 and 75%, respectively, then 875 µg/m^3 corresponds to an oral intake of 13125 µg/man/day. Assuming a body weight for man of 70 kg a PTDI of 13125/70 = 190 µg/kg bw (rounded value) can be calculated. This is a provisional value because it was derived via route-to-route calculation, a procedure involving considerable uncertainty.

BACKGROUND EXPOSURE

Unknown

MISCELLANEOUS DATA

-Absorption factors:
· inhalational: 41-70% in humans (depending on dose level and exercise) (RA 16/90, 1991)
· dermal & oral: no data found in the literature used
- Guideline values: no data found

CONCLUSION

PTDI (extrapolated from the TCA):	190 µg/kg bw/day
Background exposure:	unknown
TCA:	875 µg/m^3

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Printed february 1993.

Appendix 13: SILVER

RELEVANT ROUTE

Exposure route considered relevant in present context: oral, dermal.

Soil contamination with silver usually is associated with the use of silver salts (bromide, nitrate, thiosulfate) in photography. The discussion below is focussed on the the silver ion because the silver ion (and not the anion of the salt) determines the general toxicologic action of silver compounds. It is relevant to note that silver in soil tends to form complexes with inorganic chemicals and humic acids; this may influence the bioavailability.

TOXICITY

No IARC evaluation of the possible carcinogenicity of silver compounds is available. Experimental evidence pertaining to carcinogenicity is very limited and does not constitute adequate evidence for presence or absence of a carcinogenic action in humans or experimental animals (ATSDR, 1990, US-EPA, 1991). No mutagenicity was observed in bacterial systems (*E. coli, Salm. typimurium*). No *in vivo* mutagenicity studies are available. Two *in vitro* tests for DNA damage (DNA strand breaks, DNA repair) in mammalian cells showed positive results at moderately toxic concentrations only. (WHO-WQG, 1992; ATSDR, 1990; US-EPA, 1992)
Based on these results a threshold approach is chosen in the health evaluation for silver.

The derivation of the TDI for silver is based on toxicity data in humans. The available animal toxicity studies are of limited value. Relevant animal studies of adequate design are lacking. The data nevertheless show that in experimental animals, silver salts (mostly the nitrate was tested), produce anaemia, cardiac enlargement, growth retardation and degenerative changes in the liver. These effects have been observed at relatively high dose levels (≥ about 90 mg/kg bw/day) after semichronic administration. The studies in question are too limited for derivation of a TDI. (JECFA, 1977; Fowler & Nordberg, 1986; ATSDR, 1990; US-EPA, 1991) No studies on developmental or reproductive effects are available.

A number of case studies in humans concerning the medical use of silver compounds is available. These studies were carried out several decades ago (1930-1950). The critical effect in humans ingesting silver chronically is *argyria*, a permanent bluish-gray discolouration of the skin. Argyria results from the deposition of silver in the dermis and also from silver-induced production of melanin. The pigmentation is more pronounced in skin areas exposed to sunlight due to photoactivated reduction of the metal. Although the deposition of silver is permanent, it is not associated with adverse health effects. No pathologic changes or inflammatory reactions have been shown to result form the silver deposition. The available medical case studies have been reviewed by the US-EPA (1991, 1992). From a case review concerning intravenous use of silver arsphenamine in syphilis patients a LOAEL of 0.014 mg/kg bw/day for mild argyria was derived. This derivation was based on:
- the body accumulates silver throughout life
- a total intravenous dose of 1 g silver (4 g silver arsphenamine) will cause mild argyria in the most sensitive individuals

- an oral absorption factor of 4% to calculate the oral dose equivalent to the i.v. dose of 1 g
- the total dose is averaged over a lifetime of 70 years

Thus, an oral LOAEL of 0.014 mg/kg bw/day results[25]. From this LOAEL The US-EPA calculated a Reference Dose (≈TDI) of 0.005 mg/kg bw/day using a modifying factor of 3 (rationale: a lower factor than the standard factor 10 for intraspecies variability is warranted because the calculation already included sensitive individuals and the critical effect was a cosmetic effect and not an adverse health effect). (US-EPA, 1991, 1992) There is uncertainty in this TDI because it based on case studies in syphilis patients performed in the 1930's and not on full-value controlled studies in healthy subjects. An additional source of uncertainty is the use of route-to-route extrapolation (intravenous to oral) in the calculation.

Medical case histories describe mild allergic responses attributed to dermal contact with silver and silver compounds. The exposure concentrations involved in these cases are unknown. (ATSDR, 1990) Dermal contact with silver compounds may lead to local argyria; quantitative data on this effect (dose response relation) are lacking. The available limited inhalational data, involving reports of adverse effects after occupational exposure, do not allow derivation of a NOAEL or LOAEL for systemic or local effects. (ATSDR, 1990)

BACKGROUND EXPOSURE

Information specifically for the Netherlands is limited to the statement given in WNW (1992) that in drinking-water concentrations mostly are low (<1µg/litre) when silver is not used as a bacteriostaticum. In case of such use concentrations will be >50 µg/litre[26]. (WNW, 1992) Data from the USA indicate that for the general population the main source of exposure to silver is through the ingestion of food and drinking-water. In ambient air levels are in the ng/m^3 range. Levels in drinking-water in the USA are in the range of 0.1-10 µg/litre for 50% of the population, >30 µg/litre for 10-30% of the population and >50 µg litre for 0.02% of the population. The reported levels of total dietary exposure (including drinking-water) in the USA vary from 4.5 to 88 µg/day. (ATSDR, 1990) For a 70 kg adult the range of 4.5-88 µg/day is equal to about -0.06-1.3 µg/kg bw/day. Considerable additional exposure is possible in occupational settings with inhalation as the main route of exposure.

MISCELLANEOUS DATA

- Absorption factors:
  · oral: absorption level depends on chemical form; 4% is best estimate for humans based on data for silver nitrate (US-EPA, 1991)
  · dermal: absorption level depends on chemical form; quantitative data only available for silver nitrate, 1% (ATSDR, 1990)
  · inhalation: no data available.
- Guideline values:

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[25]Calculation: an intravenous dose of 1 g is equivalent to 25 g orally(absorption factor 4%); 25 g over a lifetime of 70 years (25,550 days) is equivalent to 0.978 mg/day; for a 70 kg person the latter value is equal to 0.014 mg/kg bw/day (US-EPA, 1992).

[26]Because these concentrations exceed the Dutch guidline value of 10 µg/litre use of silver compounds as disinfectants for drinking-water is considered acceptable only for limited periods (i.e. drinkihg-water concentrations of in excess of 50 µg/litre are to be accepted for "short periods" only) (WNW, 1992).

· WHO-drinking-water guideline: no value was allocated because concentrations normally present in drinking-water do not present a health problem (WHO-WQG, 1992)
· EC-drinking-water MAC: 10 µg/litre (80 µg/litre for non-systematic use as disinfecting agent) (WNW, 1992)
· Dutch drinking-water regulation: 10 µg/litre (health based value) (WNW,1992)
· MAC-value (occupational exposure): 0.01 mg/m^3 (as Ag) for silver & water-soluble silver compounds (SZW, 1992)

CONCLUSION

TDI:	5 µg/kg bw
Background exposure (range):	0.06 - 1.3 µg/kg bw

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Profile compilation by: P.J.C.M. Janssen.
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Appendix 14: DODECYLBENZENE

RELEVANT ROUTE

Exposure routes considered relevant in present context: oral and dermal.

INTRODUCTION

Studies with purified dodecylbenzene (either branched or linear) are scarce. Recently, a few studies on the toxicity of various technical mixtures of linear alkylbenzenes have been published. The major constituents of these mixtures were linear decyl-(C_{10}) through tetradecyl-(C_{14}) benzenes, each mixture containing between 16 and 48% dodecylbenzene. As these compounds show considerable structural similarity, the results obtained with these mixtures are considered to be of relevance for the risk assessment of the individual (medium to long-chain) mono-alkylated benzenes, among which is dodecylbenzene.

TOXICITY

The IARC has not evaluated the carcinogenic potency of dodecylbenzene. Iversen (1989, 1990) has reported two 2-year skin painting studies in hairless mice with branched and linear alkylbenzene mixtures. From these studies it may be concluded that these alkylbenzene mixtures possess a weak activity to promote dermal tumours. Systemic effects were observed as well, but the studies do not permit a reliable estimation of the systemic exposure. There is inadequate evidence to consider dodecylbenzene a genotoxic compound (Iversen, 1989). Ingram and Grasso (1991) consider dodecylbenzene to be non-genotoxic. In a test battery, including bacterial and eukaryotic mutagenicity assays, several alkylbenzene mixtures did not show genotoxic potency (Robinson and Nair, 1992;). It is therefore appropriate to derive TDI- and TCA-values via a threshold approach.

A 2-generation reproduction toxicity study with a C_{10}/C_{12} linear alkylbenzene mixture in rats revealed parental toxicity at 500 mg/kg bw/day after 14 weeks dosing and decreased maternal post-natal weight gain and retarded growth of pups at 50 mg/kg bw/day. The NOAEL from this study is 5 mg/kg bw/day. In a separate study, the NOAEL for embryo/fetotoxicity or irreversible structural changes was determined at 125 mg/kg bw., i.e. above exposure levels which caused parental toxicity in the 2-generation experiment (Robinson and Schroeder, 1992).

Skyberg et al. (1990) have reported a study in which rats were exposed to oil-mists of branched C_{11}-/C_{12}-alkylbenzenes or linear C_9-/C_{10}-alkylbenzenes for 7 h/day and 5 days/w for 2 weeks. LOAELs of 83 mg/m^3 (C_{11}-/C_{12}) and 128 mg/m^3 (C_9-/C_{10}) were found, at which decreased body weight and increased relative lung and liver weights were observed. With C_{11}-/C_{12}-alkylbenzene histological changes in lungs and adrenals were found as well.

Dodecylbenzene (concentration not specified) is a skin irritant: a single application results in inflammation, hyperplasia and hyperkeratosis. Repeated skin applications may cause severe dermal irritation and ulceration. Other organs such as the respiratory tract, lungs, kidneys, blood, haematopoietic tissue and central nervous system are affected as well. Chronic exposure may lead to thymus atrophy and possibly impairment of the immune-system. There is no evidence for allergic reactions. (Iversen, 1990)

Owing to absence of more suitable toxicity data a TDI for alkylbenzenes can only be derived from the 2-generation study by Robinson and Schroeder (1992). In this study a NOAEL of 5 mg/kg bw/day has been found. Applying a total uncertainty factor of 1000 (10 for both intra- and interspecies extrapolation and 10 for the combination of limited data set and sub-chronic study) a human TDI of 5 µg/kg bw can be calculated.

BACKGROUND EXPOSURE

No data on environmental concentration or human population exposure are available. Exposure to alkylbenzenes may occur in occupational situations as these chemicals are used as insulation fluids in cable manufacturing and as raw materials in surfactant production (major use). Linear alkylbenzenes are more readily biodegradable than branched isomers (Iversen, 1989; Robinson and Nair, 1992). Exposure of the general population to dodecylbenzene is probably low. Based on these limited data it is assumed that general population background exposure is negligible.

MISCELLANEOUS DATA

- Absorption factors: no data available
- Guideline values: none available

CONCLUSION

TDI:	5 µg/kg bw/day
Background exposure (estimate):	0 µg/kg bw/day

April 1994,
RIVM-Toxicology Advisory Centre.

Profile compilation by: W.C. Mennes.
Profile review by: M.E. van Apeldoorn, P.J.C.M Janssen, J.E.M. van Koten-Vermeulen & F.X.R. van Leeuwen.

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Appendix 15:
HIGH-BOILING AROMATIC SOLVENTS
(aromatic solvents containing high concentrations of C_3- & C_4-alkylbenzenes)

INTRODUCTION & DEFINITION

Soil pollution with this group of mixtures is a relatively frequent phenomenon. This kind of mixtures is the residue that remains after evaporation of the more volatile constituents from gasoline or from other petroleum products. The residue is a mixture rich in C_3- and C_4-alkylated benzenes. The composition of these mixtures resembles that of high-boiling aromatic solvents derived from petroleum; the latter are commonly denoted as *high-boiling aromatic solvents* (HBAS), or as *high-flash aromatic naphta* (commercial products a.o. Solvesso 100 and Shellsol A). In IARC (1989) for this petroleum fraction a boiling-range of 155-210 °C is given. The composition of this kind of mixtures will vary to some degree from one case to another. In all mixtures several alkylbenzenes are present, of which those highest in concentration are the C_3- and C_4-alkylbenzenes, i.e. trimethylbenzenes, ethylmethylbenzenes, tetramethylbenzenes and methylpropylbenzenes[27]. In view of the diversity of individual compounds in the mixture the discussion below is focussed on the toxicological data for the HBAS mixtures (instead of the individual compounds). Data on individual compounds are very limited and were found not to give additional information.

RELEVANT ROUTE

Exposure route considered relevant in present context: oral, dermal, inhalational.

TOXICITY

No IARC evaluation of the possible carcinogenicity is available (the IARC evaluation of petroleum and petroleum products is considered not to be applicable to the present mixtures because the composition of the latter is not comparable to that of products evaluated by the IARC). For the high-boiling aromatic solvents (HBAS) no carcinogenicity studies are available. Such data are also lacking for the individual alkylbenzenes present in HBAS (trimethylbenzenes, tetramethylbenzenes and methylpropylbenzenes). The only known mutagenicity study with HBAS was an *in vivo* cytogenetic study in bone marrow in rats with inhalational dosing. The result of this study was negative (no effect). (IRDC, 1988a) Further data on mutagenicity/genotoxicity for HBAS or its constituents are lacking.

No oral toxicity data are available. Several subchronic inhalation studies have been performed with HBAS. The studies done in the period 1966-1980 were limited of design and/or were reported inadequately. Clark et al. (1989) performed a 12-month inhalation study (whole body exposure,

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[27]Examples of the composition of typical HBAS-mixtures:

- "C9 aromatic naphta" as given by IRDC (1988b): o-xylene 3.2% (w/w), i-propylbenzene 2.74%, n-propylbenzene 3.97%, 1-methyl-4-ethylbenzene 7.05%, 1-methyl-3-ethylbenzene 15.1%, 1-methyl-2-ethylbenzene 5.44%, 1,3,5-trimethylbenzene 8.37%, 1,2,4-trimethylbenzene 40.5%, 1,2,3-trimethylbenzene 6.18%, ≥C10's 6.19%
- alkyl aromatic fraction obtained from petroleum distillates as given by Nau et al. (1966): paraffins 20 mol %, cyclo paraffins 6 mol %, C9 alkyl benzenes 42 mol %, C10 alkyl benzenes 20 mol %, C11 alkyl benzenes 3 mol % (Remark: C9 & C10 alkyl benzenes as given by Nau et al. are C3 & C4 alkylbenzenes in the notation used in the present document.)

exposure for 6 h/day, 5 days/week) with HBAS (a 50/50 mixture of Solvesso 100 and Shellsol A). The results showed slight, transient growth retardation at 900 and 1800 mg/m^3 and increased weights of liver and kidneys at 1800 mg/m^3 as the only effects. The NOAEL in this study was 450 mg/m^3 (adjusted to continous exposure this equals 80 mg/m^3). (Clark et al., 1989) An inhalational 3-generation reproduction study in rats was done with HBAS using test concentations of about 0, 500, 2475 and 7400 mg/m^3 (whole body exposure, administration of vapour 6 h/day, 5 days/week or, during gestation and lactation only, 6 h/day, 7 days/week). Clinical signs, including staining of the fur, unkempt appearance, hair loss, salivation, occurred at 7400 mg/m^3. The staining of the fur was also present at 2475 mg/m^3. In females mortality was increased at 7400 mg/m^3. Decreased growth and food consumption was noted in parents and in offspring at 2475 and 7400 mg/m^3 in all generations; decreased growth was also seen at 500 mg/m^3 in F_2 parents and in F_3 offspring. The latter effects (produced in the F_2 generation, the only generation in which exposure already started when the animals were 3 weeks old) indicate that young animals are more sensitive to the toxic action of HBAS. Reproductive effects were limited to decreased fertility in F_1 males and decreased pup survival in F_1pups, both at 7400 mg/m^3 only. The LOAEL in this study is 500 mg/m^3 (no NOAEL). (IRDC, 1989) In a dermal 1-generation study in rats (0.05, 0.5 and 0.30 ml undiluted HBAS applied to intact skin 6h/day) no adverse systemic effects were seen (Chevron, 1984). An inhalational teratogenicity study was done in mice using test concentrations of 500, 2500 and 7500 mg/m^3 (whole body exposure, 6h/day from day 6 through 15 of gestation). Developmental toxicity was seen at 7500 mg/m^3 (postimplantation loss, reduced fetal weights, unossified sternebrae, reduced skull ossification) and 2500 mg/m^3 (reduced fetal weights). Maternal toxicity (growth retardation, increased incidence of mortality) was observed at 7500 mg/m^3. Increased incidence of malformations (cleft palate) was found at 7500 mg/m^3 only. The NOAEL for developmental toxicity was 500 mg/m^3. The NOAEL for maternal toxicity was 2500 mg/m^3. (IRDC, 1988b)

It is known that HBAS may produce skin effects after dermal contact. Quantititative information concerning the LOAEL or NOAEL for this kind of effect is lacking.

In the absence of oral data, derivation of a TDI for the oral route is only possible via route-to-route extrapolation using the inhalational studies. All inhalational tests involved whole body exposure using heat-generated vapour. In none of the reports the issue of possible oral uptake of test compound is addressed. Such oral uptake may be expected in case deposition of test compound in the exposure chamber and on the animals occurs. Based on the available information the possibility of inadvertent oral exposure in these studies cannot be ruled out.
The result of any inadvertent oral exposure in inhalational tests is a NOAEL/LOAEL that is lower than the real NOAEL/LOAEL (i.e. an overestimation of the toxicity).

The most appropriate basis for the calculation is the NOAEL of 450 mg/m^3 (duration-adjusted value 80 mg/m^3) from the 12-months rat inhalation study of Clark et al. (with the results of the other toxicity studies as supporting information). Using safety factor 100 a TCA of 800 µg/m^3 can be derived. From this TCA a provisional TDI (PTDI) of 170 µg/kg bw can be calculated via route-to-

route extrapolation[28]. This is a provisional value because it was derived via route-to-route calculation, a procedure involving considerable uncertainty.

BACKGROUND EXPOSURE

No quantitative data are available. Low levels of C_3- & C_4-alkylbenzenes are present in white spirit and related solvents. The general population may occasionally be exposed to these solvents during do-it-yourself activities. Chronic exposure to these solvents due to this use is estimated to be low for the general population. In view of this the chronic background exposure to C_3- & C_4-alkylbenzenes for general population is estimated to be negligible.

MISCELLANEOUS DATA

- Odour threshold (in air):
· no data available for HBAS
· values for individual compounds:
  trimethylbenzenes: 0.2-12 mg/m^3 (van Gemert & Nettenbrijer, 1977)
  tetramethylbenzenes: 0.0830-0.087 mg/m^3 (van Gemert & Nettenbrijer, 1977)

-Odour threshold (in water):
· no data available for HBAS
· values for individual compounds:
  trimethylbenzenes: 0.003-0.5 mg/kg (van Gemert & Nettenbrijer, 1977)
  tetramethylbenzenes: no data
- Absorption factors:
· inhalational: HBAS are absorbed well but no quantitative data are available

CONCLUSION

PTDI (extrapolated from the TCA):	170 µg/kg bw/day
Background exposure (estimate):	0 µg/kg bw/day
TCA:	800 µg/m^3

April 1994,
RIVM-Toxicology Advisory Centre.

Profile compilation by: P.J.C.M. Janssen.
Profile review by: M.E. van Apeldoorn, J.E.M. van Koten-Vermeulen, F.X.R. van Leeuwen & W.C. Mennes.

[28]Assumptions for the calculation: ventilation volume for 70 kg adult is 20 m^3 and absorption via inhalation is 75% of the absorption after oral uptake.

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Appendix 16: 1,1-DICHLOROETHANE

RELEVANT ROUTE

Exposure routes considered relevant in present context: oral and inhalational.

TOXICITY

The available set of toxicological data for this compound is relatively limited.
No IARC-classification is available for 1,1-dichloroethane. Data on carcinogenicity in humans are lacking. A carcinogenicity study in experimental animals with oral gavage dosing in Osborne-Mendel rats and B6C3F1 mice (two dose levels/species, duration 78 weeks followed by observation periods of 33 or 13 weeks) was carried out by the NCI in 1977. The validity of this study is limited by the high mortality that was observed in all groups including the controls. The results (slight increases in tumour incidences for mammary adenocarcinomas & haemangiosarcomas in female rats, hepatocellular carcinomas in male mice, and increased incidence uterine endometrial stromal polyps in female mice) suggest a possible carcinogenic action, but the evidence is not conclusive. The only other study available is a limited drinking-water study (by Klaunig et al., 1986) in male B6C3F1 mice (two dose levels, duration only 52 weeks). No increase in tumour incidence was found in this test. In the same study the tumour promoting activity of 1,1-dichloroethane was determined in separate groups of mice after initiation with diethylnitrosamine. No effect was found. (NCI, 1977; ATSDR, 1990; US-EPA, 1990; WHO-WQG, 1992) In US-EPA (1990) it is pointed out that in the 1978 NCI bioassay with the isomer 1,2-dichloroethane (a compound considered to be a genotoxic carcinogen based on animal biassays and positive results in genotoxicity tests), the observed increased tumour incidences included several of the above tumour types (haemangiosarcomas, mammary adenocarcinomas, endometrial stromal polyps).

Genotoxicity testing with 1,1-dichloroethane gave mixed results. The results of the Ames-tests, as given in ATSDR (1990), are conflicting: negative results (with & without metabolic activation) were found in two studies and a positive result (with & without metabolic activation) was seen in another study. Two of these studies, including the positive one, were reported incompletely. (ATSDR, 1990) The most recent Ames-test results, reported by Zeiger et al. (1992), again showed no effect (with & without metabolic activation). Test results in yeasts (two studies in *Saccharomyces cerevisiae*) were negative but it is remarked that they were reported inadequately (ATDSR, 1990). In a further *in vitro* test 1,1-dichloroethane increased (in a dose dependent manner) the viral DNA transformation frequency in Simian adenovirus-treated Syrian Hamster embryo cells (test done without metabolic activation) (ATSDR, 1990, WHO-WQG, 1992). *In vivo* genotoxicity studies have not been carried out with 1,1-dichloroethane. An *in vitro* DNA repair assay in hepatocytes from rats or mice showed a positive result (US-EPA, 1990). Covalent binding of 1,1-dichloroethane to DNA and proteins was found in liver, lung, stomach and kidney tissues in an *in vivo* study in male rats and male mice following single intraperitoneal dosing of radiolabelled compound (study by Colacci et al., 1985, as cited by ATSDR, 1990 & Lattanzi et al., 1988). In ATSDR (1990) It is concluded that this latter finding suggests that 1,1-dichloroethane may have a potential to produce mutation in a mammalian system.

In conclusion, there is limited evidence for a carcinogenic effect (i.e. the results of the flawed NCI study that suggest a carcinogenic effect but are not conclusive, in combination with the observation

that several of the tumour types were also found for the isomer 1,2-dichloroethane). From the genotoxicity tests an unequivocal conclusion cannot be drawn. The few positive results that were seen, indicate that interaction with DNA is possible under *in vitro* conditions but insufficient adequate tests were done to unequivocally determine the genotoxic potential of 1,1-dichloroethane. Thus, the carcinogenic and genotoxic potential of 1,1-dichloroethane can only be assessed incompletely. In the absence of further experimental data on carcinogenicity and genotoxicity, a threshold approach is tentatively chosen in the toxicological evaluation of 1,1-dichloroethane.

Adequate oral long-term or short-term animal studies that can be used to derive a TDI are lacking. Studies for the inhalational route are scarce. Recent long-term or short-term animal toxicity studies are lacking for this route also. A 13-weeks inhalation study in several animal species dates back to 1971. Groups of rats, guinea pigs, rabbits and cats (2-5 animals/sex/group) were exposed to 2050 mg/m^3 for 13 weeks (exposure to vapour, 6 hours/day, 5 days/week) followed by exposure to 4100 mg/m^3 (same treatment schedule) for 13 additional weeks. In rats, rabbits and guinea pigs no effect on growth, serum-urea, serum-creatinin, SGOT, SGPT was seen throughout the 24 weeks treatment period and at termination no effect on weights of and histopathology in liver and kidneys was seen. In cats no effect was seen up to week 13. In the period following the elevation of the dose level to 4100 mg/m^3, in this species growth was retarded and urea and creatinin in serum were increased; at termination histopathology showed renal tubular dilation and degeneration. (Hofmann et al., 1971) No reproduction studies are available. A teratogenicity study was done in rats with inhalational exposure to 15600 or 24600 mg/m^3 from days 6-19 of gestation (exposure for 7 hours/day). Embryotoxicity (i.e. retarded ossification of the sternebrae) was seen at 24600 mg/m^3 only; no effect on dams was found. (Schwetz et al., 1974 as cited in WHO-WQG, 1992 & ATSDR, 1990)

For the dermal exposure route no toxicity data are available.

Derivation of a TDI and TCA for 1,1-dichloroethane is made difficult by the very limited toxicological data base that is available. Despite the limitations in study outline, the study by Hofmann et al. (1971) is chosen as the basis for the evaluation. In this study cats were the most sensitive test species with renal effects at 4100 mg/m^3 (with no effects at this concentration in other test species). In cats at 2050 mg/m^3 no effect was observable. After adjustment of this latter dose concentration for exposure duration[29], this gives 366 mg/m^3 as the NOAEL for derivation of a provisional TCA (PTCA). Using an uncertainty factor of 1000 (standard factor 100 for inter- and intra-species extrapolation and an extra factor of 10 for limited duration of the study) yields a PTCA of 370 µg/m^3 (rounded value). This is a provisional value because of the limitations in the underlying data base. From this PTCA a PTDI (provisional TDI) can be calculated using route-to-route extrapolation[30]. This yields a value of 80 µg/kg bw/day.

BACKGROUND EXPOSURE

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[29]The concentration of 2050 mg/m^3 applied in the experiment for 6 hours/day for 5 days/week is divided by factor 168/30 to give the equivalent concentration for exposure for 24 hours/day, 7 days/week.

[30]Standard assumptions for route-to-route calculation are: adult body weight 70 kg, daily ventilation volume 20 m^3, bioavailability (≈absorption) via inhalational route is 75% of the bioavailability via the oral route.

Data specifically for the Netherlands are lacking. Measurements in ambient air (urban air and rural air) done in the USA yielded concentrations ranging from <5 ppt to 1.5 ppb (<0.02 - 6 µg/m^3). In one study the observed median concentration in air was 55 ppt (0.22 µg/m^3). (ATSDR, 1990) In drinking-water the compound is usually absent (in the USA it was detected in about 5% of 945 public water supplies, maximum concentration 4.2 µg/litre) (WHO-WQG, 1992). Inhalation from air probably is the primary route for background exposure of the general population in the USA. In ATSDR (1990) the average inhalation exposure for an individual in the USA is estimated at 4 µg/day (based on the median air level of 55 ppt and using a average daily ventilation volume of 20 m^3). On a kg/bw-basis this exposure level is equivalent to about 0.05 µg/kg bw/day. There being no data on background exposure to 1,1-dichloroethane in the Netherlands, this US estimate of 0.05 µg/kg bw/day is used.

MISCELLANEOUS DATA

- Absorption factors:
  inhalation: data indicate that absorption occurs (no quantitative data available)
  dermal: data indicate that absorption occurs (no quantitative data available)
- Odour threshold: reported values of 480 & 800 mg/m^3 (ATSDR, 1990)
- Guideline values:
  MAC-value (limit value for occupational exposure): 410 mg/m^3 (SZW, 1992)
  WHO-drinking-water guideline value: no limit was set due to the lack of suitable toxicity data (WHO-WQG, 1992)

CONCLUSION

PTDI (extrapolated from the PTCA):	80 µg/kg bw/day
Background exposure:	0.05 µg/kg bw/day
PTCA:	370 µg/m^3

March 1995,
RIVM-Toxicology Advisory Centre.

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Appendix 17: 1,2-DICHLOROETHENE (cis- & trans-)

RELEVANT ROUTE

Exposure routes considered relevant in present context: oral and inhalational.

TOXICITY

This compound has not been evaluated by the IARC. No carcinogenicity data are available for 1,2-dichloroethene. In genotoxicity studies the results for the cis-isomer in several test systems were different from those for the trans-isomer. *In vitro* studies carried out with 1,2-dichloroethene (tests with & without activation, for gene mutations in bacteria, gene mutations & conversions in yeasts and chromosome aberrations in mammalian cells) were negative for the cis-isomer and the trans-isomer. For cis-1,2-dichloroethene an *in vivo* cytogenetic study (bone marrow) in mice with i.p. application, was positive as were host-mediated assays in mice (test organisms *Salm. typhimurium* & *S. cerevisiae*) with this isomer. In the same test sytems trans-1,2-dichloroethene showed no effect. (results as summarised in ATSDR, 1994) In a further *in vitro* test by Önfelt (1987) an increased number of aneuploid V79 Chinese hamster cells was observed following treatment with trans-1,2-dichloroethene. The cis-isomer was not tested in this study.
In conclusion, based on these data cis-1,2-dichloroethene is considered to be a genotoxic agent *in vivo*, producing gene mutations and chromosome aberrations. For the induction of this kind of genotoxic effect no threshold can be assumed to exist. The trans-isomer was negative in the same test systems, indicating that this isomer does not exert a similar action. The trans-isomer induced aneuploidy in an *in vitro* test. For cis-1,2-dichloroethene a similar study is not available. For the induction of this kind of genotoxic effect (i.e. numerical chromosome aberrations) a threshold is assumed to exist. A quantitative evaluation of the aneuploidic effect of (trans)-1,2-dichloroethene is not possible without additional experimental data.

No chronic toxicity studies (oral or inhalational) with 1,2-dichloroethene have been performed. Several oral semichronic studies are available, the results of which have been evaluated by US-EPA (1989), WHO-WQG (1992) and ATSDR (1994). A 90-days' drinking-water study with trans-1,2-dichloroethene in mice by Barnes et al. (1985) showed increased SAP in males at 175 & 387 mg/kg bw/day and decreased relative thymus weight at 224 and 452 mg/kg bw/day in female mice. This study included an evaluation for immunotoxicity (reported by Shopp et al., 1985) at day 4/5 after cessation of exposure, the result of which showed a decrease in spleen antibody-forming cells in male mice (at 175 & 387 mg/kg bw) and enhanced spleen cell response to lipopolysaccharide in females (at 452 mg/kg bw only). The NOAEL from this study is 17 mg/kg bw/day. (Barnes et al., 1985 & Shopp et al., 1985, as cited in WHO-WQG, 1992 & ATSDR, 1994) In the study by Hayes et al. (1987, as cited in WHO-WQG, 1992) the same protocol was used for trans-1,2-dichloroethene in rats, showing decreased kidney weights (without concomitant histological changes) in females as the only detectable change (at 1257 & 2809 mg/kg bw/day, absent at 352 mg/kg bw/day). A further oral semichronic study is the gavage study with cis-1,2-dichloroethene by McCauley et al. (1990). The observed effects in this study were decreased body weight (in males at 97 & 290 mg/kg bw), decreased Ht (in males at 97 & 290 mg/kg bw) and decreased Hb (in both sexes at 290 mg/kg bw).

The NOAEL in this study was 32 mg/kg bw/day. (McCauley et al., 1990, as cited in ATDSR, 1994)

Only for the trans-isomer some inhalational data are available. In a limited semichronic study (Freundt et al., 1977), rats were exposed to 780 mg/m^3 for 8 hours/day, 5 days/week during periods of 8 or 16 weeks. Effects were seen in livers (slight to severe fatty degeneration of the liver lobules and Kupfer cells) and lungs (pulmonary hyperaemia, alveolar septal distention and pneumonic infiltration). This study does not yield a NOAEL (LOAEL 780 mg/m^3, after adjustment for exposure duration[31] this equals 185 mg/m^3). A further inhalation study is the teratogenicity study by Hurtt et al. (1993) also with trans-1,2-dichloroethene. In this study maternal body weights and food consumption were decreased at 24000 and 48000 mg/m^3 (exposure for 6 hours/day, day 7-16 of gestation) and foetal body weights were decreased at 48000 mg/m^3 only. The NOAEL in this study was 8000 mg/m^3. (Hurtt et al., 1993, as cited in ATSDR, 1994)

Dermal studies with 1,2-dichlorethene are virtually lacking. The only test available showed the undiluted compound to be irritating to the skin. No further information is available for this route.

A point to be decided in the toxicological evaluation of 1,2-dichloroethene is whether or not the two isomers should be treated as separate compounds. In principle for such a decision the data on metabolism and toxic effects should be compared on all points where this is possible. In the present instance the clear-cut difference in genotoxic effect alone is considered to provide sufficient reason for a separate evaluation of the isomers.

For the trans-isomer the TDI is based on the NOAEL of 17 mg/kg bw/day from the Barnes et al. mouse drinking-water study. Using an uncertainty factor of 1000 (10x10 for interspecies and intraspecies differences and an extra factor 10 for limited duration of the study), the TDI for trans-1,2-dichloroethene is 17 µg/kg bw/day[32]. The available inhalational toxicity data for trans-1,2-dichloroethene are considered too limited to provide a sufficient basis for the derivation of a (provisional) TCA; nevertheless they can be of use as supporting information. Using route-to-route extrapolation[33], from the TDI of 17 µg/kg bw/day a provisional TCA (PTCA) of 80 µg/m^3 can be calculated. This value is *provisional* because it was derived via route-to-route calculation, a procedure involving considerable uncertainty. The ratio between the PTCA and the LOAEL of 185 mg/m^3 from the Freundt et al. study is about 2300; this margin is sufficiently wide to consider the PTCA acceptable in the light of this LOAEL.

For the cis-isomer the NOAEL of 32 mg/kg bw/day from the study by McCauley et al. is used. Based on this level and using an uncertainty factor of 5000 (10x10 for interspecies and intraspecies differences, extra factor 10 for limited duration of the study and an extra factor of 5 for severity of

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[31]The concentration of 780 mg/m^3 applied in the experiment for 8 hours/day for 5 days/week is divided by factor 168/40 to give the equivalent concentration for exposure for 24 hours/day, 7 days/week.

[32]The same derivation (same NOAEL, same TDI) is given by the WHO-WQG (1992) as applicable to both isomers (note: the WHO-WQG evaluation did not include the McCauley et al. study).

[33]Standard assumptions for the route-to-route calculation are: adult body weight 70 kg, daily ventilation volume 20 m^3, bioavailability (≈absorption) via the inhalational route is 75% of the bioavailability via the oral route.

endpoint, i.e. no-threshold genotoxic action), a TDI of 6 µg/kg bw/day (rounded value) is calculated. Using route-to-route extrapolation, from the TDI of 6 µg/kg bw/day a provisional TCA (PTCA) of 30 µg/m^3 (rounded value) can be calculated. This value is provisional because it was derived via route-to-route calculation.

BACKGROUND EXPOSURE

Data specifically for the Netherlands are lacking. No data specified for isomer are available. In the USA 1,2-dichloroethene has been detected in urban air (data reported in 1983) with average concentrations of 0.052 to 0.30 µg/m^3. Also in the USA for drinking-water prepared from surface water the compound usually is not detectable. In drinking-water (USA) prepared from groundwater the compound was found to be detectable in ≤8% of the systems with maximum concentration of 2 to 120 µg/litre. (ATSDR, 1994; WHO-WQG, 1992) Based on these data general population background exposure may be estimated at 10 µg/day for an adult (intakes of 4 µg/day via drinking-water and 6 µg/day via air). Expressed per kg bw this gives a value of about 0.15 µg/kg bw/day. This figure is used for both isomers.

MISCELLANEOUS DATA[34]

- Absorption factors:
  inhalation: several studies indicate rapid absorption, absorption percentage for humans determined in 1936: 72-75% (sum of cis & trans)(ATSDR, 1994)
  dermal: no data
- Odour threshold: 67 mg/m^3 (17 ppm) (sum of cis & trans)(Amoore & Hautala, 1983)
- Guideline values:
  MAC-value (limit value for occupational exposure): 792 mg/m^3 (200 ppm)(sum of cis & trans)(SZW, 1992)
  WHO-drinking-water guideline value: 50 µg/litre (sum of cis & trans)(WHO-WQG, 1992)

CONCLUSION

trans-1,2-dichloroethene:

TDI:	17 µg/kg bw/day
Background exposure:	0.15 µg/kg bw/day
PTCA (extrapolated from the TDI):	80 µg/m^3

cis-1,2-dichloroethene:

TDI:	6 µg/kg bw/day
Background exposure:	0.15 µg/kg bw/day
PTCA (extrapolated from the TDI):	30 µg/m^3

[34]All data refer to the sum of the isomers (no separate data for the isomers are available).

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RIVM-Toxicology Advisory Centre.

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Adviser: J.M. de Stoppelaar (aneuploidy test).

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Appendix 18: 1,1,1-TRICHLOROETHANE

RELEVANT ROUTE

Exposure routes considered relevant in present context: oral, inhalational & dermal.

TOXICITY

The IARC, in its 1987 evaluation, placed 1,1,1-trichloroethane in Group 3 (not classifiable) based on inadequate data in humans and *inadequate evidence* in experimental animals. This evaluation was based on those studies only that were included in the 1979 IARC monograph. The studies in question were the oral (gavage) NCI study from 1977 in rats and mice and an inhalation experiment in rats. These two studies, indeed, do not provide adequate evidence: in the NCI study survival was too low in rats and also in mice, and the rat inhalation study was inadequately reported. The results of these experiments were negative (tumour incidences not increased). (IARC, 1979; ATSDR, 1993) Of a similar oral carcinogenicity study in rats and mice, carried out by the NTP in 1981-1983, no official NTP-report has been issued. In WHO-WQG (1992) it is stated that this experiment was judged to be inadequate for carcinogenicity assessment (because of high mortality in female rats; grounds for inadequacy of results in mice and male rats not given). A limited oral carcinogencity study in rats, carried out by Maltoni et al. (1986), showed an increase in total leukemias (13 versus 4 in controls) at the only dose level tested (500 mg/kg bw/day) (result as cited in ATSDR, 1993). The limitations in study outline reduce the value of this result for carcinogenicity evaluation. A further carcinogenicity experiment in rats and mice involved inhalational exposure to 0, 820, 2700 or 8100 mg/m^3 for 6 hours/day, 5 days/week for 2 years. No effect was found (study by Quast et al., 1988, result as reported by IPCS, 1992 & ATSDR, 1993). Thus, in the only adequate study that is available (the 2-year inhalation experiment in rats & mice), no evidence of carcinogenicity was found.

Genotoxicity data comprise studies in bacteria, fungi, mammalian cells *in vitro*, insects and mammalians *in vivo*. The available studies were summarised by Knaap (1988) and ATSDR (1993). The results were largely negative. Results in the Ames-test were negative with the exception of one study. Tests in yeasts and fungi (several endpoints, including aneuploidy) showed no effect. The single test available for chromosome aberrations in mammalian cells *in vitro* was positive. In a test in Drosophila for sex-linked recessive lethal mutations, no effect was found. *In vivo* studies in mice (micronucleus test in erythrocytes & bone marrow) also showed no effect. In a study for binding of the compound to DNA in mouse liver a very low level (compared to several related compounds) of DNA-adduct formation was found. In both reviews it is pointed out that the positive results may have been produced by mutagenic stabilisers in the test samples and not by 1,1,1-trichloroethane itself. (Knaap, 1988; ATSDR, 1993) A further negative result was found in an additional test (not included in the two reviews) for interchromosomal mitotic recombinations in Drosophila (Vogel & Nivard, 1993).
Based on these data, a firm conclusion regarding the genotoxic potential cannot be drawn. Nevertheless it can be stated that the existing evidence for a genotoxic action by 1,1,1-trichlorethane is very weak.

Based on the above evidence, 1,1,1-trichloroethane is not classified as a genotoxic carcinogen.

Given this conclusion, in the toxicological evaluation a threshold approach is considered appropriate.

In most of the toxicological studies carried out with 1,1,1-trichloroethane the compound was tested using the inhalational dosing route. Relatively few oral studies have been carried out, none of which is adequate for derivation of an NOAEL that could serve as the basis for a TDI. Studies in humans and animals have shown 1,1,1-trichloroethane to be a neurotoxic agent. In humans acute inhalational exposures have led to dizziness, lightheadedness and loss of coordination at concentrations of ≥2700 mg/m^3; impaired performance in psychophysiological function tests has been observed at ≥945 mg/m^3. (ATSDR, 1993) In a recent study in occupationally exposed subjects neurologic effects have also been reported after long-term inhalational exposure to 1,1,1-trichloroethane. The exposure levels were not measured in this study (only the qualitative indication is given that the levels were "high"). (Kelefant et al., 1994) A long-term inhalational NOAEL in humans for neurological effects is not available. In animal studies with acute exposure, behavioural changes (effects in neuromuscular tests of learned behaviour) have been observed at ≥5400 mg/m^3 (results of several studies as incompletely summarized in ATSDR, 1993). In such a study of recent date (effect on the central vestibular system in rats), an effect was found at ≥1900 mg/m^3 (Niklassen et al., 1993). Animal studies of longer duration are relevant for further information on the neurotoxic potential. In the short-term inhalation neurotoxicity study in rats by Mattsson et al. (1993) no histological changes in brain and spinal cord were observed. The only observed change in this study was a slightly smaller forelimb grip performance at the highest exposure concentration of 10800 mg/m^3 (exposure for 6 hours/day, 5 days/week). At the next-lower concentration of 3400 mg/m^3 no change was observable (corrected for exposure duration[35] this concentration equals 610 mg/m^3). (Matsson et al., 1993) In the standard-protocol long-term inhalation toxicity study in rats by Quast et al. (1988) no histological changes in brain and spinal cord were observed (test concentrations up to 8100 mg/m^3, exposure for 6 hours/day, 5 days/week). In studies in gerbils with continuous inhalational exposure (24 hours/day) for 3 months, however, effects indicating neurotoxicity were observed. In the gerbil study by Rosengren et al. (1985), at 4 months after cessation of the 3-months' exposure period, increased concentrations of fibrillary acidic protein (GFA) were found in the sensorimotor cerebral cortex at 5000 and 1130 mg/m^3; this effect was absent at the lowest test concentration of 380 mg/m^3 (Rosengren et al., 1985 as cited in ATSDR, 1993 & IPCS, 1992). The presence of increased GFA protein levels indicates the formation of astroglial fibrils, which is a response to central nervous system (brain) damage. In an additional study also in gerbils, decreased DNA content (decrease slight but significant) in several brain regions was observed at 4 months after a 3-months' continuous exposure to 380 mg/m^3 (the only dose level tested) (Karlsson et al., 1987; ATSDR, 1993). The significance of this finding is uncertain[36]. In the light of the findings on neurotoxicity in rats and humans, i.e. adverse effects that were observable at high concentrations only, combined with the uncertain significance of the decreased brain-region DNA content in gerbils (that was observed at 380 mg/m^3 only, this

[35]The concentration of 3400 mg/m^3 applied in the experiment for 6 hours/day for 5 days/week is divided by factor 168/30 to give the equivalent concentration for exposure for 24 hours/day, 7 days/week.

[36]ATSDR (1993): the decreased DNA-content in posterior cerebellar hemisphere, anterior cerebellar vermis and hippocampus "could be due to decreased cell density , possibly due to cell loss either by cell death or inhibition of nonneuronal cell acquisition in these areas, but the significance of these changes is uncertain. These methods of ascertaining physical damage to the brain have not been applied to other species."

parameter not having been determined at the higher test concentrations used by Rosengren et al., 1985), the respons at the concentration of 380 mg/m^3 is considered a marginal effect. Thus, 380 mg/m^3 is used as NOAEL for derivation of a TCA.

The data on reproductive and developmental toxicity were reviewed in ATSDR (1993). Data on reproductive toxicity are limited (relatively few studies, each with limitations in study design). The results of these tests do not indicate that the compound is toxic to the reproductive system. Several epidemiological studies, focussed on the detection of a possible relationship between maternal exposure to 1,1,1-trichloroethane and adverse pregnancy outcome, were negative. Teratogenicity tests were performed in mice, rats and rabbits. In rats and rabbits foetoxicity (decreased weights, minor skeletal & visceral abnormalities) with or without maternal effects were observed at concentrations of ≥11340 mg/m^3 (no-effect results observed at 4700 and 5400 mg/m^3). (results as cited in ATSDR, 1993)

Skin irritation is reported for human subjects after exposure to undiluted compound. Probably (based on animal irritation studies), the compound is not a strong dermal irritant. A case of contact dermatitis (humans) has been reported. Controlled studies on sensibilisation are lacking. (ATSDR, 1993) Systemic toxicity may occur after dermal exposure. This is shown by the occurrence of severe neurological effects (peripheral sensory neuropathy) after repeated dermal exposure to high concentrations (occupational hand/arm exposure during use as degreasing agent) (House et al., 1994). A dermal NOAEL for this kind of effect is not available.

Because adequate oral data are lacking the derivation of the TDI is based on the semichronic inhalational NOAEL in gerbils of 380 mg/m^3 (continuous exposure) using route-to-route extrapolation[37]. The uncertainty factor used is 1000 (10x10 for interspecies and intraspecies differences and an extra factor 10 for limited duration of the study). This yields a TCA of 380 µg/m^3 and a provisional TDI (PTDI) of 80 µg/kg bw/day. The TDI is a provisional value because it was derived via route-to-route calculation, a procedure involving considerable uncertainty.

BACKGROUND EXPOSURE

The available information has been reviewed by Slooff et al., (1991). Few data on exposure levels in the Netherlands are available. 1,1,1-Trichloroethane has been detected in foodstuffs and drinking-water. For Germany (year 1982) the oral daily exposure was estimated at 3.8 µg/day. Reported average concentrations in ambient outdoor air in the Netherlands vary from 0.3 to 2.3 µg/m^3 (measurements from 1981, 1986 & 1988). For indoor air, exposure levels may temporarily be considerably higher as a result of use of household products containing 1,1,1-trichloroethane. (Slooff et al., 1991) The latter applications are not considered for an estimate of background exposure. Based on a daily oral exposure level of 3.8 µg and a maximum average concentration in air of 2.3 µg/m^3 the background exposure for an adult with a daily ventilation volume of 20 m^3, is estimated at 0.7 µg/kg bw/day.

MISCELLANEOUS DATA

- Absorption factors:

[37]Standard assumptions for this calculation are: adult body weight 70 kg, adult ventilation volume 20 m^3, bioavailability (≈absorption) via the inhalational route is 0.75 times the bioavailability via the oral route.

oral: no data for humans; in rats rapid & complete absorption, reported range of absorption precentages 88-98% (ATSDR, 1993)
inhalation: in humans after single exposure average lung retention 25-30%; in case of physical exercise absorption is higher than this (no quantitative indication given); in rats after single exposure 50-80% (ATSDR, 1993)
dermal: for humans no data, in rats exposure to undiluted compound under occlusion absorption about 30% (ATSDR, 1993)

- Odour threshold: 5.3 mg/m^3 (Don, 1986)
- Guideline values:
  MAC-value (limit value for occupational exposure): 1080 mg/m^3 (200 ppm) (SZW, 1992)
  WHO-drinking-water guideline value: 2 mg/litre (provisional value) (WHO, 1993)

CONCLUSION

PTDI (extrapolated from the TCA)	: 80 µg/kg bw/day
Background exposure	: 0.7 µg/kg bw/day
TCA	: 380 µg/m^3

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Appendix 19: FORMALDEHYDE

RELEVANT ROUTE

Exposure route considered relevant in the present context: inhalational and oral (standard).

TOXICITY

Owing to its chemical reactivity, formaldehyde exerts its noxious action primarily at the site of body-entry.

inhalational exposure

In a life-time inhalation study with rats (exposure 6 h/d and 5 d/wk to 0, 2400, 7600 and 17200 $\mu g/m^3$), formaldehyde has been found to produce a high incidence (67%) of squamous cell carcinomas in the nasal cavity at 17200 $\mu g/m^3$. This incidence showed an extremely steep dose-response relationship with no such carcinomas at 2400 $\mu g/m^3$ but at all exposure levels an exposure-related increase in polyploid adenomas of the nasal mucosa and other changes of the nasal mucosa were found. (Swenberg et al., 1980, Kerns et al., 1983) Similar nasal tumours were also reported in other rat studies (IPCS, 1989). The induction of squamous cell carcinomas could not be established in mice (Swenberg et al., 1980, Kerns et al., 1983).
IARC (1987) has stated that, based on several epidemiological studies, the evidence for possible involvement of formaldehyde is strongest for nasal and nasopharyngeal cancers. The IARC (1987) has classified formaldehyde as a class 2A carcinogen, based on *limited evidence in humans* and *sufficient evidence in experimental animals.*

In a number of studies using various bacterial and mammalian *in vitro* systems, it has been demonstrated that formaldehyde possesses weak mutagenic activity (Slooff et al., 1992). *In vivo* tests, however, gave inconclusive results, although in rats DNA damage (viz. DNA-protein cross-linking) could be determined in the nasal respiratory mucosa. In several studies with (occupationally exposed) humans, contradictive results on chromosomal aberrations or sister chromatid exchanges in peripheral lymphocytes have been reported (IARC, 1987).

The Gezondheidsraad (Dutch Health Council) (1984) has argued that the carcinogenicity of formaldehyde is only observed at comparatively high exposure levels which also result in cytotoxic effects on the nasal mucosa. Thus, the threshold value for cytotoxicity is also the threshold for carcinogenicity. Therefore guideline values should be based upon avoidance of exposure levels which lead to irritation of the nasal mucosa (cf. WGD, 1987).

In short-term inhalation studies rats, hamsters and monkeys have been exposed to formaldehyde in air in concentrations of 240 $\mu g/m^3$ and higher for periods of 13 to 26 weeks (various papers, listed in Slooff et al., 1992). In monkeys, the LOAEL for metaplasia of the mucosa of the nasal turbinates was 1200 $\mu g/m^3$ (22 h/d, 7 d/week, 26 weeks; Rusch et al., 1983). However, at 240 $\mu g/m^3$ increased incidence of nasal discharge was observed. This effect was also seen at higher dose levels. A similar LOAEL for nasal irritation was found in (probably short-term) studies in humans, in which 240 $\mu g/m^3$ caused transient nasal, throat and eye irritation, whereas at 120 $\mu g/m^3$ no such effects were found (Rader, 1974 and AIHA, 1968, cited by the Gezondheidsraad, 1984). From this

NOAEL (120 µg/m^3) an ambient air limit value (TCA) of 1.2 µg/m^3 can be calculated, taking into account an uncertainty factor of 100 for inter-individual variability and extrapolation from short- to long-term exposure.

oral exposure

Formaldehyde is not considered a carcinogenic compound after oral exposure (WHO, 1993). In two 2-year drinking-water studies with rats, papillary epithelial hyperplasia, hyperkeratosis and focal ulceration in the forestomach, but no treatment-related tumours were reported with dose levels up to 300 mg/kg bw/day (Til et al.1988, Tobe et al., 1989; cited in IPCS, 1989). The NOAEL from these studies is 15 mg/kg bw/day (Til et al., cited by Slooff et al., 1992). From this NOAEL, Slooff et al. (1992) have derived a TDI of 0.15 mg/kg bw, applying an uncertainty factor of 100 (to account for inter- and intraspecies differences).

Formaldehyde is a recognized skin, respiratory tract and systemic sensitizer. For these effects no quantitative data are available, however. (IPCS, 1989)

BACKGROUND EXPOSURE

Formaldehyde is a widely spread naturally occurring substance. It is also released from various human activities including the (incomplete) combustion of fossil fuels, the industrial production of formaldehyde from methanol and its use in resin- and plastic production and as a disinfectant. Guicherit and Schulting (1985) have estimated the daily outdoor intake of formaldehyde to be about 2 µg/kg bw/day. Indoor sources (among others) are smoking, cooking, open fireplaces, paints and particle board (IPCS, 1989). Reliable data on total background exposue are not available at present (Slooff et al., 1992).

MISCELLANEOUS DATA

- Odour threshold (in air): 60-1200 µg/m^3; median 100 µg/m^3; EC_{10}: 25 µg/m^3 (Slooff et al., 1992)
- Absorption factors:
  - inhalational: 100% (Slooff et al., 1992)
  - oral: 100% (Slooff et al., 1992)
  - dermal: 0.1 - 5 % (Slooff et al., 1992)
- Guideline values:
  - MAC-value (limit for occupational exposure): 1200 µg/m^3 (twa; 15 min) (WGD, 1987)
  - WHO drinking-water quality guideline: 900 µg/l (WHO, 1993)
  - Acute health-based recommendations (Gezondheidsraad, 1984):
    120 µg/m^3 (30 min average, ceiling value)
    30 µg/m^3 (24 h average; 95-percentile)
    40 µg/m^3 (24 h average; 98-percentile)

CONCLUSION

TDI:	150 µg/kg bw/day
Background exposure:	unknown (no reliable data available)
TCA:	1.2 µg/m^3

April, 1994
RIVM-Toxicology Advisory Centre.

Profile compiled by: W.C. Mennes.
Profile review by: M.E. van Apeldoorn, P.J.C.M Janssen, J.E.M. van Koten-Vermeulen & F.X.R. van Leeuwen.

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Appendix 20: METHANOL

RELEVANT ROUTE

Exposure routes considered relevant in present context: oral, dermal, inhalational

TOXICITY

No IARC evaluation of the possible carcinogenicity of methanol is available. Based on the few available animal experiments as presented by Marcus (1993), no conclusion on carcinogenicity can be drawn. The results of the mutagenicity studies are conflicting in part. Mostly negative results have been obtained (test sytems: Ames-test -/+ activation, yeast -/+ activation, micronucleus test in mice, SCE-test *in vitro*) but some studies showed a positive result at high concentrations (test systems: yeasts + activation, mouse micronucleus test, mouse bone marrow *in vivo* cytogenetic test). (Calabrese & Kenyon, 1991; Marcus, 1993) In conclusion, the available evidence concerning carcinogenicity and genotoxicity of methanol is limited and no definitive conclusion can be reached. For the time being it is assumed that methanol is not a genotoxic compound and that a threshold approach is appropriate.

For methanol toxicity data in humans are available. In the literature a large number of cases of acute oral intoxications with methanol in humans is reported. Acute effects appear after a symptomless period of approximately 1 day and consist of acidosis with superimposed ocular toxicity. Interindividual differences in susceptibility as to acute toxicity are marked. Acute methanol toxicity in humans is primarily attributable to its metabolite formate. (Kavet & Nauss, 1990, Marcus, 1993) From these case histories it is, however, not possible to derive an NOAEL or LOAEL. The available inhalational studies in workers (with exposure periods up to 30 years) also were too limited for derivation of a NOAEL or LOAEL (Marcus, 1993).

Toxicity experiments have been performed in rats, mice and monkeys. In a recent 90-days oral study in rats the tested dose levels were 0, 100, 500 and 2500 mg/kg bw/day. The result showed decreased brain weights, increased activities of SAP and ASAT and increased liver weights (without concomitant histological liver changes) at 2500 mg/kg bw. The NOAEL in this study was 500 mg/kg bw/day. (US-EPA, 1991) Several inhalational animal toxicity experiments have been performed. Kavet & Nauss (1990) and Marcus (1993) give the results of a battery of inhalational studies, carried out in Japan. This included chronic toxicity studies in mice, rats and monkeys and a 2-generation reproduction study in rats, each of which studies had dose levels of 13.3, 133 and 1330 mg/m^3 (exposure 20 h/day, probably 7 days/week). Only limited information is availble on the test results. It is stated that no chronic or reproductive effects were present at ≤133 mg/m^3. The test battery also included a teratogenicity study in rats. The results of this test showed maternal toxicity, marked embryo/foetotoxicity and "visceral terata" at 6650 mg/m^3 (administered 8 h/day from day 3 through 14 of gestation) with no effects at ≤1330 mg/m^3. (Kavet & Nauss, 1990; Marcus ,1993) A further inhalational teratogenicity study in rats was done by Nelson et al. (1985). The tested dose levels were 6650, 13300 and 26600 mg/m^3 (exposure 7 h/day from gestation day 1 through 19 or, at the highest concentration, 7 through 15). Reduced foetal weights were seen in the medium- and high-dose groups. At the same two concentrations the incidences of malformations were increased (most commonly observed: exencephaly, encephalocele, urinary tract or cardiovascular defects).

Slightly unsteady gait at 26600 mg/m^3 was the only maternal effect observed. The NOAEL from this study is 6650 mg/m^3. (Nelson et al., 1985; Calabrese & Kenyon, 1991; Marcus, 1993)

On the basis of animal tests methanol has been characterised as being mildly to moderately irritating to eyes and skin. There are no data on the concentration-response relation for these effects (this applies both for the inhalational and dermal exposure routes).

The US-EPA (1991) has derived an RfD (≈TDI) of 0.5 mg/kg bw/day from the NOAEL of 500 mg/kg bw/day from the 90-days oral study in rats. The safety factor used was 1000 incorporating an extra factor of 10 (above the usual 100) to compensate for the use of semichronic NOAEL instead of a chronic NOAEL. (US-EPA, 1991)
Derivation of a TCA for the inhalation route is based on the NOAEL of 133 mg/m^3 (exposure 20 h/day, 7 days/week) for chronic and reproduction effects as found in the animal studies carried out in Japan. After adjustment to continuous exposure (24/day) and applying standard safety factor 100 the resulting TCA is 1100 µg/m^3.[38]

BACKGROUND EXPOSURE

Total exposure of the general population to methanol in the Netherlands has not been determined. Nevertheless the available information indicates high levels of background exposure. Methanol occurs naturally in drinking-water, surface water, fruits, vegetables, grains, seeds, and foliage. In fresh fruits and vegetables it is present as free alcohol, as methyl esters of fatty acids, or as methoxyl groups on polysaccharides. For concentrations in fruit juices a range from 12 to 640 mg/litre is given with an average of 140 mg/litre. In fermented distilled beverages even higher levels are possible (for some neutral spirits a concentration as high as 1.5 g/litre has been reported). Another important source for human exposure is the formation of methanol in the normal metabolism in the body; the quantity thus formed appears to be unknown. (Marcus, 1993) Ambient concentrations of methanol in the troposphere ranging from 0.001 to 0.13 mg/m^3 are reported with natural sources including forest fires, insects, microbes, animal wastes, and volcanoes. Formate, the toxic metabolite of methanol is also present in the daily diet and is formed in the normal metabolism in humans; the total body burden of formate is not known. (Marcus, 1993) An additional source of dietary exposure to methanol is the consumption of beverages sweetened with aspartame[39]. When aspartame is consumed at the ADI-level of 40 mg/kg bw, this entails a methanol uptake of 4 mg/kg bw. Actual aspartame consumption figures for Great Britain (no data available for the Netherlands), published in 1990, show that the real intake levels in the years preceding 1990 had an upper 97.5%-percentile value of only 3 mg/kg/bw/day. (ISA, 1990) The resulting methanol intake is 0.3 mg/kg bw/day.
Given the fact that vegetables, fruits and fruit juices are major food items in the daily diet (for some quantitative data see for instance VBV, 1993 and US-EPA, 1989), the above data roughly indicate that the total background exposure to methanol generally will equal or even exceed the TDI. In the

[38]TCA-derivation from the TDI/RfD using route-to-route extrapolation yields a value in the same order of magnitude, thus supporting the TCA value given above.

[39]Aspartame consists of the amino acids phenylalanine and aspartic acid linked by a methanol moiety; upon ingestion aspartame readily breaks down to these three constituting moieties.

absence of firm figures on intake levels, background exposure is put at 0.5 mg/kg bw/day (i.e. the TDI value).

MISCELLANEOUS DATA

- Odour threshold (in air): 130-330 mg/m^3 (ATSDR, 1992)
- Odour threshold (in water): 10-1600 mg/kg (van Gemert & Nettenbrijer, 1977)
- Absorption factors:
· oral: methanol is readily absorbed (no percentages given) (Marcus, 1993)
· dermal: methanol is readily absorbed (no percentages given) (Marcus, 1993)
· inhalational: retention 45-92% (Marcus, 1993)
- Guideline values:
· MAC-value (occupational exposure): 260 mg/m^3 with notation that uptake via skin occurs (SZW, 1992)

CONCLUSION

TDI:	500 µg/kg bw/day[40]
Background exposure:	500 µg/kg bw/day[29]
TCA:	1100 µg/m^3

April 1994,
RIVM-Toxicology Advisory Centre.

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Appendix 21: 1-BUTANOL

RELEVANT ROUTE

Exposure route considered relevant in present context: oral and inhalational.

TOXICITY

No IARC evaluation of 1-butanol is available. From inadequate long-term studies with rats no conclusions could be drawn about the possible carcinogenicity of 1-butanol (IPCS, 1987). 1-Butanol was not mutagenic in the Ames test. *In vitro*, it did not induce chromosomal aberrations in human lymphocytes and sister chromatid exchanges in chinese hamster cells (IPCS, 1987; US-EPA, 1993). 1-Butanol is capable of causing disturbances in spindle function in cultured Chinese hamster V79 lung cells, resulting in aneuploidization and nondisjunction (Calabrese & Kenyon, 1991). Based on these data a threshold approach is warranted.

Limited toxicological studies are available. Oral LD_{50}-values range from 700 to 2100 mg/kg bw 1-Butanol is irritating to skin and eye. In a 13 week gavage study with rats (30/sex/group) 1-butanol was administered by gavage at doses of 0, 30, 125 or 500 mg/kg bw/day for 13 weeks. A NOAEL of 125 mg/kg bw was found, at 500 mg/kg bw ataxia and hypoactivity were observed. (IPCS, 1987)

In a teratogenicity study in rats maternal toxicity (mortality, decreased body weight and food consumption) and foetotoxicity were observed at 18000 and 24000 mg/m^3 (exposure 7h/day, day 1-19 of gestation). The NOAEL was 10500 mg/m^3. (Nelson et al., 1989)

Scarce information is available about the effects of 1-butanol in humans after inhalational or oral exposure (IPCS, 1987). Exposures ≥150 mg/m^3 1-butanol may result in headache, drowsiness and narcosis (≥300 mg/m^3) (Calabrese & Kenyon, 1991). The occurence of vertigo after severe and prolonged exposure to vapour mixtures of 1-butanol and isobutanol has been reported (IPCS, 1987). No health effects were reported in workers after occupational exposure for 10 years to concentrations in air ≤307.8 mg/m^3 (US-EPA, 1993).

Based on the NOAEL of 125 mg/kg bw/day in the short-term study in rats and making use of an uncertainty factor of 1000 (10 for intraspecies, 10 for interspecies and 10 for semi-chronic to chronic exposure extrapolation) a TDI of 125 µg/kg bw/day has been established (US-EPA, 1993).

An inhalational NOAEL for direct derivation of a TCA is lacking[41]. Using route-to-route extrapolation (assumptions: ventilation volume for a 70 kg adult 20 m^3, bioavailability via inhalation is 75% of the oral bioavailability) from the TDI a provisional TCA (PTCA) of 550 µg/m^3 can be calculated. This is a provisional value because it was derived via route-to-route calculation, a procedure involving considerable uncertainty.

BACKGROUND EXPOSURE

[41] US-EPA (1993) contains a loose statement on a 4-months rat inhalation study: a NOAEL of 0.8 mg/m^3 for reversible changes in blood cholinesterse activity and increased thyroid activity is given. Since this study was available as an abstract only (with no further information on tested dose levels and test design) and no reference is given, the validity of these data cannot be ascertained. Consequently the NOAEL was not used to calculate the TCA.

1-Butanol has been used as an intermediate in pharmaceutical manufacture, as a solvent and as a flavouring agent in butter, cream, fruit and whisky (Handler, 1992; IPCS, 1987).
No data are available concerning total exposure of the general population, but different exposure sources are known (no concentrations given) (IPCS, 1987). 1-Butanol occurs naturally as a result of carbohydrate fermentation in alcoholic beverages. It has been detected in the volatiles of hops, jack fruit, heat-treated milks, cheese and cooked rice. 1-Butanol is released from PVC linoleum plasticized with poly(dibutyl maleate) and from hardened parquet lacquer. No quantitative data on 1-butanol levels in the general environment are avaliable but, because 1-butanol is readily biodegradable, substantial concentrations are only likely to occur locally in the case of major spillages. (IPCS, 1987) Industrial emissions studies indicated that 616 tonnes of 1-butanol were released into the air over 1 year in the Netherlands (IPCS, 1987). These data suggest that background exposure occurs with the diet as the most important source of exposure. In the absence of quantitative information no estimate is possible.

MISCELLANEOUS DATA

- Odour threshold: 0.158-42 mg/m^3 (detection) 0.15-285 mg/m^3 (recognition) (van Gemert & Nettenbreijer, 1977)
- Taste threshold: 0.5-2.77 mg/kg water (van Gemert & Nettenbreijer, 1977)
- Absorption factors:
· oral : 1-butanol is readily absorbed (no percentages given) (IPCS, 1987)
· dermal: 8.8 µg/min per cm^2 (dog skin) (IPCS, 1987)
. inhalational: 37-47% in human volunteers (IPCS, 1987)
- Guideline values:
· MAC-value (limit for occupational exposure): 150 mg/m^3 (SZW, 1992)

CONCLUSION

TDI:	125 µg/kg bw/day
Background exposure:	unknown
PTCA (extrapolated from the TDI):	550 µg/m^3

April 1994,
RIVM-Toxicologie Advisory Centre.

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Appendix 22: 1-BUTYLACETATE

RELEVANT ROUTE

Exposure route considered relevant in the present context: oral and inhalational.

TOXICITY

1-Butylacetate is readily hydrolysed in the wall of the respiratory tract (Dahl et al., 1987), intestine or liver (Longland et al., 1977) yielding 1-butanol and acetic acid, which are easily metabolized to carbon dioxide (Zaleski, 1992).

The IARC did not evaluate the carcinogenicity of 1-butylacetate.
The results of an Ames-test and a chromosome abberation test indicate the absence of a genotoxic potential (Ishidate et al., 1984 and Schimizu et al., 1985; both cited in Zaleski, 1992).
Carcinogenicity data are not available. For the determination of TDI- and TCA-values a threshold approach is considered to be appropriate.

Effects resulting from exposure to butylacetate are irritation of the upper respiratory tract, skin and eye and, at high exposure levels, drowsiness, nausea and narcosis (Zaleski, 1992). For mice, rats and rabbits, oral LD_{50} values are in the range of 7 to 14 g/kg bw (Zaleski, 1992). No repeated dose studies with 1-butylacetate could be found from which human TDI- of TCA-values can be calculated.

Based on acute inhalatory toxicity studies with animals and experiments with humans, in which eye and mucous membrane irritation was found after exposure to c. 1000 $\mu g/m^3$ 1-butylacetate in the air, the American Conference of Governmental Industrial Hygienists (ACGIH, 1992) has recommended for 1-butylacetate a TLV-TWA of 100 mg/m^3. From this value a TCA-value of 1 mg/m^3 for the general population can be derived, using a factor 100 to extrapolate from occupational exposure to lifetime exposure for the general population[42]. From this TCA-value a provisional TDI-value (PTDI) of 0.2 mg/kg bw can be calculated.[43],[44] The latter value is provisional because it was derived via route-to-route calculation, a procedure involving considerable uncertainty.

BACKGROUND EXPOSURE

Butylacetates are used as solvents in various industrial processes among which are the production

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[42]Taking into account: 24/8 for working-day to full day length, 7/5 for working-week to full week length, 100/40 for working-lifetime to entire lifetime and an uncertainty factor of 10 for extrapolation from workers to entire population.

[43]Taking into account a ventilation volume of 20 m^3/day, a body weight of 70 kg and an uptake efficiency relative to the oral route, of 75%.

[44]The SCF established a temporary ADI of 6 mg/kg bw/day for butyl acatate in 1981 (SCF, 1981, 1991); this ADI was allocated to be used exclusively for evaluating uses of butylacetate as extraction solvent in the food industry. In its report the SCF does not summarize the study results on which this ADI is based; probably unpublished studies were used. Because of this lack of adequate information on the data file used by the SCF, the temporary ADI of the SCF is not adopted here.

of artifical leather, photographic films, plastic and safety glass, and in consumer products such as nail-polish (and removers), paints, food flavourings and adhesives. Due to their high volatility, inhalational exposue is likely to occur, especially in occupational situations.
Butylacetates are also naturally occuring flavours in food such as apples, bananas, baked potatoes and roasted nuts (Sandmeyer and Kirwin, 1981; Howard et al., 1991). Exposure of the general population is most likely to occur via inhalation, particularly in industrialized areas. Ambient air concentrations of butylacetate amounted 3 $\mu g/m^3$ near an industrial site in Newark (Howard, 1991). This would result in an estimated daily exposure of about 840 ng/kg bw.

MISCELLANEOUS DATA

- Odour thresholds (identification):
  36-104 mg/m^3 (ACGIH, 1986)
  0.044-96 mg/m^3 (van Gemert and Nettenbreijer, 1977)
- Absorption factors:
· oral: probably high[45]
· inhalational: 50% (ACGIH, 1992)
· dermal: 0.71 $\mu l/cm^2/h$ (diffusion rate constant; Dugard and Scott, 1986, cited in Anonymous, 1989)
- Guideline values:
· MAC-value (limit for occupational exposure): 710 mg/m^3 (SZW, 1992)

CONCLUSION

PTDI (extrapolated from the TCA):	200 µg/kg bw/day
Background exposure (estimate):	1 µg/kg bw/day[46]
TCA:	1000 $\mu g/m^3$

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RIVM-Toxicology Advisory Centre.

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[45](Partial) hydrolysis occurs at the site of first body contact. Systemic availability of butylacetate as such after oral or inhalational exposure may be low.

[46]In occupational situations exposure may be considerably above this level.

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Appendix 23: METHYL tert-BUTYL ETHER (MTBE)

RELEVANT ROUTE

Exposure routes considered relevant in present context: oral, inhalational.

TOXICITY

No IARC evaluation of the possible carcinogenicity of MTBE is available. Maltoni et al. (1992) and Duffy et al. (1992) reported carcinogenicity studies in rats and mice to be in progress (in Italy and the USA, respectively); the results of these studies have not yet been published.
All data on mutagenicity come from unpublished reports from experiments carried out for industry in the USA. The results are outlined briefly by Von Burg (1992), Conaway et al. (1985) and Duffy et al. (1992). *In vitro* studies in bacteria (Ames-test) and mammalian cells (chromosome aberrations, SCEs) showed no effect. The L5178Y mouse lymphoma assay with metabolic activation was positive (no effect without activation). For two *in vivo* studies, i.e. a cytogenetic study in rats and a sex-linked recessive lethal test in *Drosophila*, a negative (no effect) result is reported. (Conaway et al., 1985; Duffy et al., 1992; Von Burg, 1992)

Based on these results a threshold approach in the toxicological evaluation is chosen.

The US-EPA has evaluated the inhalational toxicity data on MTBE in 1993 to derive an RfC (chronic inhalational limit value ≈ TCA). In a subchronic inhalation study in rats, including a neurotoxicity evaluation, test concentrations of 0, 2884, 14421 and 28843 mg/m^3 were used (exposure for 6 h/day, 5 days/week). At the medium- and the high-dose levels the following effects were present: slight growth retardation, increased brain length, increased weights of liver, kidneys and adrenals. Corticosterone levels in blood serum were increased at the high-dose level only. The neurotoxicity evaluation (Functional Observation Battery) showed no consistent effects. The NOAEL in this study was 2884 mg/m^3 (duration-adjusted value 515 mg/m^3). (US-EPA, 1993) For a 2-generation reproduction study an NOAEL of 1442 mg/m^3 and an LOAEL of 10816 mg/m^3 are given, with reduced body weights in F_1 and F_2 pups during the lactation period as the critical effect. The duration of daily/weekly exposure in this study is not given. (US-EPA, 1993) The result of a teratogenicity study in rats and mice, not included in the US-EPA review, showed no adverse effects at concentations up to 9000 mg/m^3 (highest concentration tested) (Conaway et al., 1985). Von Burg (1992) summarizes the results of two further teratogenicity studies carried out in mice and rabbits, respectively. In mice maternal toxicity (not specified), a decrease in viable implanatations, decreased fetal weights and increased incidence of malformations (cleft palate) were seen at 14421 and 28843 mg/m^3 with 3600 mg/m^3 as NOAEL (daily exposure duration not reported). For the rabbit study the NOAEL is stated to be 3600 mg/m^3, also without further information being given. (Von Burg, 1992)

Robinson et al. (1990) carried out a 90-days oral study in rats with dose levels of 0, 100, 300, 900 and 1200 mg/kg bw/day, administered by gavage. Profound anesthesia following dosing (recovered in about 2 h) was seen at 1200 mg/kg. At the same dose level decreased body weights were observed. No other effects were found. The NOAEL in this study was 900 mg/kg bw/day. (Robinson et al., 1990)

From the duration-adjusted inhalational NOAEL of 515 mg/m^3 the US-EPA calculated a TCA of 500 µg/m^3 (rounded value) using a safety factor of 1000 (the standard factor of 100 multiplied by an extra factor of 10 for limited duration of the study and data base deficiencies). (US-EPA, 1993)
Based on the oral NOAEL of 900 mg/kg bw/day a TDI of 900 µg/kg bw can be established by application of a safety factor of 1000 (the standard factor 100 and an extra factor of 10 to compensate for the limited duration of the study).

BACKGROUND EXPOSURE

In the USA MTBE is used as a petrol octane improver with use concentrations as high as 8 to 11% (with an application to the US-EPA to increase the use level to 15%). The main source of general population exposure as a result of this use is inhalation of petrol vapour containing MTBE at service stations. (Von Burg, 1992; Conaway et al, 1985) It is not known whether MTBE is used as octane improver in petrol in the Netherlands also. An additional source of individual human exposure is the therapeutical use of MTBE to dissolve gallstones.
In conclusion, the general population background exposure is unknown.

MISCELLANEOUS DATA

- Odour threshold (in air): 87-434 µg/m^3 (Von Burg, 1992)
- Absorption factors: no data available
- Guideline values: no data available

CONCLUSION

TDI:	900 µg/kg bw/day
Background exposure:	unknown
TCA:	500 µg/m^3

March 1994
RIVM-Toxicology Advisory Centre.

Profile compilation by: P.J.C.M. Janssen.
Profile review by: M.E. van Apeldoorn, J.E.M. van Koten-Vermeulen, F.X.R. van Leeuwen & W.C. Mennes.

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Appendix 24: ACRYLONITRILE

RELEVANT ROUTE

Exposure routes considered to be relevant in present context: oral and inhalational.

TOXICITY

Extensive data on the possible carcinogenicity of acrylonitrile are available. In male and female rats, oral administration and inhalation exposure resulted in an increased incidence of tumours of the CNS (astrocytomas), tongue, forestomach, small intestine, mammary glands and Zymbal gland (Besemer et al., 1984; IARC, 1979; US-EPA, 1993). Eight of the 12 available epidemiological studies, investigating the relationship between acrylonitrile exposure by inhalation and cancer, did not indicate a carcinogenic risk (Besemer et al., 1984). The remaining epidemiological studies indicate a higher risk of lung cancer and in one study (O'Berg, 1985) also an increased incidence of prostate cancer was observed. Very recently a retrospective cohort study was carried out in the Netherlands. In workers exposed to acrylonitrile for at least 6 months between 1956 and 1979, overall, no indications were found for a carcinogenic effect in the period upto 1988 (Swaen et al., 1992).

Acrylonitrile was categorized in Group 2A *(probably carcinogenic to humans)* by IARC (1987a) on the basis of the *sufficient evidence* of its carcinogenicity in experimental animals and the *limited evidence* of its carcinogenicity in humans.

Acrylonitrile is mutagenic to bacteria (with metabolic activation) and mammalian cells *in vitro*. Acrylonitrile did not induce aneuploidy but did induce chromosomal aberrations, micronuclei and sister chromatid exchanges in mammalian cells *in vitro*. In one study with rat cells *in vitro* no chromosomal aberrations or sister chromatid exchanges were induced. In *in vivo* assays detecting dominant lethal mutations, chromosomal aberrations or micronuclei, no effects of acrylonitrile were found. Acrylonitrile did not enhance the frequency of chromosomal aberrations in lymphocytes of exposed workers. *In vitro* and *in vivo* in mammalian cells studies revealed irriversible binding to DNA. (Besemer et al., 1984; IARC, 1987b)

The Dutch Health council (1985) concluded that a conservative estimation of the health risk is necessary since it cannot be excluded that genotoxicity plays a role in the carcinogenic effects observed in animal experiments. Thus a non-threshold approach is chosen in the evaluation of acrylonitrile.

For the inhalational route excess cancer risks were calculated by Besemer et al. (1984) by lineair extrapolation based on the inhalation study in rats of Quast et al. (1980a). For lifetime exposure, concentrations of 3.7, 0.37 and 0.037 $\mu g/m^3$ entail estimated excess risks of $1:10^4$, $1:10^5$ and $1:10^6$, respectively (Besemer et al., 1984). The Dutch Health Council (1985) in its appraisal of the Besemer et al. evaluation has established values of 10, 1 and 0.1 $\mu g/m^3$ for estimated excess risks of $1:10^4$, $1:10^5$ and $1:10^6$, respectively. Since in the present context a relatively high excess lifetime risk of 1 in 10^4 is accepted, in theory it is possible that a threshold evaluation based on the other endpoints than carcinogenicity yields an acceptable concentration that is lower than the concentration derived based on the carcinogenic endpoint. For acrylonitrile such a parallel threshold evaluation is possible based on a chronic inhalational LOAEL of 7.7 mg/m^3 (duration adjusted) with inflammation of nasal respiratory epithelium and hyperplasia of mucous secreting cells as the critical

effect (Quast et al., 1980a; US-EPA, 1993). Application of a safety factor 1000 (incorporating an extra factor 10 to accomodate for the use of a LOAEL instead of a NOAEL) yields a concentration close to 10 $\mu g/m^3$ (the $1:10^4$ excess lifetime cancer risk level as calculated by the Dutch Health Council).
For the oral route US-EPA (1993) calculated extra tumour risks of $1:10^4$, $1:10^5$, and $1:10^6$ for lifetime exposure to acrylonitrile of 0.1, 0.01 and 0.001 µg/kg bw/day, respectively (extrapolation method: linearized multistage procedure, extra risk). The risk estimate was based on data from 3 rat studies in which acrylonitrile was administered in drinking-water for 18 to 24 months (Biodynamics 1980a,b; Quast et al., 1980b). The overall tumour risk was based on the number of animals having a statistically significant increase in tumour incidence at any site. A parallel threshold evaluation (based on other endpoints than carcinogenicity) yields an acceptable intake level that is clearly in excess of the oral lifetime risks as calculated by the US-EPA.

BACKGROUND EXPOSURE

Acrylonitrile is used extensively in the production of acrylic and modacrylic fibres, resins and rubbers and as a chemical intermediate. The compound has also been used as a fumigant for stored grain.
No measurable acrylonitrile concentrations have been detected in ambient air. Concentrations of acrylonitrile in "source-dominated areas" (i.e. 5 km of a chemical factory or waste site to acrylonitrile factory) range from 0.1 - 325 $\mu g/m^3$, respectively (ATSDR, 1990).
Measurements of the total dietary intake of acrylonitrile have not been made in the Netherlands. It is estimated that the intake of acrylonitrile from food is about 2 µg/day, corresponding to 0.028 µg/kg b.w. for a 70 kg adult person. The intake from drinking-water probably can be neglected. (Besemer et al., 1984)

MISCELLANEOUS DATA

- Odour threshold: 3.4 mg/m^3 (detection); 47 mg/m^3 (recognition) (van Gemert & Nettenbreijer, 1977)
- Taste threshold (in water): 18 mg/kg water (detection) (Van Gemert & Nettenbreijer, 1977)
- Absorption factors:
  - oral: 85 - 100% (Besemer et al., 1984)
  - dermal: 0.6 $mg/cm^2/h$ (Besemer et al., 1984)
  - inhalational: upto 90% with 50% resorption (Besemer et al., 1984)
- Guideline values:
  - MAC-value (limit for occupational exposure) : 9 mg/m^3 (SZW,1992)

CONCLUSION

Oral excess lifetime tumour risk 1:10^4:	0.1 µg/kg bw/day
Background exposure:	0.028 µg/kg bw/day[47]
Inhalational excess lifetime tumour risk 1:10^4:	10 µg/m^3

April 1994,
RIVM-Toxicology Advisory Centre.

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Profile review by: M.E. van Apeldoorn, P.J.C.M. Janssen, F.X.R. van Leeuwen & W.C. Mennes.

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Appendix 25: (MONO)ETHYLENE GLYCOL

RELEVANT ROUTE

Ethylene glycol is rapidly degraded in environmental media; it does not persist or bioaccumulate (ATSDR, 1993).
Exposure route considered relevant in present context: oral

TOXICITY

Ethylene glycol was not evaluated by IARC.
Long-term oral studies in mice and rats did not reveal any carcinogenic activity of ethylene glycol (De Pass et al., 1986; NTP, 1993).
No induction of gene-mutations was caused by ethylene glycol in *in vitro* studies with bacteria or yeast cells. In mammalian cells no gene mutations, chromosomal aberrations or SCE's were induced. An *in vivo* dominant lethal study in rats did not reveal a genotoxic activity of ethylene glycol. (ATSDR, 1993; NTP, 1993) Based on the foregoing data it can be concluded that ethylene glycol does not possess genotoxic properties.

Based on the data given above a threshold extrapolation method for the evaluation of the risk for humans after oral exposure, is used.

The target organ for ethylene glycol toxicity is the kidney and to a lesser extent the liver.
The most appropriate study to derive a NOAEL is a two-year oral toxicity/carcinogenicity study in rats by DePass et al. (1986). In this study F344 rats (130/sex/group) received 0, 40, 200 or 1000 mg ethylene glycol/kg bw via their diet. Mortality rate rose in males on 1000 mg/kg bw, with all animals dying by 475 days. Primary cause of death was oxalate nephrosis. Other effects noted were: reduced growth, increased water intake, increased blood urea nitrogen and creatinine levels, changes in hematological parameters, increased urinary volume, reduced urinary specific gravity and pH. Increased kidney weights and urinary calcium oxalate crystals were seen in males as well as females at 1000 mg/kg bw. In addition uric acid crystals were seen in urine of females at 1000 mg/kg bw. At 200 mg/kg bw an increased incidence and amount of calcium oxalate crystals in urine of both males and females was seen. Histopathology revealed tubular cell hyperplasia, tubular dilation, peritubular nephritis, parathyroid hyperplasia and generalized soft tissue mineralization in male rats at 1000 mg/kg bw. Fatty change of the liver was seen in female rats at 200 and 1000 mg/kg bw. The NOAEL for rats in this study is 40 mg/kg bw.[48]
Mice receiving 0, 40, 200 or 1000 mg/kg bw for 2 years via the diet, did not show clinical signs or gross or microscopic evidence for toxicity. Water intake and clinical pathologic parameters were not measured (DePass et al., 1986).
In reproduction and teratogenicity studies in mice and rats, oral administration of ethylene glycol caused decreased litter size, reduced pup birth weight, reduced pup survival or fetal craniofacal

[48]US-EPA (1989) also evaluated the study of Depass et al. (1986) and established a NOAEL of 200 mg/kg bw. Apparently EPA did not consider an increased incidence and amount of oxalate crystals in the urine, observed at 200 mg/kg b.w., as an effect.

and/or axial skeletal anomalies. In general mice exhibited more severe reproductive abnormalities at lower doses than did rats. In rabbits no evidence of teratogenicity or embryotoxicity was observed. The NOAEL for developmental toxicity, including teratogenicity, in CD-1 mice was 150 mg/kg bw. (NTP, 1993; Tyl et al., 1989)

Based on the NOAEL of 40 mg/kg bw in the two-year dietary study in rats and using a safety factor of 100 a TDI of 400 µg/kg bw can be established. As ethylene glycol and diethylene glycol are structurally closely related and as for both compounds an increased excretion of oxalate in the urine is the most sensitive parameter, it is proposed to apply the TDI to both ethylene glycol and diethylene glycol.

BACKGROUND EXPOSURE

Ethylene glycol is used as antifreeze in cooling and heating systems, as an industrial humectant, as an ingredient of electrolytic condensers, as solvent in paint and plastic industries, and in the production of ink.
No data on consumers' exposure are available, but it is assumed to be negligible.

MISCELLANEOUS DATA

- Guideline values:
· MAC-value (limit for occupational exposure): 125 mg/m^3 (SZW, 1992)

CONCLUSION

TDI (sum of mono- and di-ethylene glycol):	400 µg/kg bw/day
Background exposure (estimate):	0 µg/kg bw/day

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RIVM-Toxicology Advisory Centre.

Profile compilation by: M.E. van Apeldoorn.
Profile review by: P.J.C.M. Janssen, J.E.M. van Koten-Vermeulen, F.X.R. van Leeuwen & W.C. Mennes.

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Last revised 09/01/89.

Appendix 26: DI-ETHYLENE GLYCOL

RELEVANT ROUTE

Exposure route considered relevant in present context: oral.

TOXICITY

Diethylene glycol was not evaluated by IARC.

Long-term oral studies in rats revealed an increased incidence of bladder tumours at dietary concentrations of 2% and higher. However the tumours (benign papillomas with some showing varying degrees of malignancy) appeared to be the result of mechanical irritation due to the presence of bladder stones or other irritating factors. (Weil et al., 1965; WHO, 1980) Diethylene glycol did not induce gene mutations in bacteria or yeast cells. In mammalian cells *in vitro* no genotoxic activity of diethylene glycol was observed and an *in vivo* micronucleus assay with oral dosing did also not reveal a genotoxic activity. (BIBRA, 1993; Krug et al., 1986; Pfeiffer & Dunkelberg, 1980; Zeiger et al., 1987) Based on the foregoing data it can be concluded that diethylene glycol does not possess genotoxic properties.

Based on the data given above a threshold extrapolation method for the evaluation of the risk for man after oral exposure is used.

Diethylene glycol produces renal damage, calcium oxalate stones and liver damage (to a lesser extent) in a number of species, including man. In the rat bladder tumours, associated with stone formation, were seen at dietary levels equal ≥2%. (WHO, 1980)

The most appropriate study to derive a NOAEL is a 225-day dietary study in rats. The animals received 0, 0.085, 0.17, 0.4 or 2.0% diethylene glycol in their diet. At 2% effects on kidney function, increased water intake and signs of blood concentration were observed in males. In males as well as females relative kidney weights were increased after 225 days and urine contained oxalate crystals. Evidence of kidney damage was seen in one male rat. Dietary levels of 0.4% (ca. 300 mg/kg bw) produced oxalate crystals in the urine, particularly in females, and mild defects in kidney function in males, but no histological damage. Only a marginal increase in oxalate levels in male rats was seen at 0.17% in the diet (ca. 100 mg/kg bw). No effects were observed at 0.085% in the diet (ca. 50 mg/kg bw). (Hesser, 1986)

In teratogenicity studies in mice and rats diethylene glycol caused mild developmental toxicity at maternally toxic doses. The no-effect level for developmental toxicity was 5000 mg/kg bw/day and 1.0 ml/kg bw/day in mice and rats, respectively.

In a F_1-generation reproduction study in mice with a continuous breeding protocol diethylene glycol affected fertility and reproductive performance at high doses (3.5% in drinking-water equal to 6130 mg/kg bw). The concentration of 1.75% in drinking-water (equal to 3060 mg/kg bw) was a no-effect-level for reproductive effects in this study. (Williams et al., 1990)

Based on the NOAEL of 50 mg/kg bw in rats and using a safety factor of 100 a TDI of 500 µg/kg bw can be established. This figure is almost equal to the TDI for ethylene glycol. As ethylene glycol and diethylene glycol are structurally closely related and as for both compounds an increased

excretion of oxalate in the urine is the most sensitive parameter, it is proposed to apply the TDI of 400 µg/kg b.w for ethylene glycol, to both ethylene glycol and diethylene glycol.

BACKGROUND EXPOSURE

Diethylene glycol is used as permanent antifreeze, a constituent of brake fluids, lubricants, mould release agents, as a softening agent for textiles, as a plasticizer for cork, in paper packaging, as an intermediate for explosives production and in the production of resins, morpholine, diethylene glycol ethers and esters.
No data on consumers' exposure are available, but it is assumed to be negligible.

MISCELLANEOUS DATA

- Absorption factors:
- dermal absorption: in rat skin 3% of the dose/day after application of 50 mg/12 cm^2 of shaven skin (Mathews et al., 1991)

CONCLUSION

TDI(sum of mono- and di-ethylene glycol):	400 µg/kg bw/day
Background exposure (estimate):	0 µg/kg bw/day

April, 1994
RIVM-Toxicology Advisory Centre.

Profile compilation by: M.E. van Apeldoorn.
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