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Maximum Permissible Risk Levels for Human Intake of Soil Contaminants: Fourth Series of Compounds

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ABBREVIATIONS

ADI	Acceptable Daily Intake
ATSDR	Agency for Toxic Substances and Disease Registry (USA)
DECOS	Dutch Expert Committee on Occupational Standards
ECOTOX SCC	Ecotoxicological Serious Soil Contamination Concentration
FAO	Food and Agriculture Organisation (UN)
HUM-TOX SCC	Human-Toxicological Serious Soil Contamination Concentration
IARC	International Agency for Research on Cancer (WHO)
IPCS	International Programme of Chemical Safety (WHO)
IRIS	Integrated Risk Information System (US-EPA)
JECFA	Joint Expert Committee on Food Additives (FAO/WHO)
LOAEL	Lowest Observed Adverse Effect Level
MPR	Maximum Permissible Risk (in Dutch: MTR)
MTR	Maximum Toelaatbaar Risico
NOAEL	No Observed Adverse Effect Level
PTCA	Provisional Tolerable Concentration in Air
PTDI	Provisional Tolerable Daily Intake
RfD	Reference Dose
RIVM	Rijksinstituut voor Volksgezondheid en Milieu (National Institute of Public Health and the Environment)
TCA	Tolerable Concentration in Air
TDI	Tolerable Daily Intake
TSPC	Technical Soil Protection Committee (in Dutch: Technische Commissie Bodembescherming)
UF	Uncertainty Factor
US-EPA	United States Environmental Protection Agency
WHO	World Health Organization
WHO-WQG	World Health Organization Water Quality Guidelines

SUMMARY

This report contains the human-toxicological risk assessment work done at the Centre for Substances and Risk Assessment in the scope of the RIVM project on soil intervention values for soil clean-up, in the years 1996 and 1997. The method for derivation of the Maximum Permissible Risk (in Dutch: Maximum Toelaatbaar Risico) as described in the RIVM report by Janssen & Speijers (1997) was used for a batch of 13 chemical compounds (or groups of compounds). Within the project these compounds are referred to as the *fourth series* of chemicals (the compounds dealt with in the previous RIVM report by Vermeire et al. (1991) are series one and those reported in Janssen et al. (1995) are series two and three). For each compound that is evaluated, Maximum Permissible Risk levels are derived for the oral route; inhalation values are derived where relevant (i.e. in case substantial inhalation exposure is expected). The fourth series of compounds consists of the compounds listed in the table below (the classification in groups in this table is the same classification as that used for the first series of compounds). For some compounds no MPR value could be derived due to lack of data. In many instances only *provisional* values could be derived because of limitations in the available toxicological evidence (the items in the table marked with the letter "P").

	Maximum Permissible Risk for oral exposure (µg/kg body weight)	Maximum Permissible Risk for inhalation exposure (µg/m3)
Metals		
vanadium	2 (P)*	1
selenium	5	no value needed
tellurium	2 (P)	idem
thallium	0.2 (P)	idem
tin, (inorganic)	2000	idem
Aromatic compounds		
monochloroanilines	0.9	4 (P)
dichloroanilines	no value derivable	no value derivable
trichloroanilines	idem	idem
tetrachloroanilines	idem	idem
pentachloroaniline	idem	idem
4-chloro-2-methylphenol	20 (P)	90 (P)
4-chloro-3-methylphenol	300 (P)	1300 (P)
Chlorinated hydrocarbons		
1,1,2-trichloroethane	4 (P)	17 (P)
1,2-dichloropropane	70	12
1,3-dichloropropane	50	12 (P)
1,1-dichloroethene	3 (P)	14
Pesticides		
MCPA	1.5 (P)	7 (P)
Miscellaneous compounds		
tribromomethane	20	100 (P)
isopropanol	1000	2200
ethylacetate	900	4200 (P)
butylacetate	200 (P)	1000

* P = Provisional value

SAMENVATTING

Dit rapport geeft een overzicht van het humaan-toxicologische beoordelingswerk uitgevoerd bij het Centrum voor Stoffen en Risicobeoordeling in de jaren 1996 en 1997 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 RIVM-rapport van Janssen & Speijers (1997) werd toegepast voor een set van 13 chemische stoffen (of groepen van stoffen). Binnen het project worden deze stoffen aangeduid als de *vierde tranche* stoffen (de in het eerdere RIVM-rapport van Vermeire et al. (1991) behandelde stoffen vormden de eerste tranche en de in Janssen et al. (1995) gerapporteerde stoffen vormen de tranches twee en drie). Voor elke te beoordelen stof worden MTR-niveaus afgeleid voor de orale route; inhalatoire waarden worden afgeleid waar dat relevant is (d.w.z. voor stoffen waarvoor substantiële inhalatoire expositie te verwachten is). De vierde tranche bestaat uit de stoffen zoals die opgevoerd worden in benedenstaande tabel (de indeling van stoffen in deze tabel is conform de indeling die werd aangehouden bij de eerdere tranches). Voor sommige stoffen kon geen MTR worden afgeleid wegens het ontbreken van toxicologische gegevens. In veel gevallen konden alleen voorlopige waarden worden afgeleid omdat het beschikbare pakket aan toxicologische gegevens voor de desbetreffende stoffen incompleet is (de items in de tabel die gemerkt zijn met de letter "P" van *provisional*).

	Maximum Toelaatbaar Risico voor orale expositie (µg/kg lichaamsgewicht)	Maximum Toelaatbaar Risico voor inhalatoire expositie (µg/m3)
Metalen		
vanadium	2 (P)*	1
selenium	5	geen grenswaarde nodig
tellurium	2 (P)	idem
thallium	0.2 (P)	idem
tin, (anorganisch)	2000	idem
Aromatische verbindingen		
monochlooranilines	0.9	4 (P)
dichlooranilines	geen grenswaarde afleidbaar	geen grenswaarde afleidbaar
trichlooranilines	idem	idem
tetrachlooranilines	idem	idem
pentachlooraniline	idem	idem
4-chloor-2-methylfenol	20 (P)	90 (P)
4-chloor-3-methylfenol	300 (P)	1300 (P)
Gechloreerde koolwaterstoffen		
1,1,2-trichloorethaan	4 (P)	17 (P)
1,2-dichloorpropaan	70	12
1,3-dichloorpropaan	50	12 (P)
1,1-dichlooretheen	3 (P)	14
Bestrijdingsmiddelen		
MCPA	1.5 (P)	7 (P)
Diverse verbindingen		
tribroommethaan	20	100 (P)
isopropanol	1000	2200
ethylacetaat	900	4200 (P)
butylacetaat	200 (P)	1000

* P = *Provisional* (voorlopige waarde)

1. INTRODUCTION

In the framework of the Dutch Soil Protection Act, toxicologically based Intervention Values are derived for soil contaminants. From 1991 onwards several series of contaminants have been subjected to toxicological evaluation in this programme. The procedure used to develop proposals for soil intervention values involves the use of both ecotoxicological criteria and human-toxicological (human health-based) criteria. The application of these criteria for any soil contaminant yields two separate soil concentrations for that particular compound, i.e. the ecotoxicological *Serious Soil Contamination Concentration* (ECOTOX SCC) and the human-toxicological *Serious Soil Contamination Concentration* (the HUM-TOX SCC), respectively. From these SCC-values the proposed soil *Intervention Value* is selected or derived. This procedure has been developed in the years from 1991 onwards and is described in a number of RIVM-reports. These reports are listed in a separate section attached to the present report (see page 29). The following block diagram schematically depicts the different steps in the procedure towards proposed Intervention Values for clean-up of soil and groundwater. The shaded block in figure 1 marks the step covered in the present report, i.e. the derivation of human-toxicological (human health-based) criteria for the so-called fourth series of chemicals.

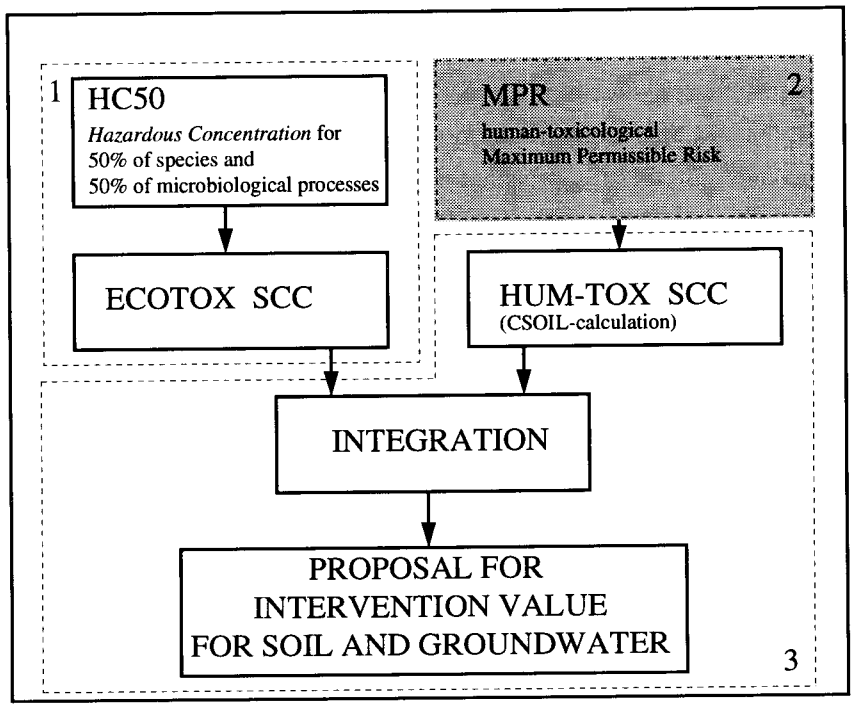

Figure 1. Diagram of pathways leading to the derivation of proposals for Intervention Values for soil and groundwater

The present report deals with the human-toxicological criteria for the compounds reviewed in the period 1996-1997. Within the scope of the project these compounds are referred to as the *fourth series* of compounds. Previous series of compounds have been reported in Vermeire et al. (1991) and Janssen et al. (1995).

Further guidance on the different steps in figure 1 is given in the following reports:
- step 1: Crommentuyn et al. (1994) - RIVM report no. 715810003;
- step 2: Janssen & Speijers (1997) - RIVM report no. 711701006;
- step 3: Kreule et al. (1995) - RIVM report no. 715810010 (third series of compounds), van den Berg et al. (1994) - RIVM report no. 715810004 (second series of compounds) and Kreule & Swartjes (1998) - RIVM report no. 711701003 (fourth series of compounds). These three reports present the *integration* step for the second, third and fourth series of compounds, respectively. The integration procedure has not been described in a separate guidance report.

The human-toxicological criterion to be used in the present scope (the derivation, within the Soil Protection Act, of intervention values for clean-up of soil and groundwater) has been defined as the *Maximum Permissible Risk*[1] (MPR). This approach was introduced in the brochure *Premises for Risk Management*[2] of the Ministry of Housing, Spatial Planning & Environment of the Netherlands (VROM, 1988).

In general, in the toxicological evaluation of chemical substances, two standard approaches are distinguished, i.e. the threshold approach and the non-threshold approach. For each compound dealt with, either one or the other of these approaches is chosen for deriving the human-toxicological criterion. The non-threshold approach is chosen for the compounds that, on the basis of the available evidence, must be regarded as genotoxic carcinogens. For other compounds (non-genotoxic carcinogens, non-carcinogens[3]) 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[4]. 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. As a theoretical premise it is assumed that any dose, however small, entails have *some* non-zero chance on an adverse effect on DNA that may ultimately lead to tumour formation. 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*. The default approach here is that in the low-dose area - that is the range

[1] In Dutch: Maximum Toelaatbaar Risico, abbreviated as MTR.
[2] Title in Dutch: "Omgaan met Risico's".
[3] The distinction genotoxic carcinogen versus non-genotoxic carcinogen as given here is the one usually given in the literature: genotoxic carcinogens as producers of tumours through direct interaction with DNA (stochastic mechanism) and non-genotoxic carcinogens as producers of tumours through an indirect mechanism for which a threshold of action exists. (For further discussion on this topic see Health Council of the Netherlands, 1994.) Strictly speaking there is yet a further category of compounds, i.e. compounds producing numerical chromosome aberrations (aneuploidy): this is a genotoxic action for which a threshold is assumed to exist (non-stochastic mechanism).
[4] The difference between TDI and ADI is that the *Tolerable Daily Intake* is allocated for contaminants whereas the term *Acceptable Daily Intake* is reserved for compounds that are deliberately added to foods or during the production process of foods.

of levels of general population exposure to environmental contaminants as encountered in practice i.e. the range of exposure levels for which the risk estimates are intended -, the cancer risk increases linearly with dose.

Conceptually, the MPR covers both approaches (threshold and non-threshold). In *Premises for Risk Management* 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} (1 in 10,000).[5] Thus, in point of terminology the MPR is equivalent with either TDI/ADI or the oral 1 in 10^4 lifetime cancer risk level (but see also footnote 8 below). The choice made as regards the cut-off points in the definition of the MPR leads to a complication in the procedure for the toxicological evaluation of individual compounds. For genotoxic carcinogens a *threshold* evaluation based on other toxic endpoints than genotoxicity/carcinogenicity may yield a lower limit value than the exposure level associated with a 1 in 10,000 excess lifetime cancer risk. For this reason for the genotoxic carcinogens a parallel threshold evaluation (parallel to the non-threshold evaluation that is warranted in principle for this group of compounds) is carried out to check whether this might be the case. If the threshold evaluation does indeed produce a lower limit value the latter is chosen as the MPR.[6]

The HUM-TOX SCC is calculated using the TDI/ADI or 10^{-4} oral excess lifetime cancer risk level. For this calculation the CSOIL model is used. CSOIL calculates total contaminant uptake (sum of oral, dermal and inhalation) for humans living on the site of soil contamination (standard situation, all exposure routes operative). That soil contaminant concentration is determined at which total uptake equals the TDI/ADI or the 10^{-4} oral lifetime excess cancer risk. This concentration in soil is the HUM-TOX SCC. As a further step specifically for volatile compounds, the concentration in indoor air as calculated by CSOIL at the HUM-TOX SCC, is compared to the toxicological limit value[7] for air, the TCA. The TCA, the Tolerable Concentration in Air, is the long-term limit value for inhalation. The TCA is the equivalent, for the inhalation route, of the TDI. For genotoxic compounds the inhalation 10^{-4} excess lifetime cancer risk is used instead of the TCA.[8] If the comparison shows the CSOIL-predicted concentration in air at the HUM-TOX SCC to exceed the TCA or the 10^{-4} inhalational excess lifetime cancer risk, the HUM-TOX SCC is adjusted downwards to the level where the predicted concentration in air is equal to the TCA or 10^{-4} inhalation cancer risk level. A detailed description of the CSOIL model is provided by the RIVM report of van de Berg (1995).

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[5] In Premises for Risk Mangement the MPR level was defined as an extra risk of 10^{-6}/year. For chemical compounds this level of risk (that also applies to exposures to radiation) was interpreted as being roughly equivalent to an excess lifetime cancer risk level of 10^{-4} (discussed in Vermeire et al., 1991).

[6] This may lead to the MPR for a genotoxic carcinogen being based not on the genotoxic *cum* carcinogenic action of the compound in question but on another toxic effect also produced by the compound. A case in point is the MPR for benzene as reported in Vermeire et al. (1991) and in Vermeire (1993).

[7] To avoid confusion over the terminology used: the term *limit value* is used generically throughout the text. This means that *limit value* is the umbrella term covering ADI, TDI, RfD, TCA, 10^{-4} excess lifetime cancer risks as well as MPR.

[8] Additional clarifaction: the MPR also covers these inhalatory limit values and in the report text below the term *inhalation MPR* is sometimes used. Thus, the MPR is the umbrella term covering both oral and inhalation limit values.

As to the use of the human-toxicological MPR in the entire procedure for deriving intervention values for soil clean-up, it should be noted that the MPR is an exposure level expressed in mg/kg body weight/day (or mg/m^3 for inhalation values). As already stated above, to derive the HUM-TOX SCC (concentration in soil expressed in mg/kg soil) from the MPR the calculation model CSOIL is used. The present report only deals with the step of MPR derivation. The results of the CSOIL calculations for the fourth series of chemicals (giving the HUM-TOX SCC values for these compounds) are presented in the RIVM report of Kreule & Swartjes (1998).

The work on the intervention values for soil clean-up is carried out in the scope of the RIVM project no. 711701. For an overview of the RIVM reports published on the subject of soil intervention values and related risk assessment see pages 29-32 below.

2. METHOD

For a detailed description of the method used to derive human-toxicological (human health-based) MPR-values the reader is referred to the recent guidance document by Janssen & Speijers (1997). In the present report only a rough outline of the method used is given.

For the compounds present as soil contaminants frequently large toxicological data bases exist. Full evaluation of all the relevant original literature for each compound is too laborious to be practicable in the present scope. For this reason the general approach is a pragmatic one in that wherever possible existing evaluations and reviews are used and the effort is focussed on detecting and evaluating only those studies that are directly relevant for derivation of the MPR. The presentation of the information is similarly focussed: for each compound a *toxicity profile* is prepared, a summary of the available data as concise as possible, with details on those studies only that are directly relevant for derivation of the TDI/ADI (or TCA) or cancer risk estimates.

As explained in section 1 (Introduction), the toxicological evaluation of chemical substances aimed at the derivation of toxicological limit values (MPR-values), makes use of either the threshold approach or the non-threshold approach. The threshold approach involves the use of uncertainty factors: the overall-NOAEL as selected from the data base is divided by the total uncertainty factor. This total uncertainty factor consists of two or three (sometimes four) subfactors, each of which covers one of the different extrapolation steps that are needed to derive the MPR. The following factors are applicable:

Table 3. Uncertainty factors for threshold evaluations

type	magnitude	explanation
Standard factors		
- interspecies	10	intended to account for uncertainty in extrapolating results obtained in animals to humans
- intraspecies	10	intended to account for variation in susceptibility among the human population i.e. high risk groups
Extra factors		
-semichronic to chronic	up to 10	intended to account for the uncertainty in extrapolating from less-than-lifetime exposure or subchronic to chronic exposure
- LOAEL to NOAEL	up to 10	intended to account for uncertainty inherent in extrapolating downward from a LOAEL to a NOAEL
- limited data set	up to 10	intended to account for deficiencies in the overall data set

The size of the total uncertainty factor depends on the data base. Where adequate chronic human data are available the single intraspecies factor of 10 is sufficient. Even this single factor may be unnecessary in case the NOAEL derives from studies in which effects of prolonged exposure have been evaluated in the human population, including sensitive subgroups. In practice this latter case,

however, is extremely rare. When fully adequate chronic human data are lacking, higher factors (than 10) are used. For a complete set of animal toxicity data (i.e. studies available for alle major toxicological endpoints: semichronic & chronic toxicity, carcinogenicity, genotoxicity, teratogenicity, reproduction toxicity and, possibly, neurotoxicity and immunotoxicity) including a NOAEL, the standard factor of 100 (factor 10 for interspecies variation and factor 10 for intraspecies variation) is sufficient. For limited data sets extra factors must be selected on a case-by-case basis. In view of the enormous variability in the extent and nature of different data bases the selection of the extra factors should be based on a careful review of the entire data base. As is also pointed out in IPCS (1994), the rigid application of the extra factors should be avoided because where the total uncertainty factor is too high the limit value that is derived will be so uncertain so as to lack meaning. As a general rule it can be stated that total uncertainty factors higher than 1000 are undesirable and must be avoided, if possible. Nevertheless, for very limited data sets such high factors may be unavoidable in that the alternative would be not to be able to estimate a limit value at all (the MPR derived in the present series of compounds for 4-chloro-2-methylphenol is a case in point).

The non-threshold approach is applied for those compounds that, on the basis of the available evidence, must be regarded as genotoxic carcinogens. As already explained in section 1 (Introduction) for this toxicological category of compounds it is assumed that any dose, however small, entails have *some* non-zero chance on an adverse effect on DNA that may ultimately lead to tumour formation. For these compounds an *excess lifetime cancer risk* is derived using *linear extrapolation* from the tumour incidences as observed in human studies or animal bioassays. Adequate human data being very rare, the derivation is based on animal bioassay results in almost all cases. The general formula used for this extrapolation is as follows:

$$D_h^x = \frac{I_{human}}{I_{exp}} \times \frac{t_{exp}}{t_{life}} \times \frac{t_{exposure}}{t_{life}} \times d_{exp}$$

Symbols in this formula:

D_h^x :	dose for humans at accepted cancer risk;
I_{human} :	accepted cancer risk (MPR: 10^{-4});
I_{exp} :	tumour incidence at lowest tumorigenic dose in animal experiment;
t_{exp} :	duration of animal experiment in days;
t_{life}:	duration of lifetime of experimental animals in days (rat 1000; mouse 750)
$t_{exposure}$:	duration of exposure in days;
d_{exp} :	lowest tumorigenic dose.

This extrapolation is a simple point estimate for the cancer risk, based on the the lowest tumorigenic dose. The result of this linear extrapolation is the estimated human dose level (as mg kg body weight or mg /m^3 air) associated with a 1 in 10,000 excess lifetime cancer risk.

As already explained in section 1 (Introduction) the limits chosen as the cut-off points in the definition of the MPR (i.e. the TDI/ADI & TCA for threshold evaluations and the estimated 10^{-4} lifetime cancer risk for non-threshold evaluations), entail the possibility that for compounds qualified as genotoxic carcinogens, derivation of a TDI or TCA for the "threshold effects" produced by these compounds, may produce a limit value that is below the 10^{-4} lifetime cancer risk level. In such a case

this lower value should be adopted as the MPR. thus, for the genotoxic carcinogens a parallel threshold evaluation based on non-carcinogenic endpoints is carried out in order to check for this. The lower value of the two (threshold value & non-threshold value) is selected as the MPR.

For further information on the approach used in the toxicological evaluation see the RIVM-report by Janssen & Speijers (1997). As to the description of the method as given in Janssen & Speijers, it should be noted that the "state-of-the-art" in the field of human health-based risk assessment is evolving. Different lines of study and evaluation are being pursued by diffenent research groups around the world in order to improve upon the methods as currently in use in chemical risk assessment. As also pointed out in the guidance document by Janssen & Speijers (1997), these developments may be expected to have significant impact on the MPR derivation method as currently in use for soil contaminants. One of the focal points of the said research efforts is the development of extrapolations in which the use of default uncertainty factors is replaced by factors that incorporate actual data (toxicological, pharmacokinetic, pharmacodynamic). Within the RIVM-project *Risks in Relation to Soil Quality* (in the scope of which proposals for intervention values are developed) all past work (i.e. the methods that have been developed and the application thereof for the individual contaminants that have been evaluated in the programme) is currently under review and evaluation. This review will include a critical look at the default uncertainty factors and the exploration of the applicability of new methods that have been proposed and the data requirements thereof. Thus, the recommendation as given by the Technical Soil Protection Committee (TSPC, 1997) in its recent evaluation of the RIVM reports on the second and third series of soil contaminants, to the effect that the default uncertainty factors used should be critically reviewed, is followed.

The present report deals with the *fourth series of compounds*. The following compounds are included therein:

- metals: vanadium, selenium, thallium, tellurium, tin (inorganic);
- aromatic compounds: chloroanilines, 4-chloro-methylphenol;
- chlorinated hydrocarbons: 1,1,2-trichloroethane, 1,2/1,3-dichloropropane, 1,1-dichloroethene;
- pesticides: MCPA (4-chloro-methylphenoxy-acetic acid);
- miscellaneous compounds: tribromomethane, isopropanol, ethylacetate and butylacetate.

For a motivation of the choice of these compounds see the RIVM-report by Swartjes (1997). The toxicity profiles for the individual contaminants included the fourth series are presented in Appendix 1 through 13. Not given in the appendices are the profiles for inorganic tin and butyl acetate. The toxicological evaluations (human health) for these two compounds have been reported previously, i.e. in Vermeire et al. (1991) (inorganic tin) and Janssen et al. (1995) (butyl acetate). For the toxicological profiles for these compounds the reader is referred to these reports.

As was the case for the large majority of the compounds from the previous three series of compounds, for the compounds dealt with in the present report in almost all instances review documents (existing evaluations such as those by RIVM, IPCS, ATSDR, US-EPA or DECOS) were available that could serve as the initial basis for the toxicological evaluation. For the present series of compounds in practically all cases additional literature searches were carried out to supplement the data base (see the *compilation record* in the individual toxicity profiles as presented in the

appendices). The results of these searches for original publications 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. In all cases where review documents (existing evaluations) were used, wherever necessary, the orginal publications of studies given in these reviews were consulted and evaluated anew. The tolerable intake levels (limit values, permissible levels) as derived in the reviews as prepared by other organisations are accepted here (including the safety factors/uncertainty factors used[9]) unless deviations were warranted because of different evaluation of crucial experimental data. Where *additional* new tolerable intakes or concentrations were derived from studies included in the review used (so the study results are given but no tolerable intake or concentration was derived in the review in question), the orginal publication was used as a check.

The available data bases for several of the compounds of the fourth series were incomplete, there being a lack of information on one or more important toxicological endpoints in such cases. For compounds with a limited data base the TDIs and/or TCAs derived, are *provisional* (PTDI, PTCA). For many compounds of the present series route-to-route extrapolation was needed to derive a limit value (TDI or TCA) for an exposure route for which the route-specific toxicological were insufficient for direct derivation. All limit values derived using route-to-route extrapolation should be regarded as provisional values (PTDI, PTCA) because this kind of extrapolation involves considerable uncertainty.

[9] Note that these factors may differ from the standard factors to be used according to the method described in the report of Janssen & Speijers (1997).

3. RESULTS

The human-toxicological criteria (Maximum Permissible Risk levels) derived for the fourth series of compounds are listed in Table 1 below (see page 25). For all compounds listed in table 1 except inorganic tin and butyl acetate the full toxicity profiles are given in the appendices. Inorganic tin[10] was already evaluated in the Vermeire et al.-report from 1991, to which report the reader is referred for the full toxicity profile on this group of compounds. Similarly, the toxicological evaluation for butyl acetate was conducted in 1994 and was reported in the RIVM-report of Janssen et al. (1995). In the present section the evaluations on the individual compounds are briefly addressed (for further details see the appendices).

For **vanadium** limit values (MPRs) have been derived both for the oral route and the inhalation route because, given its high inhalation toxicity, the exposure due to inhalation of soil particles may possibly lead to exposure levels that exceed the inhalatory limit value. The available data set for the oral route was limited, for which reason the TDI (oral MPR) of 2 µg/kg body weight, that was derived is a provisional value having low reliability. The proposed TCA (inhalation MPR) for vanadium compounds (1 µg/m^3) is the WHO Air Quality Guideline from 1987, a limit value derived from occupational epidemiology studies. **Selenium** is an essential element in humans and animals. In the Netherlands, the recommended range of selenium intake for adults is 50-150 µg Se/day (about 0.7-2.1 µg Se/kg bw/day). During pregnancy, the lower limit of this recommended range is 75 µg Se/day. In deriving toxicological limit values for selenium the level of nutritional requirement should be taken into consideration (self-evidently any limit value derived should not be in conflict with the nutrional requirement level). Information on the toxicity of selenium in humans after chronic exposure is basically derived from human populations living in seleniferous areas (areas rich in natural selenium). The derivation of the oral MPR (TDI) of 5 µg/kg body weight is based on a Chinese study in which populations living in areas with either low, medium or high selenium levels in food and food supply were evaluated for signs of selenium intoxication. For this oral MPR the derivation of the oral limit value (*Reference Dose*) value as developed by the US-EPA was adopted. **Tellurium**, a metal that resembles selenium and sulfur in its chemical properties, has a very limited toxicological data base. No or no adequate studies are available on carcinogenicity, genotoxicity, short-term & long-term toxicity and reproductive toxicity. This very limited data set does not allow derivation of a TDI. Only a *provisional* value (PTDI) could be derived (2 µg/kg body weight). For **thallium** compounds also, the available set of toxicological data is very limited. No carcinogenicity studies have been carried out and the genotoxic potential was examined to a limited extent only. Based on the available data a genetic risk cannot be excluded. The results of studies on reproductive toxicity indicate that thallium compounds adversely affect the male reproductive system. Due to the limitations in the data set only a *provisional* TDI (PTDI) could be derived for thallium and its compounds (0.2 µg/kg body weight). **Inorganic tin** compounds have low toxicity. In the 1991 evaluation in the scope of the present project RIVM/CSR adopted the provisional tolerable weekly

[10] Inorganic tin has been included in table 1 because the companion RIVM-report to the present report, i.e. Kreule & Swartjes (1998), includes the development of a proposal for an intervention value for the inorganic tins. The same applies for butyl acetate - see the text above.

intake (PTWI) of 14000 µg/kg body weight/week, proposed by the WHO/JECFA (1989), as the level to be used as the oral MPR. The full toxicity profile on inorganic tins is given, not in the present report, but in the RIVM-report of Vermeire et al. (1991).

The **chloroanilines** are a group of compounds consisting of monochloroanilines (3 isomers), dichloroanilines (6 isomers), trichloroanilines (4 isomers), tetrachloroanilines (2 isomers) and pentachloroaniline (1 isomer). Of all isomers 4-monochloroaniline is the one with the largest toxicity data base. The weight of evidence concerning genotoxicity and carcinogenicity indicates that this isomer should be considered a genotoxic carcinogen. The available toxicity data for 2- and 3-monochloroaniline indicate that these isomers produce similar health effects (including the genotoxicity and carcinogenicity, so the data suggest) as those produced by 4-monochloroaniline, for which reason a common limit value was derived for the monochloroanilines (0.9 µg/kg body weight for the oral route and a tentative value of 4 µg/m^3 for inhalation). For all other chloroanilines the available data are limited. For the dichloroanilines the limited data that *are* available indicate that their toxicological properties differ from those of the monochloroanilines. The chloroanilines containing three or more chlorine atoms have been studied to a very limited degree only. The conclusion for the di-, tri- and tetra-chloroanilines and for pentachloroaniline was that no limit value could be derived due to lack of data.

4-Chloro-methyl-phenol has two isomers: 4-chloro-2-methyl-phenol and 4-chloro-3-methyl-phenol. For both compounds only limited toxicological information is available. The results of the oral toxicity studies suggest that the two isomers have different target organs (the liver for 4-chloro-2-methyl-phenol and the kidneys for 4-chloro-3-methyl-phenol). The reliability of this conclusion, however, is limited due to the incompleteness of the available data sets. For 4-chloro-3-methyl-phenol an oral limit value (TDI) of 300 µg/kg body weight was derived based on an NOAEL from a chronic study in rats. For 4-chloro-2-methyl-phenol no chronic or semichronic toxicity studies have been carried out. Only an NOAEL from a 28-day oral toxicity study is available; derivation of a TDI from such a study led to a very high uncertainty factor being chosen (10000), extra factors being required for limited duration of the study and the overall poor quality of the data set for this isomer. The value derived in this way is 20 µg/kg body weight. Provisional inhalation MPRs for 4-chloro-methyl-phenol (1300 and 90 µg/m^3) were calculated from the respective TDIs.

For **1,1,2-trichloroethane** the data on carcinogenicity and genotoxicity are inconclusive. Based on the available evidence it cannot be excluded that this compound is a genotoxic carcinogen. Due to lack of data a non-threshold derivation of an MPR (estimation of the 1 in 10,000 excess lifetime cancer risk) is not possible. Consequently derivation of a provisional TDI value via a threshold approach is the only option feasible. Thus, the oral limit value derivation as developed by the US-EPA (derivation of the *Reference Dose*) was adopted here as the provisional TDI (oral MPR). The result was an oral MPR for this compound of 4 µg/kg body weight. For the inhalation route a provisional TCA (inhalation MPR) of 17 µg/m^3 was derived from an NOAEL from a 6-month study in several species. The available information on this study is limited and consequently the limit value derived has only low reliability. Isomers of **dichloropropane** are the following: 1,1-dichloropropane,

1,2-dichloropropane, 1,3-dichloropropane and 2,2-dichloropropane. Toxicological data are available for the 1,2- and 1,3-isomers only. The results of the oral toxicity studies indicate that the 1,3-isomer has a target organ different from that for the 1,2-isomer: the 1,3-isomer produces renal and hepatic effects whereas the 1,2-isomer primarily produces effects on the haemopoietic system including the spleen. In view of this difference in systemic effects, for these isomers separate oral limit values (TDIs) were derived (70 µg/kg body weight for 1,2-dichloropropane and 50 µg/kg body weight for 1,3-dichloropropane). For the inhalation route there are no toxicological data for the 1,3-isomer, as a consequence of which it can not be determined whether the two isomers differ in their inhalation toxicity. In absence of inhalation toxicity data for 1,3-dichloropropane the two isomers are assumed to have equal toxic potential via this route. Thus, the TCA as derived for 1,2-dichloropropane (12 µg/m^3) is assumed to apply for 1,3-dichloropropane as well (adopted as *provisional* TCA for the 1,3-isomer). For the isomers for which there are no toxicological data (i.e. 1,1- and 2,2-dichloropropane) no limit value was derived. **1,1-Dichloroethene** was concluded to be a genotoxic carcinogen. Quantitative cancer risk estimation using linear extrapolation was carried out using the result of an inhalation carcinogenicity study in mice. Cancer risk estimation for the oral route was done via route-to-route extrapolation (cross-calculation from the inhalation figure), no adequate oral carcinogenicity studies being available. A parallel threshold evaluation based on toxic effects (non-carcinogenic effects) to check if such an evaluation yields a limit value lower than the exposure level associated with a 1 in 10,000 lifetime cancer risk - (see the RIVM report by Janssen & Speijers, 1997 for further explanation of the rationale for this parallel evaluation) -, proved not to give lower limit values than the non-threshold evaluation. Thus, the result of the non-threshold evaluation was adopted as the MPR for 1,1,-dichloroethene, yielding a provisonal oral MPR of 3 µg/kg body weight and an inhalation MPR of 14 µg/m^3.

4-Chloro-2-methylphenoxyacetic acid (MCPA) is a pesticide (i.e. systemic hormone-type selective herbicide). The data do not show the compound to be carcinogenic or genotoxic, making the use a threshold approach in limit value derivation the appropriate choice. The provisional ADI of 1.5 µg/kg body weight as derived by RIVM/CSR in 1991 in its toxicological evaluation in the scope of the procedure for the national registration for use as herbicide, was adopted here as the provisional TDI (oral MPR). A provisional inhalation MPR (PTCA) of 7 µg/m^3 was derived using route-to-route extrapolation.

2-Propanol has low toxic potential, so the available data for this compound indicate. Based on limited data the compound does not pose a genotoxic or carcinogenic risk. The limit value derivation for the oral and inhalation routes was based on semichronic NOAELs, giving MPR-values of 1000 µg/kg body weight (oral) and 2200 µg/m^3 (inhalation). Application of extra uncertainty factors for limited duration of the pivotal studies was not considered necessary given the fairly elaborate data set for 2-propanol and its low toxicity as observed in the toxicological experiments carried out. For **ethyl acetate** the available data set is relatively limited. There are no data on carcinogenicity and only limited data on genotoxicity. For the oral route a limit value (TDI, oral MPR) of 900 µg/kg body weight was derived from a semichronic study in rats. A provisional inhalation MPR (PTCA) of 4200 µg/m^3 was derived using route-to-route extrapolation from the oral MPR. **Butyl acetate** has not been

studied extensively. Only very few data are available for this compound. A TCA (inhalation MPR) of 1000 μg/m^3 was calculated from the limit value for occupational exposure (TLV), as derived in the USA. Using route-to-route extrapolation a provisional TDI (oral MPR) of 200 μg/kg body weight was calculated from the TCA. The full toxicity profile on butyl acetate is given, not in the present report, but in the RIVM-report of Janssen et al. (1995). **Tribromomethane** has been shown to produce a clastogenic effect (induction of chromosome breaks) *in vivo*. The results of the carcinogenicity studies are inconclusive. Derivation of a limit value using a threshold approach is the only option feasible based on the toxicological evidence currently available. For the oral route the limit value derivation as developed by the US-EPA has been adopted. Thus, the US-EPA Reference Dose (RfD) of 20 μg/kg bw/day is proposed as the TDI (oral MPR) for use in the present scope. Inhalation toxicity data for tribromomethane are scarce precluding the derivation of a TCA (inhalation MPR) from an inhalation NOAEL. Route-to-route extrapolation has limited validity for tribromomethane since there are indications that portal-of-entry effects might be critical for the inhalation route. To account for *systemic* effects only after exposure to tribromomethane by inhalation, a provisional TCA (PTCA) of 100 μg/m^3 was derived from the oral TDI. It is stressed that this PTCA does not take into account portal-of-entry effects.

Table 1. Human-toxicological Maximum Permissible Risk levels (MPRs) for 21 compounds for deriving serious soil contamination concentration from human-toxicological data

compound	oral MPR (TDI[a] or 10^{-4} excess cancer risk) in µg/kg bw/day	UF[b]	inhalation MPR (TCA[c] or 10^{-4} excess cancer risk) in µg/m^3	UF	estimated background exposure in µg/kg bw/day
I. Metals					
vanadium	2 (P)	1000	1	20	0. 3
selenium	5	3	no value needed[d]	-	1
tellurium	2 (P)	1000	idem	-	1.4
thallium	0.2 (P)	1000	idem	-	0.03
tin (inorganic)	2000	10	idem	-	unknown
III. Aromatic compounds					
monochloroanilines	0.9[e]	-	4 (P)[f]	-	unknown
dichloroanilines	no value derivable	-	no value derivable	-	unknown
trichloroanilines	idem	-	idem	-	unknown
tetrachloronanilines	idem	-	idem	-	unknown
pentachloroaniline	idem	-	idem	-	unknown
4-chloro-2-methylphenol	20(P)	10000	90 (P)[f]	-	unknown
4-chloro-3-methylphenol	300 (P)	100	1300 (P)[f]	-	unknown
V. Chlorinated hydrocarbons					
1,1,2-trichloroethane	4 (P)	1000	17 (P)	1000	0.007
1,2-dichloropropane	70	1000	12	1000	<1
1,3-dichloropropane	50	1000	12 (P)[g]	-	unknown
1,1-dichloroethene	3(P)[f]	-	14[e]	-	0.014
VI Pesticides					
MCPA	1.5(P)	100	7(P)[f]	-	unknown
VII.Miscellaneous compounds					
2-propanol	1000	100	2200	100	unknown
ethylacetate	900	1000	4200(P)[f]	-	unknown
butylacetate	200(P)[f]	-	1000	100	1
tribromomethane	20	1000	100 (P)[h]	-	<1

[a] TDI: Tolerable Daily Intake; where only a provisional value is available this is indicated by adding (P).

[b] UF: uncertainty factor (also frequently referred to as *safety factor*).

[c] TCA: Tolerable Concentration in Air; where only a provisional value is available this is indicated by adding (P)

[d] Inhalation route not considered relevant in present context.

[e] Excess lifetime cancer risk of 10^{-4}.

[f] Tentative value derived via route-to-route extrapolation.

[g] Value as derived for 1,2-dichloropropane is adopted as provisional value for 1,3-dichloropropane.

[h] Tentative value derived via route-to-route extrapolation. This value for tribromomethane is protective of systemic effects but it does not take into account portal-of-entry effects (local effects in the lung).

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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 (1991/1995).

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.

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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. [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.

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Contains: methodology for estimating human exposure based on calculation formulas from the CSOIL model; several standard soil use categories are defined using standard assumptions as to human exposure; the result is a exposure estimate for a specific kind of site; 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; the method is yet to be further developed in future work.

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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; this methodology will be tested in practice, future adjustments may be necessary.

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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.

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

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Waitz, M.F.W., Freijer, I.J., Kreule, P. & Swartjes, F.A. (1995) The VOLASOIL risk assessment model based on CSOIL for soils contaminated with volatile compounds. RIVM-report no. 715810014, dated May 1996.

Contains: description of the CSOIL-derived model VOLASOIL that is intended for site-specific determination of risks; indoor air concentrations can be calculated for which VOLASOIL contains adjustable parameters including depth of groundwater level and some construction characteristics of the buildings on the site.

Vissenberg, H.A. & Swartjes, F.A. (1996) Evaluatie van de met CSOIL berekende bloostelling, middels een op Monte Carlo-technieken gebaseerde gevoeligheids- en onzekerheidsanalyse. [In Dutch]. RIVM-report no. 715810 018 (with separate appendix containing additional graphs and tables).

Contains: examination of reliability of exposure estimates made using CSOIL; examination carried out for five contaminants, i.e. arsenic, cadmium, benzene, atrazin and benzo(a)pyrene; using distributions of input parameters the distribution of the calculated potential exposure is determined and compared to point estimates of exposure for the same compounds.

Janssen, P.J.C.M. & G.J.A. Speijers (1997) Guidance on the Derivation of *Maximum Permissible Risk* Levels for Human Intake of Soil Contaminants. RIVM-report no. 711701 006, dated January 1997.

Contains: concise description of the method used to derive human-toxicological (human health-based) Maximum Permissible Risks levels (MPRs, in Dutch: MTRs).

Berg, R. van den (1997). Verantwoording van gegevens en procedures voor de 1e tranche interventiewaarden: van RIVM-rapporten naar de Notitie Interventiewaarden bodemsanering. [In Dutch] RIVM-report no 715810012.

Contains: description of the adjustments and changes that were made in models, parameters and data, during the period from release of the first series of proposals for intervention values (1991) up to implementation into the Dutch Act on Soil Protection in 1994.

Posthumus, R., Crommentuyn, T. & Plassche, E. van de (1997) Ecotoxicological Serious Soil Contamination Concentrations - fourth series of compounds. RIVM report 711701 003, dated March 1998.

Contains: ecotoxicological criteria (MPR-values) for 4th series of chemicals (13 chemicals).

Janssen, P.J.C.M., Apeldoorn, M.E. van, Engelen, J.G.M. van, Schielen, P.C.J.I. & Wouters, M.F.A. (1998) Human-toxicological Maximium Permissible Risk levels for use in the determination of *Serious Soil Contamination*: fourth series of compounds. RIVM report 711701 004 (the present report).

Contains: human-toxicological criteria (MPR-values) for 4th series of chemicals (13 chemicals).

Kreule, P. & Swartjes, F.A. (1998) Calculation of human-toxicological serious soil contamination concentrations and proposals for intervention values for clean-up of soil and groundwater: Fourth series of compounds. RIVM report no. 711701 005, dated March 1998.

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 proposals for intervention values; this 4rd series consists of the 13 compounds as evaluated in the RIVM-reports 711701003 and 711701004 and, in addition, inorganic tin and butyl acetate.

Swartjes, F.A. (1997) Stofselectie voor het afleiden van "voorstellen voor interventiewaarden" [in Dutch]. RIVM report 715810 016, dated September 1997.

Contains: overview of possible criteria to be used in the selection of soil contaminants for which intervention values are needed; a large number of candidate-compounds is mentioned; for the individual compounds from the 4th series of compounds, the rationale for inclusion into this 4th series is given.

APPENDIX 1: VANADIUM

INTRODUCTION

Vanadium is a natural element in the earth's crust with wide distribution and low concentrations of occurrence. The average environmental concentration is 150 mg/kg. In the environment elemental vanadium does not occur; it is generally bound to oxygen (as V_2O_5) but may also occur bound to sodium, sulfur or chloride. Vanadium has six oxidation states, from 1^- to 5^+. (ASTDR, 1991) There is no certainty about whether or not vanadium is an essential element for humans (Lagerkvist et al., 1986).

RELEVANT ROUTE

Exposure routes considered relevant in present context: oral and inhalation. Vanadium compounds have low volatility. However in view of the low inhalation effect-levels (data summarised below) the inhalation route may be relevant despite the low volatility (exposure due to inhalation of soil particles may possibly lead to exposure levels that are significant in view of the inhalation toxicity of vanadium compounds).

TOXICITY

Vanadium and its compounds have not been previously evaluated by RIVM/CSR.

The toxicological data available for vanadium and its compounds do not allow differential evaluation of the toxicological effects of the different oxidation states in which vanadium occurs. Thus, following the approach taken in the existing toxicity evaluations for vanadium (Lagerkvist et al., 1986; WHO, 1987; MAC, 1987; US-EPA, 1988; ATSDR, 1991), for the present evaluation the different ionic forms of vanadium and metallic vanadium are treated as being equipotent indicators of vanadium toxicity.

After inhalation exposure soluble vanadium compounds are for about 25% absorbed in the lungs. The absorption from the lung is dependent on the partizle size and solubility of the compounds. Ingested vanadium compounds are poorly absorbed in the gastro-intestinal tract. The absorption percentage of ingested vanadium is between 0.1 and 2.6%. After uptake into the circulation vanadium is widely distributed throughout the body. Vanadium is predominantly excreted via the urine. (ASTDR, 1991; Lagerkvist et al., 1986)

No IARC carcinogenicity evaluation for vanadium and its compounds is available. In fact, adequate data on carcinogenicity in humans or animals are lacking. As to mutagenicity results, vanadium compounds showed positive results in *in vitro* tests in bacteria, yeasts and mouse cells in culture for endpoints such as recombination, repair, gene mutation or DNA synthesis (ASTDR, 1991). More recent *in vitro* studies have shown aneuploidy in human lymphocytes and Sacharomyces cerevisiae. Tests in Chinese hamster cells *in vitro* showed no or weak induction of chromosome aberrations. (Owusu-Jaw et al., 1990; Roldan & Altamirano, 1990; Galli et al., 1991, Zhong et al., 1994) Results on two *in vivo* endpoints are given in literature: a dominant lethal assay in mice with a negative (no

effect) result (Sun, 1987 as cited in Leonard & Gerber, 1994) and an *in vivo* cytogenetic assay in mice (endpoints determined in bone marrow: micronuclei, structural and numerical chromosome aberrations). In the latter assay vanadium compounds (administered orally, one dose level tested per test compound) showed aneuploidy and a weak clastogenic activity (Ciranni et al., 1995). Given the lack of further data on *in vivo* genotoxicity (such data would be needed to better establish the genotoxic potential of vanadium compounds) and the lack of data on carcinogenicity, the only feasible option in limit value derivation is calculation of a TDI value using a threshold approach.

The amount of toxicological data for the oral route is limited, no adequate human data and only a limited number of *limited* animal studies being available. The available animal studies include a semichronic drinking-water study in rats by Domingo et al. (1985), a 2.5-year study in rats and mice (Schroeder et al., 1970; Schroeder & Mitchener, 1975), a 2-year feeding study in mice (Schroeder & Belassa, 1967) and a 2.5-year feeding in rats (Stokinger et al., 1953). Each of these studies has serious flaws in study outline and in the available information on study results. The study by Domingo et al. (1985) with three tested dose levels, included very limited histopathology only (done in 3 rats/sex/group only) and information given on the study results is insufficient. The target organs in this study were the kidneys, spleen and lungs (mild histopathological changes were present in these organs) (Domingo et al., 1985). The studies carried out by Schroeder and co-workers also have major shortcomings (only one dose level tested, insufficient report of results) (Schroeder and Balassa, 1967; Schroeder et al., 1970; Schroeder and Mitchener, 1975). Another study is the feeding study by Stokinger et al. (1953) in rats[11]. This old study is very limited (reported criteria used to evaluate the toxicity were growth rate, survival and hair cystine content) and is reported insufficiently (US-EPA, 1988).

Some oral studies have been performed for the reproduction/developmental endpoint. In an oral reproduction study by Domingo et al. (1986) rats were treated with 0, 5, 10 or 20 mg $NaVO_3$/kg bw/day for 60 days (dosing by gavage to both males and females). No effects were found on fertility, reproduction, and parturition, but the development of the offspring (parameters: body weight, body length and tail length) was significantly decreased at all dose levels at birth and during the entire lactation period. In addition relative liver weight was significantly and dose-relatedly decreased in all treated pups, while spleen and kidney weights were also decreased, but not completely dose-related. Histopathology on adults was not performed. The results of this study are reported incompletely. [Note: In a previous experiment by the same investigators 5 mg $NaVO_3$/kg bw was found to be not toxic for adult rats.] The LOAEL in this study was 5 mg $NaVO_3$/kg bw/day (≅ 2.1 mg V/kg bw/day). (Domingo et al., 1986) A reproduction study in mice with dosing to males only, showed decreased fertility at ≥60 mg/kg bw/day (NOAEL 40 mg/kg bw/day) (Llobet et al., 1993). Teratogenicity studies in mice were carried out by the same group of investigators that performed the two reproduction studies. In an oral study, $VOSO_4.5H_2O$ was administered by gavage to pregnant mice at dose levels of 0, 37.5, 75 and 150 mg/kg bw/day from day 6 through day 15 of gestation. Maternal toxicity (decreased growth, decreased liver and kidney weights) was observed at 75 and 150 mg/kg. Teratogenic effects (increased incidences of cleft palate, micrognathia and hydrocephalus) were

[11] This is the study used by the US-EPA in its Reference Dose derivation for vanadium pentoxide.

found at 75 and 150 mg/kg. Micrognathia was also seen at 37.5 mg/kg. In addition, the incidence of anopthalmia/microphtalmia was increased at 37.5 mg/kg only (incidence 10/152 in three different litters, versus zero incidence in all other groups). Further effects noted were an increased incidence of haematomas (at all dose levels, increase not consistently dose-related), an increased number of early resorptions (all dose levels, dose-related) and decreased foetal weight (all dose levels, dose-related). The LOAEL in this study was 37.5 mg $VOSO_4.5H_2O$/kg bw/day (≅ 7.5 mg V/kg bw/day) (Paternain et al., 1990). An i.p. study in mice (same strain) also showed a teratogenic effect (increased incidence of cleft palate) at the highest dose level (Gómez et al., 1992). From teratogenicity studies in rats, carried out in China, no adequate description of results is available (published abstracts provide insufficient information).

The above summary of toxicological data shows that the data set for vanadium compounds is quite limited. Only a provisional limit value can be derived. From the LOAEL of 2.1 mg V/kg bw/day from the Domingo et al. (1986) study, a provisional TDI (PTDI) is derived using an uncertainty factor of 1000 (10 for interspecies differences, 10 for intraspecies differences, extra factor 10 for using an LOAEL instead of an NOAEL and for the limited duration of the pivotal study). Thus a PTDI of 2 µg V/kg bw/day (rounded value) results. This is a provisional value because the LOAEL was derived from a limited study that was not reported in sufficient detail. Again, it is stressed that due to the limitations of the underlying data set the PTDI has only low reliability.

The inhalation toxicity of vanadium has been reviewed by the WHO in 1987 (scope: derivation of Air Quality Guidelines). Both acute and chronic poisonings have been described in workers engaged in the industrial production and use of vanadium. Most of the reported clinical symptoms reflect irritative effects of vanadium on the upper respiratory tract. These effects included irritation, coughing and injection of the pharynx. At higher concentrations (above 1 mg V/m^3) serious effects on the lower respiratory tract, including chronic bronchitis and pneumonitis are observed. There are no well-documented animal data to support the findings in human studies, although one study reported systemic and local repiratory effects in rats at levels of 3.4-15 µg V/m^3 for 30 days. (WHO, 1987)
The WHO Working Group concluded from the occupational studies that 1 µg/m^3 (24 hours average) is the allowable concentration for the general population. The basis for this value was an LOAEL of 20 µg vanadium/m^3 (critical effect: upper respiratory tract symptoms) and a 'protection factor' of 20 (WHO, 1987). This value is adopted here as the TCA.

BACKGROUND EXPOSURE

No data on general population background exposure in the Netherlands are available. In air in the USA, around a steel plant concentrations from 0.04 to 0.1 µg/m^3 were found. This concentration corresponds with 'open air' concentrations in 13 cities in Pennsylvania (on average 0.072 µg/m^3) in 1967 (MAC, 1987). In ATSDR (1991) air concentrations of approximately 50 ng/m^3 were assumed, resulting in a daily intake of 1 µg vanadium/day.

Vanadium intake from recent estimates of the American diet was found to be 10 to 60 µg/day (Domingo, 1996). In WHO (1987) total daily intake via the diet is estimated at 20 µg/day. In The

Netherlands the average vanadium concentration in drinking water in 19 cities was 1 µg/l (MAC, 1987).

From the above data the general population total background exposure is estimated at 0.3 µg/kg bw/day.

MISCELLANEOUS DATA

- Absorption factors:
  - oral: between 0.1 and 2.6% (ATSDR, 1991);
  - inhalation: 25% (Lagerkvist et al., 1986);
  - dermal: considered very low (no percentage given) (ATSDR, 1991).
- Guideline values:
  - MAC-value (limit for occupational exposure):
    0.05 mg V_2O_5/m^3 (smoke);
    0.5 mg V_2O_5/m^3 (dust) (MAC, 1987).

CONCLUSION

PTDI: 2 µg V/kg bw/day
Background exposure 0.3 µg V/kg bw/day

TCA: 1 µg V/m^3.

COMPILATION RECORD:

Database determination based on: - the review documents (as included in the reference list below)
- additional literature search (Toxline 1989-1996)

Profile compilation by: M.F.A. Wouters & P.J.C.M. Janssen
Advisers: A.H.Piersma (teratogenicity) & J.v.Benthem (genotoxicity)
Profile review by: A.G.A.C. Knaap, G.J.A. Speijers, J.v. Benthem, M.N. Pieters (Toxicology Advisory Group, 27-08-1996)

August 1996
RIVM-Centre for Substances and Risk Assesment

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APPENDIX 2: SELENIUM

INTRODUCTION

Since Selenium (Se) is interconverted between many forms, it is not clear which specific forms may be encountered as soil pollutants (analysis on specific forms has not been performed). In ATSDR (1995) the following overview is given. Selenium is ubiquitous in the environment, being released from both natural and manmade sources. Manmade emission sources of atmospheric selenium include coal and oil combustion facilities, selenium refining factories, base metal smelting and refining factories, mining and milling operations, and end-product manufacturers (e.g., some semiconductor manufacturers). The principal releases of selenium into the environment as a consequence of human activities result from the combustion of coal (as fly ash). Although selenium has been reported at hazardous waste sites (soil pollution), analysis on specific forms has not been performed. Elemental Se (Se[0]) is rarely found naturally, but is stable in soils. In air, elemental selenium and selenium dioxide are intraconvertible. Methyl selenide and dimethyl selenide can also be found in the atmosphere. Selenates (Se[+6]) and selenites (Se[+4]) are water-soluble, and can thus be found in water sources. Salts of selenic acid and selenious acids are most likely to be found in surface water and water contained in soil. Selenium sulfides would not be expected at most hazardous waste sites, since they are usually manufactured for use in shampoo. (ATSDR, 1995)

RELEVANT ROUTE

Exposure route considered relevant in present context: oral.

TOXICITY

Selenium is an essential element in humans and animals; it is part of several enzymes, such as haeme-oxidase, tetraiodothyronine deiodinase and glutathione peroxidase. Health assessment for selenium and its compounds involves the determination of the selenium status with respect to its nutritional essentiality (specified as the Recommended Dietary Allowance, RDA) and its toxicity (as the Tolerable Daily Intake, TDI). The toxicological data available for selenium and its compounds do not indicate the need for separate evaluation of the toxicological effects of the different oxidation states in which selenium occurs (exception: Se sulfide - see below). For the present evaluation the different ionic forms of selenium and metallic selenium are treated as being equipotent indicators of selenium toxicity, and, consequently the TDI refers to Se equivalents, irrespective of the oxidation state.

In the USA the RDA was set at 0.9 µg Se/kg body weight in adults (ATSDR 1995). In the Netherlands, the recommended range of selenium intake for adults is 50-150 µg Se/day. During pregnancy, the lower limit of this recommended range is 75 µg Se/day. (Voedingsraad 1989)

In humans, after ingestion of toxic levels of sodium selenate, and inhalation of elemental selenium dust or selenium oxide, a garlic-like odour of the breath was noted, most likely due to pulmonary excretion of the metabolite dimethyl selenide.

In its carcinogenicity evaluation IARC classified selenium and selenium compounds in Group 3 (*not classifiable as to its carcinogenicity to humans*). The available data are *inadequate* both in animals and in humans to evaluate the carcinogenicity of selenium and compounds. (IARC 1975, 1987) There is a substantial amount of evidence in both experimental animals and humans that some forms of Se (valence states and/ or compounds not specifiable from the available data) exert an anti-tumorigenic action. An exception to this is selenium sulfide that has been shown to produce tumours in animal experiments (liver tumours in rats and mice, lung tumours in mice). US-EPA (1991) has classified selenium sulfide as a *probable human carcinogen.*

In genotoxicity tests selenium compounds have shown both genotoxic and anti-genotoxic effects. Generally the genotoxic effects were observed at high dose levels whereas the antigenotoxic effects were found at low dose levels. A more detailed review of the available genotoxicity results is presented in ATSDR (1995).

Primary target organs in toxicity studies in animals were the liver and the nervous system. In pigs, exposed to selenite for 8 weeks, hind limb paralysis was observed (LOAEL 0.59 mg Se/kg bw, NOAEL 0.33 mg Se/kg bw/day). After chronic exposure to selenite and/or selenate, in mice amyloidosis was observed (LOAEL 0.57 mg Se/kg bw/day) and in rats in the liver slight to moderate cirrhosis (LOAEL 0.25 mg Se/kg bw) and hyperplastic lesions (LOAEL 0.1 mg Se/kg bw, NOAEL 0.025 mg Se/kg bw/day) were reported. (ATSDR, 1995)

Information on the toxicity of Se in humans after chronic exposure is basically derived from populations living in seleniferous areas (areas rich in natural selenium). Characteristic clinical signs of chronic oral exposure to selenium (selenose) are brittle hair, deformed nails, hair- or nail loss; in addition CNS abnormalities (peripheral anesthesia, acroparesthesia and pain in the extremities) were observed. The derivation of the TDI is based on a Chinese study in which populations living in areas with either low, medium or high Se levels in food and food supply were evaluated for signs of Se intoxication. This same study (reported by Yang et al., 1989) was the basis for the Reference Dose (RfD)[12] derivation as given by the US-EPA (1991) and for the TDI as derived by the WHO-WQG (1991/1996). Mean daily intake levels in the low, mid and high selenium areas were 70, 195 and 1438 µg, respectively, for males and 62, 198 and 1238 µg, respectively, for females. Selenium intake levels (estimated based on levels in food and soil) showed a good correlation with selenium blood concentrations (r=0.962). From the Yang et al. study, an LOAEL of 1.26 mg Se/day and an NOAEL of 0.85 mg Se/day were derived. The quantitative correlation between selenium levels in food and soil and those in blood as found in the Chinese study, was confirmed in a similar US study in which 142 volunteers were monitored (Longnecker et al., 1991). In the latter study no signs of selenium toxicity were observed. The average selenium intake was 239 µg/day with individual intake levels up to 724 µg/day.

[12] The RfD is the acronym that was introduced by the US-EPA in the early 1980's to replace the TDI or ADI. The status and toxicological significance of the RfD is equal to TDI or ADI.

Based on the NOAEL of 0.85 mg Se/day from the Chinese study, the US-EPA calculated an RfD of 5 µg Se/kg bw/day. An uncertainty factor 3 was applied to account for sensitive individuals. The usual factor of 10 was not considered necessary, since similar NOAELs were derived in two moderate-sized human populations exposed to selenium levels in excess of the RDA throughout a lifetime, without apparent clinical signs of selenosis. (US-EPA, 1991) The RfD of 5 µg Se/kg bw/day is accepted as the TDI to be used in the present scope.[13]

BACKGROUND EXPOSURE

Selenium levels in drinking water in the Netherlands are below 2 µg/litre (Versteegh et al. 1996). In the Netherlands, the total selenium intake via food was estimated to be 78 µg/day (based on the diet of 16-18 year old males) (Voedingsraad 1989). This level is equivalent to about 1 µg Se/kg bw/day. General population exposure via air is estimated to be low compared to the amounts ingested via food (concentrations in air are below 10 ng/m^3). In specific situations (in the vicinity of selenium-emitting industries, in occupational settings) exposure levels via air may be higher.

MISCELLANEOUS DATA

Absorption factors:

- oral: water-soluble Se compounds and Se from food: >80%; elemental Se and Se-sulfide are poorly absorbed (no absorption percentage known) (ATSDR, 1995);
- inhalation: no data;
- dermal: no data.

Guideline values:

- MAC-value (limit for occupational exposure): 0.1 mg Se/m^3 (WGD, 1989);
- WHO drinking-water quality guideline: 10 µg Se/l (WHO-WQG, 1991/1996).

CONCLUSION

TDI[14]	: 5 µg Se/kg bw/day
Background exposure	: 1 µg Se/kg bw/day

[13] It should be noted that for the derivation of this TDI the carcinogenicity data for selenium sulfide were not taken into account. The reason for this is that this compound is not expected to be present at sites of soil contamination. A further point to note here is that, as for other selenium compounds, in routine chemical analyses of soil, selenium sulfide is analysed as *total* selenium (i.e. the concentration of selemium *sulfide* is not determined separately)

[14] The carcinogenicity data for selenium sulfide have not been included in the derivation of this TDI - see footnote 2 on previous page).

COMPILATION RECORD:

Database determination based on: - review documents (as included in the reference list below)

Profile compilation by: J.G.M. van Engelen & P.J.C.M. Janssen

Profile review by: J.v. Benthem, A.G.A.C. Knaap, M.N. Pieters & G.J.A. Speijers Toxicology Advisory Group, 27-08-1996.

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RIVM-Centre for Substances and Risk Assessment

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APPENDIX 3: TELLURIUM

INTRODUCTION

Chemically tellurium resembles selenium and sulfur. It forms compounds in oxidation states -2, +2, +4 and +6. Toxicological data (mostly very limited data) are available for elemental tellurium, tellurates (TeO_3^{2-}), tellurites (TeO_4^{2-}), tellurous acid (H_2TeO_3), telluric acid (H_2TeO_4) and tellurium dioxide.

RELEVANT ROUTE

Exposure route considered relevant in present context: oral.

TOXICITY

There is no evidence that tellurium is essential for either humans or animals (Gerhardsson et al. 1986).

Some data on metabolism are available. After oral administration of soluble salts of tellurium (sodium tellurite & tellurate) absorption percentages of 25% ± 10% were found in humans. With metallic tellurium this was about 10%. (Kron et al., 1991) After absorption into the body tellurium is stored in bones, from which it is subsequently eliminated very slowly (rough estimate of half time: 600 days with standard deviation 5000 days). A small part (0.1%) of the absorbed amount is exhaled (probably as methyl tellurium) producing a garlic-like odour of the exhaled breath (this was observed in both experimental animals and humans). In rats tellurium has been demonstrated to cross the blood-brain barrier and the placenta. (Gerhardsson et al., 1986)

Tellurium has not been evaluated by IARC. Data on carcinogenicity are very limited, there being no data for humans and only two limited drinking-water studies in rats and mice, respectively. In the latter studies sodium tellurite and sodium tellurate were administered to drinking-water at a concentration of 2 mg Te/litre during the entire lifetime of the animals. No increase in tumour incidence was seen. (Schroeder & Mitchner, 1972; Gerhardsson et al., 1986) There are no data on the genotoxicity of tellurium compounds.

Adequate toxicological studies (short-term or long-term) are lacking. In Gerhardsson et al. (1986) the results of a rat feeding study, reported in 1948, is given. Liver effects (reportedly ranging from cellular swelling to hydropic and fatty degeneration and cell necrosis) and kidney effects (cellular swelling, necrosis accompanied in some rats by oliguria and anuria) were seen after administration of TeO_2 in feed at concentrations of 375 to 1500 mg Te/kg feed for 24-128 days. In this study there was no NOAEL. (De Meio & Jetter, 1948 as cited in Gerhardsson et al., 1986) In several studies in rats (mostly young rats) peripheral neuropathy with weakness and/or paralysis of the hind legs has been observed at dietary concentrations of 1% to 1.25% (study duration not given). These effects are due to damage to the Schwann cells of the nervous system. An oral NOAEL for these effects is lacking. In some studies (rat, Peking duck) damage to brain cells has been detected at high dose levels. The dose-response relation for this effect has not been determined. In a behavioural study in weanling rats

severe impairment of learning ability was observed after 6 months' exposure to elemental tellurium at 3000 mg Te/kg diet; for this study also, no NOAEL is given. (Gerhardsson et al., 1986)

In rats tellurium has been demonstrated to be teratogenic. These findings, originally made in the 1960's and early 70's have been confirmed in the more recent study in rats reported by Johnson et al. (1988). In the latter study metallic tellurium was tested. In rats test concentrations of 0, 30, 300, 3000 and 15000 mg Te/kg feed were administered from day 6 through day 15 of gestation. Toxic effects (growth retardation, clinical symptoms) in maternal animals were seen at ≥ 300 mg/kg. Teratogenic effects in foetuses (i.e. hydrocephalus, tail abnormalities, shortened radius, rotation of hind limbs) were observed at 3000 and 15000 mg/kg. The NOAEL in this study was 30 mg Te/kg feed (equal to 2.1 mg/kg bw/day). (Johnson et al., 1988) The same authors report the results of an oral teratogenicity study with metallic tellurium in rabbits. The tested dose levels were 0, 17.5, 175, 1750 and 5250 mg Te/kg feed and administration was from day 6 through day 18 of gestation. Maternal toxicity (including growth retardation, decreased motor activity) was seen at ≥ 1750 mg/kg. The only effect on foetuses was a slight increase in the incidence of retarded skeletal development and non-specific abnormalities, both ocurring at 5250 mg/kg only. The NOAEL in this study was 175 mg Te/kg feed (equivalent with 5.25 mg/kg bw). (Johnson et al., 1988)
No reproduction studies are available.

The available human data are limited. Some cases of oral intoxications are known; the only conclusion to be derived from these cases is that 30 mg Te/kg bw orally is a lethal dose. (Gerhardsson et al., 1986)
For the detection of exposures the presence or absence of the garlic-like odour in exhaled breath is a sensitive indicator. For worker exposure it has been estimated that concentrations of ≤ 0.01 mg Te/m^3 are needed to avoid the smell entirely (cf. MAC-value = 0.1 mg/m^3). (Gerhardsson et al. (1986)

The above shows the available data set for tellurium to be very incomplete. No or no adequate studies are available on carcinogenicity, genotoxicity, short-term & long-term toxicity and reproductive toxicity. This very limited data set does not allow derivation of a TDI. A *provisional* value (PTDI) may be derived as follows. Based on the NOAEL of 2.1 mg/kg bw/day from the rat teratogenicity study reported by Johnson et al. (1988), a PTDI of 2 µg/kg bw/day is calculated. The uncertainty factor used is 1000 (10 for interspecies variation, 10 for intraspecies variation, extra factor 10 for the limitations in the data set). Again, it is stressed that the reliability of this value is low because of the large gaps in the data base (an adequate semichronic animal study that, where usable human data are lacking, in general should be considered as a sort of minimum requirement for a TDI is not available for tellurium; using the NOAEL from the rat teratogenicity study is a make-shift but unavoidable step when a quantitative indication of a chronic limit value for tellurium is to be given).

BACKGROUND EXPOSURE

Few data are available. Food is considered the major source of background exposure for the general population. Gerhardsson et al. (1986) cite a publication from 1967 in which total daily intake via food

in the USA was estimated at 100 µg/day (equivalent to 1.4 µg/kg bw/day for a 70 kg adult). Further information is lacking.

MISCELLANEOUS DATA

- Absorption factors:
  - oral: metallic tellurium 10%, tellurites & tellurates ≤ 35% (mean + one s.d.);
  - inhalation: no data;
  - dermal: no data.

Guideline values:

- MAC-value (limit for occupational exposure): 0.1 mg Te/m^3 (SZW, 1995).

CONCLUSION

PTDI:	2 µg/kg bw/day
Background exposure	1.4 µg/kg bw/day

COMPILATION RECORD:

Database determination based on: - the review document by Gerhardsson et al. (1986), RTECS file & HSDB file;
- additional literature search (Toxline 1988-1996)

Profile compilation by: P.J.C.M. Janssen & M.E. van Apeldoorn

Profile review by: G.J.A. Speijers, M.N. Pieters & J.v. Benthem (Toxicology Advisory Group, 13-08-1996)

August 1996

RIVM-Centre for Substances and Risk Assessment

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APPENDIX 4: THALLIUM

Introduction

Pure thallium is a soft, bluish-white metal that is widely distributed in trace amounts in the earth's crust. In the environment thallium can be found in pure form or mixed with other metals in the form of alloys. It can also be found combined with other substances such as bromine, chlorine, fluorine and iodine to form salts. (ASTDR, 1992) Thallium exists in two chemical states, Tl^{+1} and Tl^{+3}. Inorganic Tl^{+1} compounds are more stable than their Tl^{+3} analogues. However Tl^{+3} can also form stable complexes with many ligands. (US-EPA, 1993) Thallium is present in emissions from coal-burning power plants and from copper, lead and zinc smelters. It has been extensively used as a rodenticide and, more recently, in the production of photovoltaic cells, in electronic synthesis and in myocardial imaging. (European , 1994)

Relevant route

Exposure route considered to be relevant in the present context: oral.

Toxicity

The toxicological data available for thallium and its compounds do not allow differential evaluation of the toxicological effects of the different oxidation states in which thallium occurs. Thus, following the approach taken in the existing toxicity evaluations for thallium (Kazantzis, 1986; US-EPA, 1990 ; ATSDR, 1992; US-EPA, 1993), for the present evaluation the different ionic forms of thallium and metallic thallium are treated as being equipotent indicators of thallium toxicity.

The data on metabolism may be summarised as follows. Thallium is readily absorbed by humans and laboratory animals following oral and dermal administration (US-EPA, 1992). Measurements concerning thallium concentrations in tissues and blood carried out in a female cancer patient dosed orally with thallium sulfate and thallium nitrate suggest that in humans most of the ingested thallium is absorbed. An early (1960) study in rats indicates complete absorption from the gastrointestinal tract. (ATSDR, 1992) Limited animal data indicate that Tl distributes throughout the body, including testes, muscle and kidneys. The highest concentrations were found in kidneys. For humans the US-EPA established an excretion half-life of 21.7 days. (ASTDR, 1992; IPCS, 1996) Limited data indicate that thallium can be absorbed through the skin and undergoes rapid transplacental transfer in mice and rats (US-EPA, 1992).

No IARC evaluation is available for thallium. Relevant studies regarding carcinogenicity are not available. Thallium carbonate induced single stranded DNA breaks in rat and mice embryo cells *in vitro* (Zasukhina et al., 1983). Reverse mutation assays in *Salmonella typhimurium* and *Escherichia coli* were negative (US-EPA, 1992), but limitations of the Ames assay for detection of metal induced mutagenesis make the results inconclusive. Thallium nitrate caused DNA damage in *Bacillus subtilis*. In an *in vitro* assay thallium acetate produced a significant and dose related enhancement of viral-induced cell transformation of Syrian hamster embryo cells (US-EPA, 1992). In an *in vitro* experiment Zhang (1988) showed that thallium carbonate induced SCEs and chromosome

aberrations in one cell line and HGPTR mutations in another cell line. However, no SCEs were observed in bone marrow cells *in vivo* of Chinese hamsters administered thallium chloride (US-EPA, 1992). Thallium induced dominant lethals in male rats *in vivo* after oral exposure as thallium carbonate (Zasukhina et al., 1983).

Based on this limited set of mutagenicity studies an overall conclusion with respect to the genotoxicity of thallium is not possible. However, a genetic risk of thallium can not be excluded, the more so since several animal experiments (summarized in IPCS, 1996) showed that thallium reaches the testes. Given the lack of a conclusion with respect to genotoxicity and the lack of data on carcinogenicity the only feasible option in limit value derivation is calculation of a (provisional) TDI value using a threshold approach.

The only adequate oral study with repeated exposure is a 90-day gavage study in rats performed at the U.S.-EPA. This is an unpublished study by Stolz et al. (1986) of which only the summary of results as given in US-EPA (1993) is available. In this study rats were treated by gavage with 0, 0.01, 0.05 or 0.25 mg/kg bw/day of an aqueous solution of thallium sulfate (dose levels as thallium sulfate) for 13 weeks. No gross-pathological or histopathological effects were observed. The only changes found were increased activities of ASAT and LDH and blood serum sodium concentrations. In the available abstract it is pointed out that these changes were statistically significant but that it was not possible to ascertain whether these effects were dose-related due to scattering of data points. The US-EPA concluded that, based on the absence of gross pathological and histopathological effects at this dose level, the highest tested dose level of 0.25 mg Tl_2SO_4/kg bw/day (equal to 0.2 mg Tl/kg bw/day) was the NOAEL in this study. (US-EPA, 1993)

With respect to the reproduction and teratogenicity endpoints some studies were performed, the results of which are summarised in US-EPA (1993) and IPCS (1996). Teratogenicity studies were carried out in rats and mice by Claussen et al. (1981) using thallous acetate and chloride as test compounds. Pregnant mice were dosed by gavage at daily doses of 0, 3 or 6 mg/kg bw/day on days 6 through 15 of gestation. In the groups treated with thallous chloride, a slight increase in postimplantation loss and postnatal mortality was noted only at the 6 mg/kg dose level. The NOAEL was concluded to be 3 mg TlCl/kg bw/day (equivalent to 2.3 mg Tl/kg bw/day). For groups receiving thallous acetate, slightly increased incidences of cleft palate (incidences not given) were observed at 3 and 6 mg/kg and a slight reduction in fetal weights was noted at 6 mg/kg only. The LOAEL was 3 mg thallous acetate/kg bw/day (equivalent to 2.6 mg Tl/kg bw/day). (Claussen et al., 1981 as cited in US-EPA, 1993) A similar experiment was performed with rats using dose levels of 0, 3, 4.5 or 6 mg thallous acetate or thallous chloride/kg bw/day administered by gavage on days 6 through 15 of gestation. At the two highest dose levels all maternal animals died. At the lowest dose developmental effects including wavy ribs and dumbbell-shaped sternebrae in fetuses, and a very slight increase in postnatal mortality were observed. For both thallous acetate and chloride the LOAEL was 3 mg/kg bw/day (equivalent to 2.3 mg Tl/kg bw for thallous acetate and to 2.6 mg Tl/kg bw/day for thallous chloride). (Claussen et al., 1981 as cited in US-EPA, 1993) Decreased sperm maturation and mobility, inhibition of β-glucuronidase activity and histopathological alterations of the testes were

observed in male rats after an average daily intake of 0.27 mg Tl/rat (approximately 0.74 mg Tl/kg bw/day, administered as thallium sulfate; only one dose level tested) in the drinking-water for 60 days (Formigli et al., 1986). Several early studies in rats and mice (acute or semichronic duration) also have shown adverse effects on testes and spermatogenesis. Reported effects include testes atrophy, decreased sperm fertility and motility and histological changes of the germinative epithelium (IPCS, 1996). These limited studies provide only limited information on the exact nature of, and the dose response relation for, the effect of thallium on the male reproductive system.

Limited human data are available. Formerly (before 1945) thallium was used in medicine, mainly as a depilatory drug. Many cases of thallium intoxications have been reported. The reported cases relate to both unintentional exposures (worker exposures, presence as contaminant in herbs) and intentional exposures (medicinal use, suicide attemps, use as abortion-inducing agent). In cases of accidental oral exposures the critical organ mostly was the central nervous system. The minimum oral dose for Tl in adult humans is estimated to be in the range of 0.2 to 1.0 grams (3 to 14 mg Tl/kg bw for a 70-kg adult). In the case studies a wide range of symptoms, including ataxia, alopecia, impairment of renal function, tachycardia, high blood pressure, coma and death have been reported. (US-EPA, 1992 & 1993) A comprehensive review of the reported cases of thallium intoxications in humans is given in IPCS (1996). In this same review it is stated that intake of 10 µg thallium is unlikely to cause adverse health effects. From the information given, however, it cannot be determined how this figure was derived from the data.

From the above data a TDI can be derived as follows. The available data set for thallium compounds is very limited. A genetic risk cannot be excluded. Due to the limitations in the data set only a *provisional* TDI (PTDI) can be derived. Based on the NOAEL of 0.20 mg Tl/kg bw/day from the 90-day gavage study in rats (Stolz et al., 1986 as cited in US-EPA, 1990 & 1993) a PTDI is calculated using an uncertainty factor of 1000 (10 for interspecies variation, 10 for intraspecies variation and an extra factor 10 for using a subchronic study instead of a chronic study). The result is a PTDI of 0.2 µg/kg bw. The TDI is provisonal because of limitations in the data set including limited available information on the pivotal study.

BACKGROUND EXPOSURE

There are no data on general population background exposure to thallium in the Netherlands (only information for other countries is available). The mean thallium concentration in the earth's crust is 1 µg/g (US-EPA, 1993).

Thallium is present in the sea at concentrations of around 0.01 µg/litre and in freshwater the levels ranged from 0.01 to 14 µg/litre. Air levels reported from Nebraska were in the order of 0.04 to 0.48 ng/m^3. (Kazantzis, 1986) In six United States cities the thallium concentrations in air ranged from 0.02 to 0.1 ng/m^3, with a typical concentration of 0.04 ng/m^3. Geometric mean concentrations measured during 1985-1986 in Genoa, Italy were about 0.015 µg/m^3. (ASTDR, 1991) The dietary intake of thallium has been estimated at about 2 µg/day, based on the sparse data available (Kazantzis, 1986; European, 1994).

From the above data the general population total background is estimated to be 0.03 µg/kg bw/day.

Miscellaneous data

- Absorption factors:

  No quantitative data on oral, dermal or inhalational absorption are available. According to US-EPA (1993) thallium is readily absorbed by humans and laboratory animals following oral, dermal or intratracheal absorption.

- Guideline values:

  MAC value (limit for occupational exposure): 0.1 mgTl/m^3 (SZW, 1995).

Conclusion

PTDI: 0.2 µg/kg bw/day

Background exposure: 0.03 µg/kg bw/day

COMPILATION RECORD:

Database determination based on: - the review documents (as included in the reference list below)
- additional literature search (Toxline 1989-1996)

Profile compilation by: M.F.A. Wouters & P.J.C.M. Janssen

Adviser: J. van Benthem (genotoxicity)

Profile review by: A.Knaap, G.Speijers, J.v Benthem (Toxicology Advisory Group d.d.10-9-1996)

September,1996

RIVM- Centre for Substances and Risk Assessment

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APPENDIX 5: CHLOROANILINES

INTRODUCTION

The chloroanilines (CA) are a group of compounds consisting of monochloroanilines (3 isomers, i.e. 2-, 3- and 4-MCA), dichloroanilines (6 isomers, i.e. 2,3-, 2,4-, 2,5-, 2,6-, 3,4 and 3,5-DCA), trichloroanilines (4 isomers, i.e. 2,3,4-, 2,3,5-, 2,4,5- and 2,3,6-TCA), tetrachloroanilines (2 isomers, i.e. 2,3,4,5- and 2,3,4,6-TeCA) and pentachloroaniline (PCA, 1 isomer). 2- and 3-MCA are used as intermediates, mainly in the production of pesticides and herbicides, pigments and pharmaceuticals (BUA, 1991). 4-MCA is widely used in the dye, chemical, textile, rubber and pharmaceutical industries (NTP, 1989; IARC, 1993). 2,4- and 2,5-DCA are used as precursors for the synthesis of dyestuffs and pigments. 3,4-DCA is used for the production of herbicides (e.g. linuron, diuron and propanil).

4-MCA is a known environmental degradation product of several herbicides (including linuron, monolinuron, buturon and dibenzofluron) (Anonymous, 1989; IARC, 1993). Chloroanilines are also primary plant metabolites of acylanilide, phenylurea and carbamate pesticides (Sandermann et al., 1992, Barnett et al., 1992). Chloroanilines may thus be released into the environment due to the (bio)degradation (hydrolysis, reduction) of pesticides and, additionally, pigments, but also as an impurity of pesticides and herbicides (RIVM, 1991; BUA, 1991, BUA, 1993b). For the TCAs, TeCAs and PCA there are no data on possible uses or sources of environmental occurrence (RIVM, 1991).

RELEVANT ROUTE

Exposure routes considered relevant in present context: oral, dermal, and inhalation[15]. Absorption through the skin is especially recognized (IARC, 1993; NTP, 1989; BUA, 1991; BUA, 1993b)

TOXICITY

For each of the monochloroanilines toxicity data are available. 4-MCA is the isomer with the largest data base. For the dichloroanilines and 2,4,6-TCA, limited toxicity data are available. No toxicity data are available for the other TCAs, TeCAs and PCA.

Monochloroanilines

4-MCA

In metabolism studies carried out in rats, mice and monkeys 4-MCA was shown to be readily absorbed through the gastrointestinal tract after oral dosing. Of the applied ^{14}C-4-MCA 67-90% was excreted in urine and 1-8% in faeces. The major urinary metabolite in all three species was 4-chloroaniline-2-sulfate. In monkeys, *p*-chloroacetanilide and 4-chloroaniline-2-sulfate were the major metabolites found in plasma. (IARC, 1993) There are data indicating ready absorption through the

[15] According to the RIVM classification system for volatility as developed for the evaluation of environmental fate of pesticides (scope: national pesticide registration) the MCAs and DCAs are *volatile*. For the TCAs, TeCAs and PCA no data on volatility were found in literature.

skin (no quantitative determination of dermal absorption available, however) (NTP, 1989). Absorption levels after inhalation are unknown.

The IARC classified 4-MCA in group 2B (possibly carcinogenic to humans), based on *inadequate evidence* in humans and *sufficient evidence* in experimental animals (IARC, 1993). This conclusion is based on the carcinogenicity studies carried out within the US-National Toxicology Program. Feeding experiments in rats and mice were carried out in the 1970's (NCI, 1979) and gavage studies were done in rats and mice in the 1980's (NTP, 1989). The rationale for the repetition of the experiments was that in the first experiment the animals could have received the chemical at less than the target dose, since 4-MCA appeared to be unstable in feed.

In the NCI (1979) experiment, mice fed a diet containing 2500 or 5000 mg 4-MCA/kg food for 78 weeks (followed by a 13-week observation period) showed a statistically significant increase of the incidence of hemangiosarcomas in subcutaneous tissue, spleen, liver, and kidney (sum-incidences in males: 2/20, 9/50, and 14/50 at 0, 2500 and 5000 mg/kg, respectively; in females: 0/18, 3/49 and 7/42). Rats (Fischer 344/N) receiving a diet containing 250 or 500 mg 4-MCA/kg food for the same period (followed by a 24-week observation period) revealed a statistically significant increase of the incidence of mesenchymal tumours (fibroma, fibrosarcoma, osteosarcoma, sarcoma unspecified) of the spleen or splenic capsule in both males (0/20, 0/49 and 10/49) and females (0/18, 2/49 and 5/42). (NCI, 1979) In the NTP (1989) study, 0, 2, 6 or 18 mg 4-MCA/kg bw/day was administered by gavage in aqueous hydrochloric acid, to F344/N rats for 5 days/week for 103 weeks. B6C3F_1 mice received 0, 3, 10 or 30 mg/kg/day on the same schedule. In male rats, an increase was found in the incidence of proliferative mesenchymal lesions in the spleen, varying from non-malignant fibrosis to highly malignant sarcomas. The incidence of fibrosarcoma, osteosarcoma and hemangiosarcoma together was 0/49 (controls), 1/50 (2 mg/kg group), 3/50 (6 mg/kg group) and 38/50 (18 mg/kg group). While the increased incidence of splenic fibrosis was also found in the females, the neoplastic changes were not. The incidence of pheochromocytomas (benign and malignant combined) was elevated with a statistically significant positive trend and statistically significantly different compared to controls in the males of the 18 mg/kg group (incidences: 13/49, 14/48, 15/48, 26/49).
In male mice, a statistically significant increase was found in the number of hepatocellular carcinomas in the 10 and 30 mg/kg group, and in all groups when hepatocellular adenomas and carcinomas were combined (incidences: 3/50, 7/49, 11/50, 17/50). No such increase was found in the females. The incidence of hemangiosarcomas in male mice of the 30 mg/kg group was marginally elevated compared to the controls (incidences: 4/50, 4/49, 1/50, 10/50). (NTP, 1989)

No mutagenic activity of 4-MCA was observed in most gene mutation tests with bacteria. For *Salmonella typhimurium* tester strains TA98 and TA100 results were conflicting (with metabolic activation positive for TA98 and weakly positive for TA100 in some, but not all, tests). 4-MCA induced gene mutations in *Aspergillus Nidulans* and in mouse L5178Y lymphoma cells *in vitro* (both with and without activation). 4-MCA with metabolic activation induced chomosomal aberrations in one *in vitro* assay with CHO cells but results of two other tests in the same test system were either negative, or weakly positive (without activation). Sister chromatid exchanges were seen in two tests

in CHO-cells *in vitro*. Finally, 4-MCA gave a positive result in one out of two *in vitro* UDS-tests in rat hepatocytes (NTP, 1989). A positive result of 4-MCA in one *in vitro* cell transformation assay with Syrian hamster embryo cells was reported but no effect was found in another such test (IARC, 1993). The only *in vivo* study available is an unpublished mouse bone marrow micronucleus study. The only information available on this study is the summary of its results as given in the US-EPA OTS TSCATS data file. In NMRI mice receiving doses of 0, 50, 100 and 200 mg 4-MCA/kg bw no increase in the numbers of micronuclei in polychromatic or normochromatic erythrocytes was found (summary only, report submitted to EPA/OTS as cited in the TSCATS-file).

In toxicological experiments in animals methemoglobin formation is the conspicuous effect produced by 4-MCA. In this respect, key studies are the two-year NTP carcinogenicity studies (NTP, 1989 - study already mentioned above), and the two 13-week studies in mice and rats, respectively (NTP, 1989; Chhabra et al., 1990). In the 13-week studies, rats were treated with 0, 5, 10, 20, 40 or 80 mg 4-MCA /kg bw/day (5 days/week) and mice were treated with 0, 7.5, 15, 30, 60 or 120 mg 4-MCA/kg bw/day, according to the same schedule. Treatment with 4-MCA caused a statistically significant increase of methemoglobin levels in blood at all dose levels, both in mice and rats (exception: female mice at 7.5 mg/kg). Other parameters indicative of regenerative anemia changed accordingly, e.g., there was a decrease in haematocrit values, and an elevation of nucleated erythrocytes, in mice as well as rats. The LOAEL from these studies is 5 mg/kg bw/day (no NOAEL), based on methemoglobinemia as the critical effect. In the 2-year NTP carcinogenicity study in rats, blood-biochemical parameters were recorded at 6, 12, 18 and 24 months. Methemoglobin levels were increased (statistically significant) at all time points in the 6 and 18 mg/kg groups, and at 6 and 18 months in the 2 mg/kg group. Again, other parameters indicative of regenerative anemia changed accordingly. The LOAEL from these studies is 2 mg/kg bw/day.

Information on the toxicity of 4-MCA in humans is limited. In case studies, after short-term exposure, cyanosis has been reported. Similar data for long-term exposure showed that 4-MCA may produce reversible anemia. (Linch et al., 1974; Gosselin et al., 1984) Methemoglobinemia and hemolytic anemia were found in patients treated with high doses of sulofenur, a drug that is metabolized partly into 4-MCA (Ehlhardt, 1991, as cited in IARC, 1993). Severe methemoglobinemia was found in premature neonates intoxicated with 4-MCA, originating from chlorhexidine gluconate, a desinfectant for incubators (Van der Vorst et al, 1990, as cited in IARC, 1993).

No data are available on the inhalational and dermal effects of 4-MCA.

2-MCA

The available data on metabolism are very limited. Based on the toxic effects in mammals after oral, dermal and inhalational administration of 2-MCA, absorption by these routes may be anticipated, although no quantitative data are available on absorption levels. 2-MCA is rapidly excreted in the urine, mainly as metabolites; rabbits treated orally with 2-MCA, predominantly excreted 4-amino-3-chlorophenol in the urine, indicating that hydroxylation is the predominant phase I-reaction (BUA, 1991).

For 2-MCA there are no data on carcinogenicity. As to mutagenicity results for 2-MCA, the compound has given consistently negative results in gene mutation tests with bacteria and yeast. In contrast, 2-MCA was positive in a reverse mutation test with *A. Nidulans*, an *in vitro* gene mutation test with Chinese hamster V79 cells, and an *in vitro* mouse lymphoma test. The compound, however, did not cause chromosome aberrations in an *in vitro* test with Chinese hamster lung fibroblasts. 2-MCA was positive in DNA repair tests in *E. coli* strains, but did not cause an effect in a UDS-test with primary rat hepatocytes. In *in vivo* studies 2-MCA-treatment induced a slight elevation of micronuclei-bearing polychromatic erythrocytes in two micronucleus tests in mice (single oral (toxic) doses of 1000 and 1500 mg/kg bw). (BUA, 1991)

For the oral route two 13-week toxicity studies, carried out in rats and mice, respectively, are available. These are unpublished studies the results of which are available as a summary only (BUA, 1993a). In one study, Fischer 344/N rats were treated orally with 0, 10, 20, 40, 80, and 160 mg 2-MCA/kg bw/day for 13 weeks. The predominant effect in this study was a rise in methemoglobin levels in all 2-MCA-treated groups, accompanied by cyanosis, tremor, enlarged spleen, hematopoiesis in spleen and bone marrow at ≥ 40 mg/kg. The same effects were seen in B6C3F1 mice treated according to an identical protocol. Thus, the LOAEL from these studies is 10 mg/kg bw/day (critical effect: increased blood methemoglobin levels in both mice and rats) (BUA, 1993a). A further relevant study for the oral route is a teratogenicity study. Rats orally treated with either 0, 10, 50 or 250 mg 2-MCA/kg bw/day on days 6-15 of gestation, showed no teratogenic effect (BUA, 1991).

The only inhalation study available is a subacute rat study. This is an unpublished study the only information on which is the summary of results as given in BUA (1993a). In rats after exposure to 0, 39, 217, or 886 mg 2-MCA/m^3 air for 4 weeks (5 days/week, 6 hours/day) increased methemoglobin levels, presence of Heinz bodies and decreased erythrocytes and hematocrit values were found at ≥39 mg/m^3. The LOAEL from this study is 39 mg/m^3 (BUA, 1993a).

No dermal toxicity studies are available for 2-MCA. The only information for the dermal route involves skin irritation, 2-MCA being classified as non-irritating for the skin according to EC guidelines (BUA, 1991).

Human data are limited to a report of anemia and cyanosis in factory workers who were exposed chronically to a number of aromatic nitro and amino compounds, including 2-MCA and 3-MCA (BUA, 1991).

3-MCA

The available data on metabolism are limited. Based on the toxic effects in mammals after oral, dermal and inhalational administration of 3-MCA, absorption by these routes may be anticipated, although no quantitative data are available on absorption levels. The predominant metabolic reaction in rats after a single oral dose of 150 mg 3-MCA/kg bw was hydroxylation. The main metabolite was a derivative of 4-amino-2-chlorophenol, 2-amino-4-chlorophenol being a minor metabolite. Only 1%

of the administered dose was excreted in the urine as 3-MCA. Excretion was rapid, being practically complete at 24 hours after administration. The above metabolites were also found in the urine of 3-MCA-treated rabbits (BUA, 1991).

For 3-MCA there are no data on carcinogenicity. In mutagenicity assays 3-MCA did not elevate the number of revertants in gene mutation tests with bacteria. Similarly to 2-MCA, results in a gene mutation test with *A. Nidulans* were positive. Moreover, 3-MCA caused gene mutations in an *in vitro* test with Chinese hamster V79 cells. Additionally, an *in vitro* mouse lymphoma test gave a positive result. 3-MCA also increased the number of SCE in CHO cells *in vitro*, but the amount of DNA repair in primary hepatocytes in an UDS test was not influenced by treatment with 3-MCA. *In vivo* genotoxicity tests with 3-MCA gave equivocal results. In one experiment, 3-MCA caused a slight but statistically significant increase of the number of micronuclei in male (but not female) mice (single i.p. injection). In a second study this result was not reproduced, but the validity of this test is uncertain since in this experiment there was no proof that the compound had reached the bone marrow (BUA, 1991).

Data on oral toxicity (semichronic, chronic) of 3-MCA are scarce, only one 13-week study with Fischer 344 rats and B6C3F1 mice being available. These unpublished studies used the same protocol as the unpublished studies for 2-MCA given above. From the studies with 3-MCA also no full report but only the summary as given in BUA (1993a), is available. The predominant effect in rats and mice was, similarly as for the other MCAs tested, a rise in methemoglobin levels in all 3-MCA-treated groups, accompanied by hematopoiesis in the spleen. Besides, Heinz bodies and anemia were found in the groups treated with ≥40 mg/kg bw/day (≥80 mg/kg bw for mice). (BUA, 1993A) The LOAEL from these studies is 10 mg/kg bw/day (critical effect: elevation of blood methemoglobin levels in both mice and rats).

For the inhalation route the only study to be mentioned is a subacute inhalational study in which rats were exposed to 0, 32, 160, or 265 mg 3-MCA/m^3 air for 2 weeks (5 days/week, 6 hours/day). An elevation of methemoglobin levels and a decrease of erythrocytes and hematocrit values were seen at ≥32 mg/m^3. These parameters had returned to normal after a two-week recovery period. The LOAEL from this study is 32 mg/m^3 (BUA, 1991) .

The only data on the effects of 3-MCA after dermal application are skin irritation tests, showing that 3-MCA is slightly irritating to the skin (BUA, 1991).

Data on toxicity in humans are scarce. Cyanosis was the main effect in two reported accidental exposures to high oral doses of 3-MCA. Of 26 dye factory workers in India, who suffered from hand-eczema, 8 gave a positive reaction in a patch test with 3-MCA.HCl, indicating that 3-MCA may be a sensitizing agent (BUA, 1991).

Dichloroanilines

General

Data on the toxicity of the dichloroanilines are limited, only limited data being available for 2,4-, 2,5- and 3,4-DCA. For these dichloroanilines, absorption through the gastrointestinal tract, skin, and lung is indicated by the formation of methemoglobin in acute toxicity tests (although quantitative data are not available). In one study in rabbits fed a diet containing either 2,4-, 2,5 or 3,4 DCA, hydroxylated compounds were found in the urine, in ortho- and para-positions of the amino-group, but quantitative data on the metabolites found were not given.

For the dichloroanilines no carcinogenicity data are available. The main effect of the above dichloroaniline isomers is methemoglobinemia, but to date no comparative studies to reveal the relative capacity of the various dichloroanilines are available. Data on the toxicity of dichloroanilines in humans are rare. Of 325 cases of cyanosis in England between 1961 and 1980, five were attributed to exposure to dichloroanilines. (BUA, 1993b)

2,4-DCA

2,4-DCA gave negative results in two gene mutation tests with bacteria. Moderate irritation was observed in a skin irritation test with 2,4-DCA. No other data on the toxicity of 2,4 DCA are available.

2,5-DCA

Most data on the genotoxicity of 2,5-DCA are available in summary only. Gene mutation tests with bacteria are reported as being negative. This was also the case for both an *in vitro* cytogenetic test with Chinese hamster V79 cells, and *in vitro* UDS-tests in rat hepatocytes. (NTP, 1989; BUA, 1993b)

The only oral toxicity study with 2,5-DCA to be mentioned is an oral test in Wistar rats. This is an unpublished study; the only information available on this study is the summary of results as given in AIDA (1992). After oral dosing with 0, 30, 150 or 750 mg 2,5-DCA/kg bw/day for 28 days hemolytic anemia, and medullary and extra-medullary erythropoiesis were reported to be the main effects. The study authors reported the NOAEL to be 30 mg/kg bw/day. (AIDA, 1992)

No inhalation data are available for 2,5-DCA. For the dermal route the only items found were an irritation test, in which 2,5-DCA appeared to be negative, and a sensitisation test with guinea pigs in which 2,5-DCA appeared to cause a positive reaction (BUA, 1993b).

3,4-DCA

Of a single oral administration of 3,4-DCA, 81% was found in the urine, and 26% in the faeces, the larger part of this amount being excreted within 24 hours after administration. (BUA, 1993b)

3,4-DCA was reported to be negative in a large number of gene mutation tests with bacteria, but positive in a test with *A. Nidulans* (BUA, 1993b). Results were also negative when 3,4-DCA was tested in *in vitro* cytogenetic tests with Chinese hamster V79 cells, and human lymphocytes, and in an UDS test with rat hepatocytes *in vitro*. In contrast, 3,4-DCA gave positive results in an SCE test with human lymphocytes *in vitro* (only in combination with metabolic activation), in a DNA-damage test

with bacteria, and in another UDS test with primary rat hepatocytes. 3,4-DCA caused no elevation of micronuclei in bone marrow of male or female mice treated orally with 100 or 1000 mg 3,4 DCA/kg bw, or i.p with 20, 70 or 200 mg/kg bw (BUA, 1993b; IUCLID, 1996)

Data on the oral toxicity (acute, semichronic) of 3,4-DCA are available in summary only (BUA, 1993b; AIDA, 1992; UNEP-IRPTC, 1984), indicating that the main effect of 3,4-DCA in rats, both in oral and dermal studies, is the (dose-dependent) induction of methemoglobinemia. The available studies, however are not adequate to derive a reliable NOAEL/LOAEL. Results of 3,4-DCA in a skin-irritation test in rabbits provided no ground for classification. 3,4-DCA appeared to be sensitising in a test with guinea pigs. (BUA, 1993b)

Tri-, tetra-, pentachloroanaline(s)

These chloroanilines are almost uninvestigated. 2,4,6-TCA was weakly positive in a gene mutation test with bacteria, and elevated the number of spots in an *in vivo* spotted wing *Drosophila* test (Kugler-Steigmeier et al., 1992). Male, but not female, mice developed hepatomas (incidence: 1/16 (controls), 10/18 (low dose), 12/16 (high dose)), and vascular tumors (incidence: 2/16 (controls), 5/16 (low dose), 1/16 (high dose)) when fed a diet containing 6000 or 12000 mg 2,4,6-TCA/kg food for 18 months. In the same study, 2,4,6-TCA had no carcinogenic effect in rats treated with a diet supplemented with 3000 or 6000 mg/kg food for 5 months and 1500 and 3000 mg/kg food, respectively, for an additional 13 months. (Weisburger et al., 1978)

Evaluation and derivation of limit values

Of the **monochloroanilines**, carcinogenicity data are available for 4-MCA only. In rats 4-MCA produced a reproducible increase in splenic tumours. The spontaneous frequency of this kind of tumours in rats, is low. There are data indicating that the induction of the splenic tumours is related to the toxicity also observed in this organ. The mechanism for the formation of the splenic tumours has not been fully elucidated. The evidence currently available does not provide sufficient support for the notion that the underlying mechanism is exclusively non-genotoxic[16]. In addition, given the positive results in the genotoxicity assays with 4-MCA it cannot be ruled out that 4-MCA-produced genotoxic events contribute to this tumour formation. Similar considerations as for the splenic tumours in rats apply to the hemangiosarcomas that were observed in mice (i.e. the mechanism may be non-genotoxic but genotoxic events cannot be excluded yet). The relevance for humans of the other tumours observed in the animal bioassays carried out with 4-MCA, i.e. pheochromocytomas in rats and hepatocellular tumours in mice, cannot be established conclusively.[17] In conclusion, the weight of evidence concerning genotoxicity and carcinogenicity indicates that 4-MCA should be considered a genotoxic carcinogen.

[16] For some relevant discussion on this point see the considerations of Goodman et al. (1984) and Weinberger et al. (1985).

[17] For the hepatic tumours in mice the biological significance is difficult to establish given the high spontaneous frequency of these tumours in this particular strain of mice. An increased incidence of this kind of tumours is not considered sufficient proof for a carcinogenic action.

2-MCA and 3-MCA are structural analogues of 4-MCA, having in common with 4-MCA the structural alert for carcinogenicity (the aromatic NH_2-moiety). 2-MCA and 3-MCA gave positive results in a number of *in vitro* genotoxicity tests. In addition, both compounds were weakly positive in an *in vivo* genotoxicity test. The similarities in observed genotoxic effects and in chemical structure, are indications that, at least in a qualitative sense, 2-MCA and 3-MCA may induce the same effects as 4-MCA and consequently, that these isomers may also provisionally be regarded as genotoxic carcinogens. As to the quantitative potency of the two other monochloroanilines relative to 4 -MCA, no conclusion can be drawn due to the lack of data on this point. Since the available evidence indicates that 2-MCA and 3-MCA produce similar health effects compared to 4-MCA (i.e. genotoxicity, probably carcinogenicity, but also methemoglobinemia) derivation of a common limit value for all the monochloranilines, based on the data available for 4-MCA, is considered appropriate.

In general, derivation of the the limit value for genotoxic carcinogens warrants a non-threshold evaluation by linear extrapolation from the lowest observed tumorigenic dose. For the monochloroanilines tumour incidences selected from the bioassay results reported for 4-MCA are the basis for the non-threshold cancer risk estimation. In the present scope, the excess lifetime cancer risk level of $1 : 10^4$ is used (this is the cut-off point as incorporated in the definition of the *Maximum Permissible Risk*, MPR). As explained in a recent RIVM-report (RIVM, 1996), for genotoxic carcinogens a parallel threshold evaluation based on non-carcinogenic effects should be developed in order to check if this yields a limit value that is lower than the estimated 10^{-4} excess lifetime cancer risk. The lower value of the two (10^{-4} excess cancer risk or limit value derived via threshold approach) is chosen as the MPR. Below, the results of a threshold and a non-threshold extrapolation for 4-MCA are presented. Since only oral studies are available the oral limit value is extrapolated *route-to-route* yielding an estimate for the inhalation route.

The non-threshold cancer risk estimation for the monochloroanilines proceeds as follows. Based on the 2-year study with 4-MCA in rats (NTP, 1989) with its lowest tumorigenic dose of 18 mg/kg bw/day (tumour incidence at this dose level 38/50) and using the RIVM linear extrapolation model (formula given in VROM, 1984) the excess 10^{-4} cancer risk per person exposed to monochloroanilines (lifetime exposure) is calculated to be 0.9 µg/kg bw/day (rounded value). This value applies for the oral exposure route. For the inhalation route, a cancer risk of 1 per 10^4 lifetime exposed persons is calculated from the oral cancer risk estimate using route-to-route extrapolation. This yields a value of 4 $\mu g/m^3$. The latter value is *provisional* because it was derived using route-to-route extrapolation, a procedure involving considerable uncertainty.

For the dermal route no limit value is derived because of lack of appropriate toxicological data for this route. Route-to-route extrapolation from the oral limit value is not a feasible option at present. However, it is stressed that the available data indicate that chloroanilines, like anilines, are readily absorbed through the skin. Consequently dermal contact with soil contaminated with chloroanilines may lead to toxicologically relevant systemic exposures.

The threshold evaluation for the monochloroanilines is based on the LOAEL of 2 mg/kg bw/day from the 2-year study with 4-MCA in rats (NTP, 1989). This LOAEL after adjustment for intermittent exposure equals 1.43 mg/kg bw/day (adjustment from 5 days/week to 7 days/week). An uncertainty factor of 1000 is applied (factor 10 for use of a LOAEL, factor 10 for extrapolation from animal data to humans and a factor 10 for protection of the sensitive human subpopulations). The result is a limit value of 1.4 µg/kg bw/day.
Comparison of this limit value with the 10^{-4} excess lifetime cancer risk derived above (0.9 µg/kg bw/day) shows that the threshold derivation does not give a lower limit value.

Compared to the monochloroanilines, data on the genotoxicity of the **dichloroanilines** are even more limited. The results do not indicate that the dichloroanilines are genotoxic. Since 2,4-, 2,5-, and 3,4-DCA invariably induce methemoglobinemia, a limit value for the entire group of dichloroanilines could be based on this endpoint and for such a derivation a threshold approach would be approapriate. However the lack of adequate toxicity studies that could serve as the basis for the limit value derivation, precludes calculation of a TDI. The oral 28-day study with 2,5-DCA is not considered appropriate for this purpose (on this limited study only the very limited information as given in AIDA, 1992 is available). Despite the fact that methemoglobinemia is a well-established effect of both the mono- *and* the dichloroanilines, the potency of the dichloroanilines relative to that of the monochloroanilines, for producing this effect is unknown, precluding the use of NOAELs or LOAELs as found in studies for monochloroanilines, for the derivation of a limit value for the dichloroanilines. In conclusion, the data do not allow deriving a limit value for the dichloroanilines.

The data for 2,4,6-TCA (including a limited carcinogenicity bioassay) suggest that the **trichloroanilines**, like many other aniline derivatives, may be genotoxic carcinogens, but the data are too limited to firmly establish this. Since no semi-chronic or long-term toxicity studies are available with trichloro-, **tetrachloro-** and **pentachloroaniline(s)**, a limit value derivation for these groups of compounds is not feasible at present. Since methemoglobinemia is not a well-established effect for these groups of compounds, derivation of a limit value based on this endpoint (possibly using the data for other chloroanilines concerning this effect), is not appropriate.

BACKGROUND EXPOSURE

Data on the occurrence of chloroanilines in the Netherlands are available for mono- and dichloroanilines only. In 1990 concentrations of chloroanilines in surface waters never exceeded 0.1µg/l. In 1982, monochloroanilines concentrations of 0.21-0.46 mg/kg dry weight were determined in sediment. Because of a trend for the concentration of CA to decline in surface waters, concentrations in sediment may be lower at present (RIVM, 1991). Reportedly, dichloroaniline concentrations of 0.1-1 µg/l were found in Dutch drinking water obtained from Rhine water. (BUA, 1993b). Concentrations of dichloroanilines in the Main river in Germany were maximally 0.68 ug/l between 1989 and 1991, and sum concentrations of 2,4-DCA and 2,5-DCA in the Rhine were, in the same time period, generally lower. (BUA, 1993b)
Currently, no data are available on the occurrence of chloroanilines in food, or emission of chloroanilines, in the Netherlands.

The available data are too limited to allow estimation of general population background exposure.

MISCELLANEOUS DATA

- Absorption factors:
  - oral: 4-MCA: >84% (NTP, 1989);
  - inhalation: no data;
  - dermal: no data.
- Odour threshold when added to water (UNEP/IRPTC):
  - for 2,5-DCA: 0.02 mg/l;
  - for 3,4-DCA: 0.05 mg/l.

Taste threshold when added to water (UNEP/IRPTC):

- for 2,5-DCA: 0.02 mg/l;
- for 3,4-DCA: 0.03 mg/l.

Guideline values:

- In the Netherlands no limit value for occupational exposure has been promulgated.

CONCLUSION

Monochloroanilines

Oral excess 10^{-4} lifetime tumour risk:	0.9 µg/kg bw
Background exposure:	unknown
Provisional inhalational excess 10^{-4} lifetime tumour risk:	4 µg/m^3

Dichloroanilines, trichloroanilines, terachloroanilines and pentachloroaniline

No limit value can be derived due to lack of appropriate toxicity data

Background exposure: unknown.

COMPILATION RECORD:

Database determination based on:
- the review documents as included in the reference list below;
- EPA TSCA Test Submission (TSCATS) Data Base April 1996.
- IUCLID (1996) EU Existing Chemicals Data Base
- additional literature search: Toxline Plus, 1992-1996.

Profile compilation by: Peter Schielen & P.J.C.M. Janssen

Advisers: J. van Benthem (genotoxicity) & E.D. Kroese (carcinogenicity).

Profile review by: J. van Benthem, A.G.A.C. Knaap & G.J.A. Speijers (Toxicology Advisory Group 13-9-1996 and 17-9-1996)

September, 1996

RIVM-Centre for Substances and Risk Assessment

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APPENDIX 6: 4-CHLOROMETHYL-PHENOL

INTRODUCTION

4-Chloro-methyl-phenol has two isomers: 4-chloro-2-methyl-phenol and 4-chloro-3-methyl-phenol. 4-Chloro-2-methylphenol (*p*-chloro-*o*-cresol; PCOC) is used as an intermediate in the synthesis of the chlorophenoxy pesticides methylchlorophenoxy acetic acid (MCPA), methylchlorophenoxy butyric acid (MCPB), and mecoprop in which it is present as an impurity (0.04-4%). (BUA, 1993) In addition, PCOC is the main environmental degradation product of these pesticides. Only limited toxicological information is available for PCOC. At present, the compound is under evaluation in the EU Existing Chemicals Programme, and the information presented below is primarily taken from the draft report as prepared for this EU programme (EU, 1996).

The isomer 4-chloro-3-methylphenol (*p*-chloro-*m*-cresol; PCMC) is used as a preservative in the preparation of coatings for food packagings (RIV, 1983) and as a preservative in cosmetics (CEC, 1987). For this compound also, only limited information is available.

RELEVANT ROUTE

Exposure routes considered relevant in present context: oral and inhalation[18].

TOXICITY

4-Chloro-2-methylphenol (PCOC)

No IARC classification is available for PCOC. IARC classified the group of chlorophenoxy herbicides, in which PCOC is present as an impurity, in group 2B (*possibly carcinogenic to humans*) (IARC 1987). For PCOC itself no carcinogenicity data are available. As to genotoxicity, PCOC was negative in the Ames test. In a micronucleus test in mice (oral administration, maximum tolerated dose of 1600 mg/kg, only one dose level tested) a significant increase in the frequency of micronuclei (4-6 times higher than in the control group) was observed at all three harvest times. (Scantox, 1982f as cited in EU, 1996) Although this micronucleus test was a limited test (only one dose level), the results are unequivocally positive and thus lead to the conclusion that, in the absence of more complete data for this endpoint, the compound must be considered genotoxic *in vivo*. For the induction of this genotoxic effect, no threshold is assumed to exist (for some further explanation on this point see RIVM, 1996) and for its quantitative evaluation a non-threshold approach is warranted. However, as data on carcinogenicity are not available and, consequently, a non-threshold evaluation (quantitative cancer risk assessment based on observed tumour incidences) is not possible, derivation of a limit value via a threshold approach is the only option feasible.

[18] For PCMC the relevance of the inhalation route cannot be determined reliably due to lack of sufficient data concerning vapour pressure and volatilisation to air. For PCOC however, there are data showing that volatilisation from soil is to be expected (ref: EU, 1996).

No semichronic or chronic toxicity studies using PCOC were carried out. In a 28-day oral study PCOC was administered to rats (5/sex/group) at dose levels of 0, 50, 200 or 800 mg/kg bw/day in oleum arachidis (administration by gavage). In the highest dosed group mild liver toxicity was observed (increase in ALAT, increased liver weights). In addition, decreases were observed in erythrocyte counts, thromboplastin time and number of leucocytes. No histopathological changes were seen in any organ. The NOAEL in this study was 200 mg/kg bw. (Scantox, 1982a as cited in EU, 1996) A further 28-day oral study in rats was inadequately reported and for this reason cannot be used in the evaluation (Hattula et al., 1979 as cited in EU, 1996). With PCOC a combined repeated-dose/reproduction screening study has been performed, in which rats (10/sex/group) were administered PCOC in soybean oil by gavage at dose levels of 0, 50, 200 or 600 mg/kg for two weeks prior to mating until day 20 of gestation. In the parental animals of the high dose group, weight gain was slightly reduced. In males of this group, the hemoglobin concentration was significantly decreased. No behavioural changes were found in a neurotoxicity evaluation using a functional observation battery. No effects on reproductive or developmental parameters were observed in this study. In this study the NOAEL was 200 mg/kg bw/day. (Hansen, 1996 as cited in EU, 1996)

For the inhalation route no toxicity data that could be used in the derivation of a limit value are available for PCOC.

Dermal data for PCOC are limited to some studies concerning irritation and sensitisation. PCOC is corrosive to the skin and the eyes (effect concentrations ≥80%, NOAEL not determined). The substance was not sensitizing in the guinea pig maximization test. (EU, 1996)

4-Chloro-3-methylphenol (PCMC)

No IARC evaluation on the possible carcinogenicity of PCMC is available. Of an unpublished chronic toxicity/carcinogenicity feeding study in rats only an interim report is available (Miles Inc., 1992a) stating that evaluation of neoplastic lesions is in progress. There are no other studies on carcinogenicity. Limited mutagenicity data are available. PCMC was not mutagenic in the Ames test (+/- activation). In mammalian cells *in vitro* a test for gene mutations without and with activation, was also negative. In rat hepatocytes *in vitro* no unscheduled DNA synthesis was found. (Unpublished data of Bayer AG as cited in the IUCLID data base) *In vivo*, a micronucleus test in mice was negative (Bayer AG, 1981 as summarised in RIV, 1983). The latter assay was limited as to study outline: relatively low dose levels, no cytotoxicity in bone marrow, only one sampling time, sampling at 6 hour instead of 12 hours after last treatment. These factors reduce the value of the negative result of this assay. A further limited *in vivo* micronucleus test in mice with i.p. administration (only one dose level tested, sampling times 24, 48 and 72 hours after administration) also was negative (Unpublished data of Bayer AG as cited in the IUCLID data base).

The available limited results regarding genotoxicity and carcinogenicity as summarised above, do not indicate that PCMC is genotoxic or carcinogenic. For this reason a threshold approach is chosen in the health evaluation of PCMC.

Limited oral toxicity data are available. A standard 13-week feeding study in rats with dose levels of 0, 150, 500 and 1500 mg/kg feed showed no adverse effect (NOAEL > 1500 mg/kg feed, equivalent to > 75 mg/kg bw/day) (Bayer AG, 1981 as summarised in RIV, 1983). The interim report of the chronic feeding study in rats (Miles Inc., 1992a) already mentioned above, contained the results on growth, blood parameters, organ weights and a brief summary on the histopathology for non-neoplastic lesions. The tested dose levels in this study were 0, 400, 2000 and 10000 mg/kg feed which were given for 104 weeks. The reported effects at 10000 mg/kg were: decreased growth, clinical signs (females), increased kidney weights (males and females) and papillary necrosis, cortical dilation and fibrosis in kidneys (males only). The NOAEL in this study was 2000 mg/kg feed (equal to 103 mg/kg bw/day in males and 134 mg/kg bw/day in females). (Miles Inc., 1992a) Of an unpublished oral teratogenicity study in rats only a short summary of results is available. Pregnant rats were given 0, 30, 100 or 300 mg/kg bw/day by gavage on days 6-15 of gestation. The reported effects were: increased mortality in dams (300 mg/kg), clinical signs (unspecified) in dams (300 mg/kg), decreased growth and decreased food consumption in dams (100 mg/kg), increased incidence of early resorptions and decreased mean foetal body weight (300 mg/kg). The NOAEL in this study was 30 mg PCMC/kg bw/day. (Miles Inc., 1992b as cited in the EPA/OTS TSCATS data file) No further oral studies are available.

For the inhalation route no toxicity data that could be used in the derivation of a limit value are available for PCMC.

Dermal data for PCMC are limited to some studies concerning irritation and sensitisation. Undiluted PCMC was found to be strongly irritating for the eyes in rabbits (NOAEL not determined). Repeated application to the skin of guinea pigs produced irritation at a concentration of 30% but not at 10%. In the guinea pig maximization test for sensitising potential showed a positive response at ≥ 25% but not at lower concentrations. (RIV, 1983)

Limit value derivation

The available toxicity data are relatively limited. The results of the oral toxicity studies suggest that the two isomers have different target organs (the liver for PCOC and the kidneys for PCMC). The reliability of this conclusion, however, is limited due to the incompleteness of the available data sets. For PCMC the data base contains no information on reproduction toxicity and only limited information on teratogenicity, genotoxicity and carcinogenicity. Included in the data set for PCMC was a chronic rat study with a NOAEL of 103 mg/kg bw/day. The NOAEL from the oral teratogenicity study in rats (Miles Inc., 1992b) is lower (30 mg/kg bw/day; LOAEL 100 mg/kg bw) but from this study the available report is insufficient as a consequence of which the study cannot be evaluated properly. Despite this limitation as to available information on this study, the NOAEL of 30 mg/kg bw/day is used for calculation of the TDI. The chronic study serves as supporting information in the derivation. Using an uncertainty factor of 100 (10 for interspecies variation, 10 for intraspecies variation) a *provisional* TDI (PTDI) of 300 µg/kg bw is calculated. This is a provisional value because of the limitations in the data set including limited information on the pivotal study.

Only limited oral toxicity data are available for PCOC (no semichronic or chronic toxicity studies, no data on carcinogenicity or teratogenicity). These data are too limited to allow derivation of a reliable TDI. The only available basis for a *provisional* TDI is the NOAEL of 200 mg PCOC/kg bw/day as found in both the 28-day gavage study in rats and the repeated-dose/reproduction screening study in rats (Scantox, 1982a and Hansen 1996 both as cited in EU 1996). Based on this level and using a very high uncertainty factor of 10000 (10x10 for interspecies and intraspecies differences, an extra factor 10 for limited duration of the study and an extra factor of 10 for limitations in the data base, a PTDI of 20 µg/kg bw/day is calculated. Due to the very high uncertainty factor used in the derivation this value has low reliability (given the very limited data base for PCOC the alternative for the use of such a high uncertainty factor would be not to derive a limit value at all).

For the inhalation route no toxicity data that could be used for derivation of a limit value, are available. Provisional values may be derived from the oral PTDIs using *route-to-route* extrapolation. Using the standard assumptions for such a calculation (adult daily ventilation volume 20 m^3, absorption after inhalation 75% of oral absorption) the resulting PTCA for PCMC is 1300 µg/m^3 (rounded value) and for PCOC it is 90 µg/m^3 (rounded value). These are provisional values because they were derived from provisonal TDIs using route-to-route extrapolation, a procedure involving considerable uncertainty.

BACKGROUND EXPOSURE

No data available.

MISCELLANEOUS DATA

No data available.

CONCLUSION

4-chloro-2-methylphenol (PCOC)

PTDI:	20 µg/kg bw/day
Background exposure	unknown
PTCA:	90 µg/m^3

4-chloro-3-methylphenol (PCMC)

PTDI:	300 µg/kg bw/day
Background exposure	unknown
PTCA:	1300 µg/m^3

COMPILATION RECORD:

Database determination based on: - the review documents as included in the reference list below;
- additional literature search for PCMC (Toxline Plus, 1985-1996);
- EPA TSCA Test Submission (TSCATS) Data Base April 1996.

Profile compilation by: J.G.M. van Engelen & P.J.C.M. Janssen

Profile review by: J. van Benthem, A.G.A.C. Knaap and G.J.A. Speijers (Toxicology Advisory Group d.d. 13-9-1996)

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APPENDIX 7: 1,1,2-TRICHLOROETHANE

RELEVANT ROUTE

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

TOXICITY

IARC evaluated 1,1,2-trichloroethane (1,1,2-TCE) in 1990 (IARC, 1991) and concluded that there was *limited evidence for carcinogenicity in experimental animals*. No data on carcinogenicity of 1,1,2-TCE in humans were available. IARC placed 1,1,2-TCE in Group 3 (*not classifiable as to its carcinogenicity to humans*) (IARC, 1991).

The carcinogenicity of 1,1,2-TCE was examined in an early NCI study (NCI, 1978). In B6C3F1 mice dose levels of 195 and 390 mg/kg bw/day were administered by oral gavage (solvent corn oil) for 78 weeks with a post-dosing observation time of 12-13 weeks. The results showed a statistically significant dose-related increase in the incidences of hepatocellular carcinomas at both dose-levels (incidences in males 4/37, 18/49 & 37/49 in the control, low-dose and high-dose groups, respectively; in females 2/40, 16/48 & 40/45). In addition, significantly increased incidences of adrenal phaeochromocytoma were seen at 390 mg/kg in both males (8/48 vs. zero incidence in other groups) and females (12/43 vs. zero incidence in other groups). In this study no significant toxicity was seen in the treated groups. In an identical study in Osborne-Mendel rats with dose levels of 46 and 92 mg/kg bw/day (exposure for 78 weeks, post-dosing observation time 33-35 weeks), no significantly increased tumour incidences were seen. In this study also no significant toxicity was seen. (NCI, 1978; IARC, 1991; BUA, 1994) A 2-year subcutaneous study in rats (two dose levels, compound administration once per week) also showed no significantly increased tumour incidences (Norpoth et al., 1988 as cited in BUA, 1994 & IARC, 1991). In an initiation-promotion study in male rats, 1,1,2-TCE did not show tumour-initiating properties (Story et al., 1986). Tumour promoting assays performed with 1,1,2-TCE showed equivocal results (Story et al., 1986).

In vitro mutagenicity assays in bacteria were mostly negative in the absence as well as in the presence of a metabolic activation system. An indication for the induction of aneuploidy was found in an assay with *Aspergillus nidulans*. Assays detecting DNA-repair in prokaryotes were negative. *In vitro* UDS assays in primary mice and rat hepatocytes showed questionable results (positive in rat hepatocytes and negative in mice hepatocytes; no study details were given). An *in vitro* cell transformation assay in mouse embryonic cells showed a weakly positive effect. An *in vivo* UDS assay and a DNA-unwinding assay, both performed in mice (hepatocytes evaluated), showed negative results. An assay in *Drosophila melanogaster* detecting somatic eye mutations was weakly positive after inhalation exposure, but no dose-relationship was seen. *In vivo* studies showed DNA adduct formation in mouse and rat liver, to a greater extent in mouse liver. DNA adduct formation was also seen *in vitro* with calf thymus DNA. (BUA, 1994)

With regard to the above data on carcinogenicity and genotoxicity the following is concluded. The NCI bioassay with rats has limited value because of the absence of any signs of toxicity in this 2-year study, implying that the dose levels tested were too low (at least clearly below the Maximum Tolerated Dose). Thus, the negative result (no effect) of the rat study is not conclusive evidence for the absence of a carcinogenic effect in this species. The relevance for humans of the liver tumours as observed in the mouse NCI bioassay cannot be established conclusively.[19] The observed adrenal phaeochromocytoma are non-malignant tumours that are not considered as sufficient proof for a carcinogenic action. The data on genotoxicity do not allow drawing a firm conclusion as to the genotoxic potential of 1,1,2-TCE. The compound binds to DNA as shown in the adduct studies. An adequate evaluation of the genotoxicity endpoint requires the results of adequate tests for chromosome aberrations (*in vitro* and *in vivo*) and a test for gene mutations. A point to be noted is that in the 1,1,2-TCE metabolism *in vivo* a supposed intermediate is 2-chloroacetaldehyde, a compound that is known to be genotoxic and that may be carcinogenic[20].

In conclusion, the data on carcinogenicity and genotoxicity are inconclusive. Based on the available evidence it cannot be excluded that 1,1,2-TCE is a genotoxic carcinogen. For the genotoxic carcinogens a non-threshold approach, i.e. linear extrapolation from the lowest observed tumorigenic dose, is considered appropriate. However, in view of the lack of tumour incidences for tumour types that creditably can be used for this purpose (the relevance of the liver tumours and the phaeochromocytoma being questionable, as explained above) such an approach is not possible for 1,1,2-TCE. Derivation of a provisional TDI value via a threshold approach is the only option feasible.

1,1,2-TCE is absorbed readily through the gastrointestinal tract, the skin and the respiratory tract. After metabolisation, 1,1,2-TCE is excreted mainly in urine as S-carboxymethylcysteine and thiodiacetic acid. Via the lung, 1,1,2-TCE is excreted primarily as CO_2. 1,1,2-TCE is mainly metabolized with dependence on cytochrome P-450. (BUA, 1994) 2-Chloroacetaldehyde is assumed to be the reactive intermediate, suspected to be responsible for the toxic effects produced by 1,1,2-TCE (statements to that effect are given in ATSDR, 1989 and BUA, 1994).

The target organs for 1,1,2-TCE toxicity (oral and inhalation) are the central nervous system, the liver and the kidneys.

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[19] The determination of the biological significance of increased incidences of this kind of tumours in this strain of mice is difficult given the high spontaneous frequency of these tumours in this particular strain of mice. In the present study the incidence in the control group was somewhat below the range usually observed in controls. The marked increases in mouse liver tumours produced by 1,1,2-TCE *may* be induced via a non-genotoxic mechanism but the available evidence does not support this notion. Two relevant findings to be noted at this point is the absence of toxicity in the liver in this study (this makes an aspecific toxic mechanism (non-genotoxic) of tumour formation for the observed tumours less plausible) and the demonstration of DNA adduct formation in mouse liver *in vivo* (the significance of which, however, cannot be clarified without additional experimental evidence).

[20] Carcinogenicity data for 2-chloroacetaldhyde are too limited for an adequate evaluation of its potential for this endpoint. The compound is one of the presumed active metabolites of the known human carcinogen vinly chloride, which suggests that it may have a carcinogenic action (see US National Research Council, Drinking water and health - volume 7; National Academy Press, Washington DC, USA. 1987; ISBN 0-309-03741-7).

With respect to neurological symptoms after single oral exposure, LOAELs of 450 mg/kg bw (sedation) and 128 mg/kg bw (motor impairment) in mice and a NOAEL of 144 mg/kg bw (drowsiness) in dogs were reported (ATSDR, 1989). Concerning repeated oral exposure the most appropriate study for an oral NOAEL for limit value derivation is a 90-day drinking-water study in mice. This is the study also used by the US-EPA in its derivation of the RfD[21] for 1,1,-2-TCE (US-EPA, 1995). The concentrations administered in this study were 0, 20, 200 and 2000 mg/litre (corresponding to 0, 4.4, 46 and 305 mg/kg bw/day for males and 0, 3.9, 44 and 384 mg/kg bw/day for females). In both males and females changes in clinical chemical parameters indicative for liver damage (i.e. increased ASAT, ALAT, SAP) were observed at 2000 mg/litre. At 200 and 2000 mg/litre reduced hemoblobin and hematocrit were seen in females and a depressed humoral immune status in both sexes. The NOAEL in this study is 20 mg/litre (≅ 3.9 mg/kg bw). (Sanders et al., 1985; White et al., 1985) The only oral study on reproduction, teratogenicity or embryotoxicity is a screening test for developmental effects in mice with dosing by gavage (solvent corn oil) from day 8-12 of pregnancy (only one dose level tested: 350 mg/kg bw/day). The only effect found was increased mortality among dams (3/30 animals died). No effect was seen on growth, number of litters, average number of live offspring/litter and average weight of offspring on 1st and 3rd day after birth. No details of this study are available. (Seidenberg and Becker, 1987 as cited in BUA, 1994; Seidenberg et al., 1986 as cited in BUA, 1994)

For the inhalation route few toxicity data are available. With respect to neurological symptoms after single inhalation exposure LOAELs of 418-3750 mg/m^3 in mice (effects: CNS depression, lying down on side, loss of reflex control and anesthesia) and of 1654 mg/m^3 in rats (effect: somnolence) were reported (ATSDR, 1989). Concerning repeated inhalation exposure only one unpublished study from Dow Chemical Company (Dow, 1981, cited by Torkelson in Clayton and Clayton, 1994), is available. The available information on this study is very limited. The results are summarised in Clayton & Clayton (1994) as follows (wording slightly changed). Exposure of rats, guinea-pigs and rabbits 7 hours/day, 5 days/week, for 6 months to 82 mg/m^3 did not cause any effect on mortality, growth, hematology, clinical chemistry or histopathology. To this it was added that it has to be noted that sixteen 7 hour exposures of rats to 164 mg/m^3 resulted in minor fatty changes and cloudy swelling in the livers of female rats. Male rats appeared unaffected although the pneumonitis incidence was slightly higher in the 10 exposed male rats. (Clayton and Clayton, 1994) Based on this study 82 mg/m^3 can be considered as a NOAEL for repeated inhalation exposure. The very limited information that is available for this study precludes adequate evaluation of its result and for this reason the NOAEL derived from it has low reliability. Inhalation studies on reproduction, teratogenicity or embryotoxicity are not available.

[21] The RfD is the acronym that was introduced by the US-EPA in the early 1980's to replace the TDI or ADI. The status and toxicological significance of the RfD is equal to TDI or ADI.

For the dermal route of exposure limited data are available. 1,1,2-TCE is not highly irritating to the skin but injures the skin by defatting. No data with respect to sensitization are available. (Clayton and Clayton, 1994) In a study with a human subject a 5 minutes dermal exposure to 1.5 ml undiluted 1,1,2-TCE on the forearm under occlusion produced stinging and burning sensations with transient whitening of the skin. An uncovered dermal application with 0.1 ml (undiluted) to the same subject did not cause an effect on blood flow and no visible erythema. (Wahlberg 1984a as cited in ATSDR, 1989) A daily uncovered application of 0.1 ml for 15 days to a volunteer did not cause visible skin reactions, nor was there an increase in skin-fold thickness. (Wahlberg, 1984b as cited in ATSDR, 1989) Guinea-pigs and rabbits, receiving the same treatment (0.1 ml undiluted 1,1,2-TCE to uncovered skin) for 10 days, however did show increased skin-fold thickness. All animals showed marked erythema and edema, fissuring and scaling (Wahlberg, 1984b as cited in ATSDR, 1989).
Dermal toxicity studies in guinea pigs and rabbits with single application revealed systemic effects (including increased mortality, liver and kidney injury) at high dose levels (application of undiluted compound) (Clayton & Clayton, 1994; ATSDR, 1989). A NOAEL for repeated dermal exposure could not be established based on the limited data available.

In agreement with the RfD derivation as given by the US-EPA (1995) a TDI is derived based on the NOAEL of 3.9 mg/kg bw/day from the 90-day drinking water study in mice with the use of an uncertainty factor of 1000 (10 for interspecies variation, 10 for intraspecies variation and an extra factor of 10 for using a subchronic study instead of a chronic study). In view of the inconclusiveness with regard to carcinogenicity and genotoxicity the TDI derived is a *provisional* TDI (PTDI). Thus, a PTDI of 4 µg/kg bw is calculated.

For inhalation exposure also, only a *provisional* limit value can be established based on the NOAEL of 82 mg/m^3 from a 6-month study in several species (Dow, 1981 as cited in Clayton & Clayton, 1994). This is a provisional value because this NOAEL has low reliability and because of the inconclusiveness with regard to carcinogenicity and genotoxicity. Adjustment of this NOAEL of 82 mg/m^3 (exposure for 7 hours/day, 5 days/week) to continuous exposure (24 hours/day, 7 days/week) gives a duration-adjusted value of 7/24 x 5/7 x 82 = 17 mg/m^3. Using an uncertainty factor 1000 (10 for interspecies variation, 10 for intraspecies variation and an extra factor of 10 for using a subchronic study instead of a chronic study) a provisional TCA (PTCA) of 17 µg/m^3 can be derived. This PTCA is supported by the result of the *route-to-route* extrapolation from the oral TDI (of 4 µg/kg bw) as presented in RIVM (1993) since the latter extrapolation gave nearly the same value as preliminary limit value for air (i.e. 18.6 µg/m^3).

For the dermal route no limit value is derived because of lack of appropriate toxicological data for this route. Route-to-route extrapolation from the oral or inhalation limit values is not a feasible option.

BACKGROUND EXPOSURE

Natural sources of 1,1,2-TCE are unknown. A mean daily intake of 0.24 µg/day can be calculated from 1,1,2-TCE levels measured in Germany during 1980-1983 in 50 of the most important types of foodstuffs and drinks which make up over 90% of the average food uptake (BUA, 1994). Data for the Netherlands are not available. Few data are available on 1,1,2-TCE in ambient air. The most recent studies performed in Germany during 1986-1987, showed mean values of 0.05 µg/m^3 (BUA, 1994). Based on these data general population background exposure is estimated at 0.007 µg/kg bw (sum of intake via food and air for a 70 kg adult).

MISCELLANEOUS DATA

Absorption factors:

- oral : >81% in mice and rats (ATSDR, 1989);
- inhalation: >90% in humans (ATSDR, 1989);
- dermal : >99% in mice (ATSDR, 1989).

Guideline values:

- MAC value (limit for occupational exposure): 45 mg/m^3 (skin absorption) (SZW, 1995)

CONCLUSION

PTDI:	4 µg/kg bw
Background exposure:	0.007 µg/kg bw
PTCA:	17 µg/m^3

COMPILATION RECORD:

Database determination based on: - the review documents as included in the reference list below;
- additional literature search: ToxLine Plus 1994-1996

Profile compilation by: M.E. van Apeldoorn & P.J.C.M. Janssen
Advisers: J. van Benthem (genotoxicity) & E.D. Kroese (carcinogenicity).
Profile review by: A.G.A.C. Knaap, G.J.A. Speijers, J.v. Benthem, M.N. Pieters (Toxicology Advisory Group, 27-08-1996)

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APPENDIX 8: DICHLOROPROPANES

INTRODUCTION

Isomers of dichloropropane are the following: 1,1-dichloropropane, 1,2-dichloropropane, 1,3-dichloropropane and 2,2-dichloropropane. Toxicological data are available for the 1,2- and 1,3-isomers only. 1,2-Dichloropropane is used as an intermediate in chemical synthesis (major use), as dry-cleaning solvent, paint remover, metal degreaser and as a component in soil fumigants. Several of these applications are no longer practised. (IARC, 1986; ATSDR, 1989; IPCS, 1993) 1,3-Dichloropropane is used as an auxiliary agent in chemical syntheses and it is present as a contaminant in soil fumigants containing 1,3-dichloropropene (WHO-WQG, 1996).

RELEVANT ROUTE

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

TOXICITY

For 1,3-dichloropropane only limited toxicity data are available. The compound was positive in mutagenicity assays in some of the bacterial strains tested (*S. typhimurium* TA 100, TA 1535). In other bacterial assays that included the strains in which the positive results had been observed, however, no effect was seen. (WHO-WQG, 1996) The only other studies available are subacute and semichronic oral studies both carried out in rats. No long-term toxicity studies, carcinogenicity, reproduction and teratogenicity studies have been performed for this isomer. In the subacute study, dose levels of 0, 200, 600 and 1800 mg/kg bw/day were administered by gavage on 7 days/week for 14 days. At 1800 mg/kg all animals died. Concentrations of protein and albumin in blood serum were increased in females at 200 and 600 mg/kg. The weights of kidneys and liver were increased at 600 mg/kg. In the semichronic rat study with 1,3-dichloropropane the dose levels were 0, 50, 200 and 800 mg/kg bw/day (administration by gavage on 7 days/week for 13 weeks). Growth was decreased at 800 mg/kg (males only). Clinical chemistry showed increases in AP (800 mg/kg, males only), ALAT (800 mg/kg, males & females), serum protein (200 mg/kg, females) and albumin (200 & 800 mg/kg, males and/or females). The weights of liver and kidneys were increased in males and females at 200 and 800 mg/kg; liver weights were increased in the females of the 50 mg/kg group also. Histopathology showed an increased incidence of centrilobular hepatocellular hypertrophy at 800 mg/kg (males & females and chronic progressive nephropathy at 800 mg/kg (in 7/10 males and 3/10 females versus 0/20 in controls) and 200 mg/kg (in 3/10 males only). (Terrill et al., 1991) The effect at 50 mg/kg (increased liver weight in females without concomitant histopathological changes effects) is considered a marginal effect. This leads to an NOAEL for this study of 50 mg/kg bw/day.
As already indicated above, for 1,1- and 2,2-dichloropropane no toxicity data are available.

For 1,2-dichloropropane the toxicological data base contains animal studies for most of the standard toxicological endpoints. Both oral studies and inhalation studies are available. For this compound there are existing toxicological evaluations by ATSDR (1989), WHO-WQG (1996) (this evaluation was carried out in 1991), US-EPA (1991), RIVM (1993b) and IPCS (1993). 1,2-Dichloropropane was evaluated by IARC in 1986 and 1987 and classified in Group 3 (*not classifiable*) based on *no*

evidence in humans and *limited evidence in experimental animals*. (IARC, 1986 and 1987) The only studies in the IARC evaluation were the NTP gavage studies in rats and mice, respectively. In both studies dose levels of 0, 125 and 250 mg/kg bw/day were administered for 103 weeks. In B6C3F$_1$ mice an increased incidence of hepatocellular tumours (combined adenomas and carcinomas) was seen at both dose levels. Increases in incidence of this kind of tumours in this strain of mice mostly does not provide unequivocal evidence for a carcinogenic action by the tested compound (this is determined on a case-by-case basis also using the other available evidence for the compound under scrutiny). In rats (F344/N) in females the incidence of mammary-gland adenocarcinomas was slightly increased (incidences of 1/50, 2/50 and 5/50 in the control, low-dose and high-dose groups, respectively). Survival, however, was low in the high-dose females. It was concluded that the observed increased incidence of mammary-gland tumours provides equivocal evidence only for carcinogenicity in the female rat. (IARC, 1986; WHO-WQG, 1996; RIVM, 1993b) No other carcinogenicity studies are available. In mutagenicity studies *in vitro*, 1,2-dichloropropane was positive in *Salmonella typhimurium* without and with metabolic activation and in *Aspergillus nidulans* (forward mutation to 8-azaguanine resistance) with activation. An *in vitro* study for chromosome aberrations in Chinese hamster ovary cells was positive without and with activation, as was an *in vitro* test for gene mutations in mouse lymphoma cells with activation. These positive responses were seen at high concentrations of 1,2-dichloropropane. Two *in vivo* tests were done in *Drosophila melanogaster* (sex-linked recessive lethal assay) and in rats (dominant-lethal assay), respectively. The results of these studies were negative (no effect). (IARC, 1986; WHO-WQG, 1996; RIVM, 1993b, IPCS, 1993) At present, *in vivo* tests to confirm the induction of gene mutations found *in vitro*, are not available. Given the inconclusive evidence for carcinogenicity, the only feasible option in limit value derivation is using a threshold approach.

For the oral route the most relevant 1,2-dichloropropane studies are the 13-week gavage study in male rats by Bruckner et al. (1989), the developmental studies in rats and rabbits by Kirk et al. (1995) and the 2-generation reproduction study in rats by Kirk et al. (1990). No chronic oral study is available. Bruckner et al. (1989) administered 0, 100, 250, 500 or 750 mg/kg bw/day by gavage to male rats on 5 days/week for 13 weeks. The observed effects were: increased mortality (at 750 mg/kg >50% dead after 10 days and at 500 mg/kg 50% dead by week 13), growth retardation (all dose levels, dose-related), histopathological changes in liver (mild hepatitis at 750 mg/kg, periportal vacuolisation and active fibroplasia at 500 mg/kg), testicular degeneration with an increased number of degenerate spermatogonia in the epididymis (500 & 750 mg/kg), decreased blood haemoglobin and hematocrit (250 & 500 mg/kg), increased serum bilirubin (all dose levels, dose-related), haemosiderosis and hyperplasia of the erythropoietic elements of the spleen (all dose levels, dose related) and increased weights of liver and spleen (250 & 500 mg/kg). In this study there was no NOAEL (LOAEL 100 mg/kg bw/day). (Bruckner et al., 1989; WHO-WQG, 1996) Kirk et al. (1995) report the results of teratogenicity studies in rats (gavage-dosing of 0, 10, 30, or 125 mg/kg bw/day on days 6 through 15 of gestation) and rabbits (gavage-dosing of 0, 15, 50 or 150 mg/kg bw/day on days 7 through 19 of gestation). In rats at the highest dose level in dams toxic effects were seen (decreases in growth, food consumption, muscle tone and extensor flux reflex) and in foetuses the incidence of delayed ossification of skull bones was increased. The NOAEL in rats was 30 mg/kg bw/day. In rabbits

similar findings were made: maternal toxicity (anorexia, anaemia) at 150 mg/kg and increased incidence of delayed ossification of skull bones among foetuses also at 150 mg/kg only. The NOAEL was 50 mg/kg bw/day. (Kirk et al., 1995; US-EPA, 1991) The oral 2-generation reproduction study in rats by Kirk et al. (1990) is an unpublished study the results of which are summarised in US-EPA (1991) and IPCS (1993). Rats were given the test compound in drinking-water at concentrations of 0, 240, 1000 or 2400 mg/litre. At the highest dose level the effects were: decreased water consumption and decreased growth in parent animals (both generations), decreased red blood cell count, haemoglobin, and hematocrit (F_0 females only), mild liver lesions in parent animals (both generations), decreased neonatal body weight and decreased neonatal survival (first generation only). No other effects were found. The NOAEL in this study was 1000 mg/litre (based on measured drinking-water intake calculated to be equal to 100 mg/kg bw/day). (US-EPA, 1991)

The inhalation toxicity data for 1,2-dichloropropane were evaluated by the US-EPA in 1991 and by the RIVM in 1993. Studies primarily relevant for limit value derivation are the 13-week studies in mice, rats and rabbits conducted by Nitschke et al. (1988) and the subacute inhalation studies in mice, rats and rabbits, reported by Nitschke & Johnson (1983) (the latter studies were preliminary to the later 13-weeks studies). The results of these studies have not been published in detail; only the summary of results as presented in US-EPA (1991) is available. In rats and mice exposure concentrations were 0, 69, 231 and 693 mg/m^3 to which the animals were exposed for 6 hours/day, 5 days/week for 13 weeks. In mice no treatment-related pathological effects were found (no further details given). In rats body weights were decreased at 693 mg/m^3. The only other effects observed in rats were histopathological effects in the upper respiratory tract: very slight to slight degeneration of the olfactory mucosa in the nasal cavity (231 & 693 mg/m^3, males & females), very slight to slight hyperplasia of the respiratory epithelium of the nasal cavity (231 & 693 mg/m^3, males & females; marginal effect in a few 69 mg/m^3 males). The NOAEL in rats was 693 mg/m^3. In rabbits test concentrations were 0, 693, 2310 and 4621 mg/m^3 (exposure 6 hours/day, 5 days/week for 13 weeks). Dose-related anaemia was observed at all test concentrations with signs of a regenerative response (bone marrow hyperplasia and hemosiderin-laden macrophages) at the two highest dose levels. Degeneration of olfactory epithelium was observed at the highest dose level only. The LOAEL in rabbits was 693 mg/m^3 (no NOAEL in this study). The most significant finding in the subacute studies (duration 2 weeks) was severe degeneration of the nasal olfactory epithelium in rats exposed to 4621 mg/m^3 and slight to moderate degeneration in rats exposed to 1386 mg/m^3 and 462 mg/m^3 (the latter level was the lowest level tested). (US-EPA, 1991; RIVM, 1993b)

For the dermal route the only information available are some observational data for worker exposure (case studies) to 1,2-dichloropropane. In two studies reported in IPCS (1993) a total number of 12 cases of 1,2-dichloropropane allergic dermatitis were identified. Patch testing showed that concentrations of $\geq$ 2% produced a positive reaction in these subjects (NOAEL not determined). (IPCS, 1993) There are no further usable data for humans.

From the above data a TDI and TCA are derived as follows. Toxicological data are available for two isomers only, i.e. 1,2- and 1,3-dichloropropane. The data set for 1,3-dichloropropane is limited. The

results of the oral 13-week study with the 1,3-isomer (Terrill et al., 1991) showed that after oral administration, the 1,3-isomer has a target organ different from that for the 1,2-isomer: the 1,3-isomer produces renal and hepatic effects whereas the 1,2-isomer primarily produces effects on the haemopoietic system including the spleen. In view of this difference in systemic effects, for these isomers separate oral limit values (TDIs) are derived. After inhalation 1,2-dichloropropane produces histopathological effects in nasal epithelium (results described above). There are no toxicological data for the 1,3-isomer on this point as a consequence of which it can not be determined whether the two isomers differ in their potency to produce effects on the respiratory tract. In absence of inhalation toxicity data for 1,3-dichloropropane the two isomers are assumed to have equal toxic potential for this endpoint. Thus, the TCA as derived for 1,2-dichloropropane is assumed to apply for 1,3-dichloropropane as well (adopted as *provisional* TCA for the 1,3-isomer).
For the isomers for which there are no toxicological data (i.e. 1,1- and 2,2-dichloropropane) no limit value is derived.

For 1,2-dichloropropane, the isomer for which there are studies for many toxicological endpoints, the oral LOAEL of 100 mg/kg bw/day from the 13-week study in rats (Bruckner et al., 1988) is the basis for the calculation of a TDI. This LOAEL is from a gavage study with dosing on 5 days/week. The LOAEL corrected for intermittent exposure is 70 mg/kg bw/day (rounded value). Using an uncertainty factor of 1000 (10 for interspecies variation and 10 for intraspecies variation and an extra factor of 10 for the use of an LOAEL instead of an NOAEL) a TDI of 70 µg/kg bw is derived. A further factor for limited duration of the study is not applied because of the quality of the data base for the oral route (it includes a recent 2-generation reproduction study with its NOAEL of 100 mg/kg bw/day). For the inhalation route the limit value of 12.4 µg/m^3 as derived for 1,2-dichloropropane by the RIVM (1993b) is adopted here as the TCA. This derivation was as follows. The NOAEL of 69 mg/m^3 from the 13-week study in rats (Nitschke et al., 1988) was duration-adjusted (back-calculation from 6x5 hours/week to 7x24 hours/week) giving a duration-adjusted NOAEL of 12.4 mg/m^3. To this level an uncertainty factor of 1000 (10 for interspecies differences, 10 for intraspecies differences, an extra factor of 10 for using a semichronic NOAEL instead of a chronic NOAEL) was applied. (RIVM, 1993b)

For 1,3-dichloropropane the oral NOAEL of 50 mg/kg bw/day from the 13-week study in rats (Terrill et al., 1991) is the basis for the calculation of a TDI. Using an uncertainty factor of 1000 (10 for interspecies variation and 10 for intraspecies variation and an extra factor of 10 for the use of a semichronic NOAEL instead of a chronic NOAEL) a TDI of 50 µg/kg bw is derived. Because no inhalation toxicity data are available for 1,3-dichloropropane the TCA for 1,2-dichloropropane is assumed as provisional TCA (PTCA) for 1,3-dichloropropane (see discussion above).

BACKGROUND EXPOSURE

Only data for 1,2-dichloropropane are available. Even for that isomer, however, relatively few data on background exposure in the Netherlands are available. In the USA and Japan detected levels in urban air were ≤ 1µg/m^3 (IPCS, 1993). In the Netherlands 1,2-dichloropropane is found in raw

groundwater for 13 out of 169 supplies (range 0.6-2.1 µg/litre) and in drinking-water for 11 out of 52 groundwater supplies (range 0.05-0.12 µg/litre). (Personal communication A. Versteegh, RIVM). No data on the occurrence of 1,2-dichloropropane in food were found in literature.
From these data general population background exposure to 1,2-dichloropropane is estimated at <1 µg/kg bw/day.

MISCELLANEOUS DATA

Only data for 1,2-dichloropropane are available.

- Absorption factors reported for 1,2-dichloropropane:
  - oral: 75-95% (ATSDR, 1989);
  - inhalation: 60% (ATSDR, 1989);
  - dermal: no quantitative data available; based on the dermal lethality data it may be concluded that dermal absorption does occur (ATSDR, 1989).

Odour threshold reported for 1,2-dichloropropane:

- widely different values of 1.2 mg/m^3 and 420 mg/m^3 given by US-EPA (1985) and ATSDR (1989), respectively.

Guideline values reported for 1,2-dichloropropane:

- MAC-value (limit for occupational exposure): 350 mg/m^3 (SZW, 1995).

CONCLUSION

1,2-dichloropropane

TDI:	70 µg/kg bw/day
Background exposure	<1 µg/kg bw/day
TCA:	12 µg/m^3 (rounded value)

1,3-dichloropropane

TDI:	50 µg/kg bw/day
Background exposure	unknown
PTCA:	12 µg/m^3 (value for 1,2-isomer adopted)

COMPILATION RECORD:

Database determination based on: - the review documents as included in the reference list below;
- additional literature search (Toxline 1991-1996).

Profile compilation by: P.J.C.M. Janssen & J.G.M. van Engelen

Profile review by: J.v. Benthem, A.G.A.C. Knaap, M.N. Pieters & G.J.A. Speijers (Toxicology Advisory Group, 27-08-1996)

August 1996

RIVM-Centre for Substances and Risk Assessment

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APPENDIX 9: 1,1-DICHLOROETHENE

RELEVANT ROUTE

Exposure routes considered to be relevant in the present context: oral & inhalation.

TOXICITY

IARC evaluated 1,1-dichloroethylene (also called vinylidene chloride) in 1985 (IARC, 1986) and decided that there was *limited evidence* for carcinogenicity in experimental animals and *inadequate evidence* for carcinogenicity in humans. IARC (1987) has placed vinylidene chloride in Group 3 (*not classifiable* as to its carcinogenicity to humans).

Vinylidene chloride was tested for carcinogenicity in oral studies in mice and rats, in a dermal study in mice, in a subcutaneous study in mice and in inhalation studies in mice, rats and Chinese hamsters (ATSDR, 1994; IARC, 1986). The only study giving evidence for a carcinogenic action is an inhalation study in mice. In this study, Swiss male and female mice were exposed to 0, 40, 100, 200, 400 or 800 mg/m^3 4 hours/day, 4-5 days/week for 52 weeks and observed for life span. At concentrations ≥ 200 mg/m^3 a high mortality was seen within 2-4 days and the surviving animals were withdrawn from the study. An increase of renal adenocarcinomas was seen in males at 100 mg/m^3, accompanied by severe nephrotoxic effects including nephrosis (incidences of kidney tumours in male rats 0/126, 0/25 and 28/119 at 0, 40 and 100 mg/m^3, respectively) (Maltoni et al., 1977, 1985 as cited in US-EPA, 1989). The negative findings of several of the inhalation studies may be due to inadequate test conditions (e.g. less than life-time exposure, use of doses either well below or above the maximum tolerated dose, small number of animals, and/or limited gross or microscopic examinations) (ATSDR, 1994). Epidemiological studies in workers exposed to vinylidene chloride, were judged to be inadequate for the evaluation of carcinogenic effects in humans (IARC, 1986).

Vinylidene chloride induced gene-mutations and chromosomal aberrations in *in vitro* systems, mostly in the presence of a metabolic activation system. Host-mediated assays in mice with yeast cells also revealed positive results. In *in vivo* micronucleus studies in mice and rats negative results were reported whereas a micronucleus test in Chinese hamsters showed positive results both after oral and inhalation exposure. An *in vivo* UDS study showed also a positive result. Dominant lethal studies in mice and rats showed negative results. Low rates of alkylation in liver of mice and rats were seen after inhalation (low compared to DMNA, the positive control in this study). In addition DNA repair mechanisms were induced *in vivo* in the kidneys of mice in cells in which normal replicative DNA synthesis had been inhibited. No significant increase in DNA repair rates *in vivo* was observed in mouse liver or rat kidneys or rat liver. (ATSDR, 1994) Based on the data given above vinylidene chloride is concluded to be a genotoxic carcinogen.

Toxicity of vinylidene chloride (non-carcinogenic effects) is due to metabolites and not to the parent compound. Oral and inhalation studies suggest that mice metabolize vinylidene chloride to a greater extent than rats. Vinylidene chloride is initially oxidized by hepatic cytochrome P-450 to epoxides, acyl chlorides and halogenated chlorides, which are responsible for liver toxicity via alkylation of macromolecules. Detoxification occurs via conjugation with glutathione. GSH S-conjugates that are primarily secreted from hepatocytes into plasma and S-conjugates entering the circulation after

reabsorption from the small intestine are ultimately delivered to the kidney where they undergo glomerular filtration. In the liver GSH S-conjugate formation from nephrotoxic haloalkenes competes with hepatic cytochrome P-450 for substrates. The relative extent to which these reactions occur *in vivo* appears to be decisive for the initiation of adverse effects either in the liver (via oxidation products generated by the P-450 system) or in the kidney (via formation and renal processing of S-conjugates). (ATSDR, 1994)
At higher dose-levels (≥ 50 mg/kg bw orally, ≥ 600-800 mg/m^3 by inhalation) there is evidence of saturation of the metabolic process, with rapid elimination of unchanged vinylidene chloride in the expired air (US-EPA, 1989).

As already concluded above, based on the results of genotoxicity and carcinogenicity studies, vinylidene chloride is considered genotoxic carcinogen. For the genotoxic carcinogens a non-threshold evaluation (i.e. linear extrapolation from the lowest observed tumorigenic dose) is warranted. In the present scope the excess lifetime cancer risk level of 1 : 10^4 is used (this is the cut-off point as incorporated in the definition of the MPR). As explained in an RIVM -report (1996), for genotoxic carcinogens a parallel threshold evaluation based on non-carcinogenic effects should be developed in order to check if this yields a limit value (TDI or TCA) that is lower than the estimated 10^{-4} excess lifetime cancer risk. The lower value of the two (10^{-4} excess cancer risk or TDI/TCA) is chosen as MPR. Below, for both the oral and the inhalational route the results of a threshold and a non-threshold extrapolation for vinlylidene chloride are given. Since oral studies did not show significantly increased tumour incidences the oral excess lifetime tumour risk of 1:10^4 is extrapolated *route-to-route* from the figure for the excess lifetime tumour risk of 1: 10^4 for inhalation exposure.

Primary target organs after repeated oral and inhalation exposure in animals are the liver and the kidneys. The most appropriate study to derive an oral NOAEL/LOAEL for calculation of a TDI is a 2-year drinking-water study in rats (Quast et al., 1983 as cited in US-EPA, 1989). In this study pathological changes in the liver were seen at the two highest dose-levels in males and at all dose levels in females (dose levels were 7, 10 or 20 mg/kg bw/day for males and 9, 14 or 30 mg/kg bw/day for females). Slight pathological changes in the liver were also seen at the lowest dose level of 9 mg/kg bw/day in a three generation reproduction study in rats receiving vinylidene chloride via the drinking-water *in utero*, during lactation through weaning onto adulthood (Nitschke et al., 1983 as cited in ATSDR, 1994). No effect on the reproductive capacity in rats of either sex was seen up to concentrations of 200 mg/L of drinking water (equal to about 30 mg/kg bw) in the oral three-generation reproduction study of Nitschke et al. (1983). Vinylidene chloride did not reveal teratogenic properties but induced embryotoxic effects mostly at maternally toxic doses. The oral NOAEL for these effects was 40 mg/kg bw/day in the rat (Murray et al., 1979 as cited in ATSDR, 1994 and IPCS, 1990)

With respect to repeated inhalation exposure, animals appear to be less tolerant of continuous exposure than of intermittent exposure. During intermittent exposure the animals are better able to compensate for the toxic effects. This observation supports the hypothesis of involvement of depletable stores of liver GSH as a mediator of vinylidene chloride-induced hepatotoxicity. In guinea

pigs and monkeys exposed continuously to vinylidene chloride for 90 days a NOAEL of 20 mg/m^3 can be derived based on increased enzyme activities (guinea pigs) and decreased body weight (monkeys) as the critical effects. The LOAEL in this study, for both guinea-pigs and monkeys, is 192 mg/m^3 (Prendergast et al., 1967). In the same study, in rats (also with continuous exposure for 90 days) a NOAEL of 60 mg/m^3 was observed based on renal effects (Prendergast et al., (1967). In a study in mice exposed for 52 weeks, 4 hours/day, 5 days/week, a NOAEL of 40 mg/m^3 based on renal effects was seen (Maltoni et al., 1985 as cited in ATSDR, 1994). An 18-month inhalation study in rats (6 hours/day, 5 days/week) showed a LOAEL of 100 mg/m^3; the effects were decreased liver weights and fatty changes in midzonal region in the liver. There was no NOAEL in this study. (Quast et al. 1986 as cited in ATSDR, 1994)

No adverse effect on fertility of male mice or rats was observed up to concentrations of 120 mg/m^3 (6 hours/day for 5 days) and 220 mg/m^3 (6 hours/day for 11 weeks), respectively (Anderson et al., 1977 as cited in ATSDR, 1994; Short et al., 1977a as cited in ATSDR, 1994 and IPCS, 1990).

After inhalation exposure vinylidene chloride did not reveal teratogenic properties, but induced embryotoxic effects, usually at maternally toxic doses. In early inhalation studies (with continuous exposure) in mice and rats a LOAEL of 60 mg/m^3 was reported (Short et al., 1977b as cited in ATSDR, 1994 and IPCS, 1990) while in a later study in rats (intermittent exposure 7 hours/day) a NOAEL of 80 mg/m^3 could be established (Murray et al., 1979 as cited in IPCS, 1990 and ATSDR, 1994).

Non-threshold extrapolation

For the inhalation route the results of the studies of Maltoni et al. (1977, 1985) (as cited in US-EPA, 1989) are suitable for non-threshold extrapolation. Using the RIVM linear extrapolation model (formula given in VROM, 1984) an extra cancer risk of 1 per 10^4 lifetime exposed persons was calculated at 14 µg/m^3.

None of the long-term studies performed via the oral route, showed a significant dose-related increase of malignant or benign tumours[22]. Therefore *route-to-route* extrapolation is applied on the figure for the excess lifetime tumour risk of 1:10^4 for inhalation exposure, yielding a provisional figure, because this procedure involves considerable uncertainty. Using the standard assumptions for this procedure (adult daily ventilation volume 20 m^3, 100% absorption after oral exposure instead of 75% after inhalation) (RIVM, 1996), an oral excess lifetime tumour risk of 1:10^4 at an oral exposure level of 3 µg/kg bw/day can be calculated.

Threshold extrapolation

For the inhalation route a TCA of 20 µg/m^3 can be established based on a NOAEL of 20 mg/m^3 in the 90-day inhalation study with continuous exposure (Prendergast et al., 1967) and using an uncertainty

[22] The incidences for adrenal phaeochromocytoma from the oral NTP study in rats (NTP, 1982) were used by the US-EPA for oral cancer risk estimation (US-EPA (1989). Because, however, the response in this study was not unequivocally positive (the increase in tumour incidence was not significant, the tumour type is considered to be less relevant for man, the large number of accidental deaths may have influenced the result of the study and IARC (1986) considered this study as negative), this result is not used in the present evaluation.

factor of 1000 (10 for interspecies variation and 10 for intraspecies variation and a factor 10 extra for using a subchronic study instead of chronic study).
For the oral route a TDI of 9 µg/kg bw can be established based on a LOAEL of 9 mg/kg bw/day in a long-term drinking water study (Quast et al. 1983 as cited in US-EPA, 1989) using an uncertainty factor of 1000 (10 for interspecies variation and 10 for intraspecies variation and a factor 10 extra for the use of a LOAEL instead of a NOAEL).

The non-threshold and threshold evaluations as presented above, result in limit values in the same range. The values obtained via the non-threshold evaluation are slightly lower and adopted as the MPR.

BACKGROUND EXPOSURE

For the Netherlands no data are available. In the UK the maximum possible daily intake of vinylidene chloride *per capita* from packaged food was estimated at 1 µg/day (equivalent to 0.014 µg/kg bw for a 70 kg adult person) (MAFF, 1980).In the USA estimated levels indoor and outdoor are < 4 ng/m^3 (ATSDR, 1994). This indicates that exposure via air will be negligible for the general population.

MISCELLANEOUS DATA

- Absorption: no absorption percentages (oral, inhalation, dermal) are known; qualitative information given in ATDSR (1994): Vinylidene chloride is well absorbed orally and by inhalation. Dermal absorption is expected to occur regarding the physical and chemical properties of the compound. However with a vapour pressure of 500 mm Hg at 20°C (215 mm Hg at 0°C) the evaporation rate would be rapid leaving only a short time for skin penetration.
- Odour threshold: for odour detection 2000-4000 mg/m^3 (IPCS, 1990)
- Guideline values:

MAC value (limit for occupational exposure):	20 mg/m^3	(SZW, 1995)
WHO-drinking water guideline value:	30 µg/L	(WHO, 1991/1996)

CONCLUSION

Provisional oral excess 10^{-4} lifetime tumour risk:	3 µg/kg bw
Background exposure:	0.014 µg/kg bw
Inhalational excess 10^{-4} lifetime tumour risk:	14 µg/m^3

COMPILATION RECORD:

Database determination based on: - the review documents as included in the reference list below.

Profile compilation by:	M.E. van Apeldoorn & P.J.C.M. Janssen
Profile review by:	G.J.A. Speijers, M.N. Pieters & J.v. Benthem (Toxicology Advisory Group, 13-08-1996)
Adviser:	E.D. Kroese

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APPENDIX 10: 2-METHYL-4-CHLOROPHENOXYACETIC ACID (MCPA)

RELEVANT ROUTE

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

TOXICITY

4-Chloro-2-methylphenoxyacetic acid (MCPA) is a systemic hormone-type selective herbicide. The compound was evaluated by RIVM/ACT in 1991 (scope: registration for use as herbicide).

Metabolism data for MCPA show that in mice, MCPA was readily absorbed from the gut but percutaneous absorption was low. Rats treated orally with MCPA excreted nearly all of the compound during the first 24 hours after intake (90% in urine, 7% in faeces). In humans, 50% of the total dose was detected in the urine within 48 hours. (WHO-WQG, 1992, IARC, 1983)

IARC classified the group of chlorophenoxy herbicides in group 2B (*possibly carcinogenic to humans*). This classification was based on studies in which MCPA was part of a (chlorophenoxy herbicide) mixture, and not on studies concerning exposure to MCPA alone. (IARC 1987) The data for MCPA alone were evaluated by IARC in 1983 - (this is the only IARC evaluation available for MCPA alone) - leading to the conclusion that the level of available evidence is *insufficient* in humans and *inadequate* in experimental animals (IARC, 1983). In two chronic toxicity/carcinogenicity tests in rats and mice, respectively, reported in 1988, no increased tumour incidences were found (RIVM, 1991, WHO-WQG, 1992).
MCPA was not mutagenic in gene mutation tests on bacteria and in *in vivo* cytogenetic tests (micronucleus and chromosomal aberrations). MCPA is weakly mutagenic in *Saccharomyces cerevisiae* and *Drosophila melanogaster*. MCPA induces sister chromatid exchanges in *in vitro* tests but has given contradictory results for this endpoint *in vivo*. (WHO-WQG, 1996; IARC, 1983)

Based on the above data on carcinogenicity and genotoxicity a threshold approach is considered appropriate in the toxicological evaluation of MCPA.

MCPA was not sensitising in guinea pigs (Maximization test). In a subacute dermal study in rabbits (0.5, 1.0 or 2.0 g/kg bw/day for 3 weeks) animals lost weight and showed slight erythema; upon microscopic examination of the skin, hyperplasia and hyperkeratosis were observed. Semi-chronic oral experiments were carried out in dogs. In two 13-week studies with dose levels ranging from 0.3 to 48 mg/kg bw/day decreased kidney and liver function, characterised by increases in blood urea, SGPT and creatinine, were seen at ≥ 3 mg/kg bw/day. The NOAEL from these studies is 1 mg/kg bw/day. (WHO-WQG, 1996) A further study in dogs was a 52-week feeding study with test concentrations of 0, 6, 30 and 150 mg/ kg feed. The observed effects in this study were: growth retardation (30 & 150 mg/kg, in males only), increased blood urea and creatinine (30 & 150 mg/kg, females only), dark brown discolouration of the kidneys histologically determined as pigment deposition in the epithelium of the proximal tubuli (30 & 150 mg/kg, males & females), increased

thyroid weight (150 mg/kg, females & males). The NOAEL in this study was 6 mg/kg feed (equivalent to 0.15 mg/kg bw/day). (BASF AG, 1986 as summarised in RIVM, 1991)
At a high oral dose level (350 mg/kg bw, single oral dose, administered on day 9 of the pregnancy), teratogenicity and embryotoxicity have been reported in rats (IARC, 1983). No foetotoxicity or teratogenicity was observed, however, in rabbits at dose levels up to 75 mg bw/kg/day (administered by gavage, on days 6-18 of gestation) or in rats at dose levels up to 125 mg/kg bw/day (administered by gavage, on days 6-15 of gestation) (WHO-WQG, 1996).

In its 1991 evaluation the RIVM/ACT based the derivation of a provisional ADI[23] on the NOAEL of 0.15 mg/kg bw/day from the oral semi-chronic (1-year) study in dogs (BASF AG, 1986 as summarised in RIVM, 1991). Using this value and applying an uncertainty factor of 100 (a factor 10 for interspecies differences and a further factor of 10 for intraspecies differences), a tentative ADI of 1.5 µg/kg bw was calculated. (RIVM, 1991) This value is adopted here as the provisional TDI (PTDI)[24].

No data on inhalation toxicity are available. *Route-to-route* extrapolation based on the oral PTDI calculated above[25], results in a provisional TCA (PTCA) of 7 µg/m^3. This TCA is provisional because it was derived from a provisional TDI and because it was obtained via route-to-route calculation, a procedure involving considerable uncertainty.

BACKGROUND EXPOSURE

No data on background exposure in the Netherlands are available. In the USA, MCPA was found in a number of surface water samples at levels of 0.04-0.54 µg/litre (US-EPA, 1989). Data for other countries are lacking.

MISCELLANEOUS DATA

Guideline values:
- Residue tolerances in mg/kg as given in the Dutch Pesticide Act (Bestrijdingsmiddelenwet) (1995): residue tolerance for all commodities: 0.1 mg/kg[26].

[23] This ADI was considered provisional because genotoxicity could not be evaluated fully due to lack of a mammalian gene mutation test (the applicant was requested to provide such a test for renewal of the approval for use as pesticide).
[24] Both the US-EPA and the WHO calculated a TDI of 0.5 µg/kg b.w., based on the same NOAEL (as used by the RIVM) of 0.15 mg/kg bw. Both EPA and WHO used an additional uncertainty factor of 3 to account for the lack of a complete data base on chronic toxicity In the RIVM evaluation, however, such data *were* included since 2 chronic toxicity/carcinogenicity tests (1 in rats, 1 in mice) were discussed in this evaluation. Teratogenicity studies in two species, the lack of which was taken into account in the evaluation by the US-EPA, were included in the WHO-WQG monograph.
[25] Standard assumptions for the calculation: ventilation volume for a 70 kg adult is 20 m^3 /day, absorption via inhalation is 75% of the absorption after oral uptake.
[26] no detectable residue

CONCLUSION

PTDI: 1.5 µg/kg bw/day

Background exposure: unknown

PTCA (extrapolated from the PTDI): 7 µg/m^3

COMPILATION RECORD:

Database determination based on: - the review documents (as included in the reference list below)
- additional literature search (Toxline 1990-1996)

Profile compilation by: J.G.M. van Engelen & P.J.C.M. Janssen

Profile review by: G.J.A. Speijers, M.N. Pieters & J.v. Benthem (Toxicology Advisory Group, 13-08-1996)

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APPENDIX 11: 2-PROPANOL

RELEVANT ROUTE

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

TOXICITY

2-Propanol (isopropanol) is readily absorbed into the body both after ingestion and after inhalation. Acetone is the major metabolite in humans and animals. Excretion is mainly via exhaled breath (80-90% of the dose both after ingestion and inhalation) as acetone, CO_2 or as unchanged parent compound (shown in rats and mice). (IPCS, 1990; Slauter et al., 1994) Limited qualitative data show dermal absorption to occur in humans (DECOS, 1994).

2-Propanol was evaluated by IARC in 1987. The compound was classified in Group 3 (*not classifiable*) based on *inadequate evidence in humans* and *inadequate evidence in experimental animals*. (IARC, 1987) More recent epidemiological studies among workers have been reviewed in DECOS (1994) where these studies were concluded not to provide evidence for a carcinogenic effect in humans. New chronic animal experiments have been reported to be in progress in the USA (Insall, 1993) but, as yet, no results of such a study or studies have been published in literature. The genotoxicity of 2-propanol was evaluated by the Scientific Committee for Food of the EU in 1992. In all assay systems tested (including bacterial systems ± activation, forward mutations in mammalian cells *in vitro* ± activation, mouse *in vivo* bone marrow micronucleus test) negative results (no effect) were found. In this evaluation it was concluded that for a more complete genotoxicity evaluation an *in vitro* cytogenetic assay for chromosome aberrations would be needed (an important consideration for this conclusion was the inconclusiveness of the negative result in the mouse micronucleus assay because of absence of any toxic effect in bone marrow cells in this study). (SCF, 1992)

Given these limited data concerning carcinogenicity and genotoxicity a threshold approach is chosen in the evaluation.

For the oral route the most relevant studies[27] are the 12-week drinking-water study of Pilegaard & Ladefoged (1993), the developmental toxicity studies by Bates et al. (1994) and Tyl et al. (1994) and the 2-generation reproduction study reported by Bevan et al. (1995). No chronic oral study is available.

Pilegaard & Ladefoged (1993) administered 2-propanol at concentrations of 0, 1, 2, 3 and 5% in drinking-water of male rats for 12 weeks. The following effects were observed: decreased water consumption at 2, 3 & 5%, growth retardation at 3 & 5% and dose-related increases in the weights of liver, kidneys and adrenals at 2, 3 & 5%. The finding of increased incidences of formation of hyaline casts and droplets in the proximal tubules of the kidneys (dose-related increase in all dose groups) is not considered relevant for humans because of the known large interspecies difference (male rat vs. humans) in sensitivity for this effect (for discussion see US-EPA, 1991). In this study brain cells were

[27] The other oral studies available are discussed in IPCS (1990) and Tyl et al. (1994). Both these reviews point out the limitations of these studies *qua* study design and detail of reporting.

examined histologically for cell damage, the result of which examination was negative (no effect). The NOAEL in this study is 1% (equivalent to 500 mg/kg bw/day). Tyl et al. (1994) performed two standard teratogenicity studies in rats and rabbits respectively. In the rat study dose levels of 0, 400, 800 and 1200 mg/kg bw/day were administered by gavage from day 6 through 15 of gestation. The observed effects were: slightly increased mortality of dams at 800 & 1200 mg/kg (1/25 and 2/25, respectively, versus 0/25 groups in all other groups), reduced maternal growth (in part due to decreased gravid uterine weight) at 1200 mg/kg, and decreased foetal weights at 800 & 1200 mg/kg. The NOAEL (for both maternal and foetotoxicity) in this study is 400 mg/kg bw/day. In rabbits doses of 0, 120, 240 and 480 mg/kg bw/day were given by gavage on gestation days 6 through 18. In the does of the 480 mg/kg group mortality was increased (4/15 *versus* 0/15, 2/15 and 0/15 at 0, 120 & 240 mg/kg, respectively), clinical signs (mainly flushed and/or warm ears, occasional cyanosis) were seen and food consumption and growth were decreased. At the same dose level fetal weights were decreased slightly. The NOAEL in this study was 240 mg/kg bw/day. The oral developmental neurotoxicity study in rats by Bates et al. (1994) showed no adverse effect (tested dose levels up to 1200 mg/kg bw/day). In the oral 2-generation reproduction study by Bevan et al. (1995) rats were given 0, 100, 500 and 1000 mg/kg bw/day by gavage. In parent animals the observed effects were: increased weights of liver and kidneys (500 & 1000 mg/kg), centrilobular hepatocyte hypertrophy in some P_2-males (1000 mg/kg) and formation of hyaline droplets in renal proximal tubuli with associated histological changes (in males at 500 & 1000 mg/kg). In the offspring at 1000 mg/kg there was increased mortality and decreased body weight gain in the early postnatal period (both generations). In the parameters for reproductive performance the only change was a decrease in male mating index among the P_2-males (1000 mg/kg). The NOAEL in this study was 100 mg/kg bw/day. (Bevan et al., 1995)

For the inhalation route the most relevant studies are the acute neurotoxicity study by Gill et al. (1995), the 13-week study by Burleigh-Flayer et al. (1994) and the teratogenicity study of Nelson et al. (1988). No chronic inhalation study is available. In the acute study reported by Gill et al. (1995) rats were exposed to isopropanol for 6 hours and behavioural obervations (including motor activity tests) were made up to 24 hours after cessation of exposure. Decreased activity was seen at concentrations of $\geq$ 3750 mg/m^3 (with narcosis-like signs at $\geq$ 12500 mg/m^3). The NOAEL in this study was 1250 mg/m^3. Burleigh-Flayer et al. (1994) carried out inhalation 13-week studies in rats and mice. In both rats and mice test concentrations of 0, 250, 1250, 3750 and 12500 mg/m^3 were used with exposure for 6 hours/day, 5 days/week for 13 weeks. In mice the following changes were observed: narcosis, ataxia and hypoactivity during dosing at 3750 & 12500 mg/m^3, increased body weights in females at 12500 mg/m^3, increased liver weights (without histological changes) in females at 3750 and 12500 mg/m^3. The NOAEL in this study is 1250 mg/m^3. The 13-week inhalation study in rats included a neurotoxicity evaluation in animals of all dose groups using the *functional observational battery* (for neurobehavioural evaluation) on several occasions thoughout the study with a neuroanatomical histopathology evaluation at testend. The observed effects in the rat study: narcosis, ataxia and hypoactivity during dosing at 3750 & 12500 mg/m^3, increased incidence of swollen periocular tissue in females at 12500 mg/m^3, increased incidence of perinasal encrustration at 1250, 3750 & 12500 mg/m^3, increases in food and water consumption and growth at 3750 and/or 12500

mg/m^3, increased motor activity in females at 12500 mg/m^3, slightly increased liver weights at 12500 mg/m^3. The finding of hyaline droplets in kidneys of the males (dose-related increase in all dose groups) is not considered relevant for humans because of the known large interspecies difference (male rat vs. humans) in sensitivity for this effect (for discussion see US-EPA, 1991). The neurotoxicity evaluation showed no effect. The only effect at 1250 mg/m^3, i.e. the irritative effect perinasal encrustration, constitutes a less-severe toxic effect (local effect of compound exposure). The NOAEL for systemic effects in this study is 1250 mg/m^3. (Burleigh-Flayer et al., 1994) In the teratogenity study in rats reported by Nelson et al. (1988) embryotoxicity was seen at all dose levels including the lowest of 8750 mg/m^3 (exposure 7 hours/day, day 6-19 of gestation). Maternal toxicity was observed at 17500 & 25000 mg/m^3. The LOAEL in this study is 8750 mg/m^3 (no NOAEL in this study).

For the dermal route no animal toxicity studies are available. There are no animal data on sensitisation. Undiluted 2-propanol was not irritating to the skin in guinea pigs and rabbits. (IPCS, 1990; DECOS, 1994)

Limited data in humans are available. Some cases of contact dermatitis are known (no quantitative information regarding dose-response for induction of effect). Dermal exposure to undiluted 2-propanol produced skin irritation in some tested subjects. The NOAEL for this effect has not been determined. In a controlled oral study in adult volunteers (n=8) no effect on haematology, blood biochemistry and ophthalmology was found after giving 2.6 or 6.4 mg/kg bw/day for 6 weeks. (IPCS, 1990, DECOS, 1994) The available human data are too limited for establishing an NOAEL that might be used in the derivation of limit values.

From the above data a TDI is derived based on the oral NOAEL of 100 mg/kg bw/day from the rat two-generation study (Bevan et al., 1995). Using an uncertainty factor of 100 (10 for interspecies variation and 10 for intraspecies variation) a TDI of 1 mg/kg bw is derived. Application of an extra uncertainty factor (above the standard factor 100 for more or less complete data sets) is not considered necessary given the fairly elaborate data set for 2-propanol and its low toxicity as observed in the toxicological experiments carried out.

The TCA derivation is as follows. Given the similar disposition of 2-propanol in the body after oral and inhalation uptake (described briefly above), a reasonable requirement for the limit value for in the inhalation route is that it should not lead to a systemic dose that is widely different from that reached when the oral intake level is at the TDI. For the inhalation route the semichronic study by Burleigh-Flayer et al. (1994) is the most suitable basis for derivation of a TCA. Using the NOAEL for systemic effects of 1250 mg/m^3 from this study a TCA of 2.2 mg/m^3 is derived. In this derivation the NOAEL was adjusted for discontinuous exposure in the animal experiment (duration-adjusted NOAEL 223 mg/m^3) and an uncertainty factor of 100 (10 for interspecies variation and 10 for intra-species variation) was applied. The margin between this TCA and the test concentration at which the less-severe local irritative effect was observed in the Burleigh-Flayer et al. study is sufficiently wide to be protective for such an effect in case of human exposure at the TCA level.

BACKGROUND EXPOSURE

2-Propanol is formed in the normal metabolism in humans. For persons not externally exposed to the compound, concentrations of 2-propanol in blood of <0.1-3.32 mg/litre are given; in urine normal physiological levels are <0.1 mg/l. Physiological levels of acetone, the main metabolite of 2-propanol, in blood are between 0.5 and 7.0 mg/litre (inter- and intra-individual variation within this range). For acetone in urine, levels up to 3.5 mg/litre are considered normal in unexposed persons. (DECOS, 1994)

The level of external background exposure to 2-propanol for the general population is not known (IPCS, 1990; DECOS, 1994). High residues in foodstuffs may occur due to use as a carrier solvent for flavourings. Indicated levels for non-alcoholic drinks are 0.2-600 mg/litre and for other foodstuffs 50-3000 mg/kg (Insall, 1993). General population exposure via the inhalation route is low. Higher-than-usual inhalation exposures may occur in the vicinity of point sources (e.g. paint manufacturing plants) and in occupational settings.

MISCELLANEOUS DATA

- Absorption factors:
  - oral: 99% (single dose animal study) (DECOS, 1994);
  - inhalation: absorption percentage unknown (retention in rats & mice after single dose 26-49% (DECOS, 1994);
  - dermal: qualitative data show that absorption occurs but absorption percentage unknown (DECOS, 1994).

Odour threshold:

- 7.9-90 mg/m^3 (perception);
- 18.4-120 mg/m^3 (recognition)(DECOS, 1994).

Guideline values:

- MAC-value (limit for occupational exposure): 650 mg/m^3 (DECOS, 1994).

CONCLUSION

TDI:	1000 µg/kg bw/day
Background exposure	unknown
TCA:	2200 µg/m^3

COMPILATION RECORD:

Database determination based on: - the review documents as included in the reference list below;
- additional literature search (Toxline 1988-1996)

Profile compilation by: P.J.C.M. Janssen & M.E. van Apeldoorn

Profile review by: G.J.A. Speijers, M.N. Pieters & J.v. Benthem (Toxicology Advisory Group, 13-08-1996)

August 1996

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APPENDIX 12: ETHYL ACETATE

RELEVANT ROUTE

Exposure routes considered to be relevant in the present context: oral, dermal & inhalation.

TOXICITY

Because of its characteristic fruity odour and pleasant taste when diluted, ethyl acetate is used as fruit essence (Opdyke, 1974).

Ethyl acetate is absorbed from the gastrointestinal tract and is soluble in blood plasma. It is hydrolysed by the liver and plasma esterases and pancreatic lipase to ethanol and acetate. The ethanol is partly excreted in the expired air and the urine; the remainder is metabolized. The acetate fraction is incorporated in the body acetate pool. (WHO, 1967)

No IARC carcinogenicity evaluation for ethyl acetate is available. In fact, adequate data on carcinogenicity in humans or animals are lacking. With respect to mutagenicity a conventional Ames test with and without metabolic activation showed a negative effect for ethyl acetate dissolved in DMSO. In *Saccharomyces cerevisiae* ethyl acetate (2.44% in medium) induced aneuploidy, but no mitotic recombinations or point mutations. This effect was seen at a high dose level with artificial cold treatment. Ethyl acetate dissolved in ethanol caused structural chromosome aberrations in a Chinese hamster cell line. *In vivo* micronucleus studies in mice and Chinese hamsters gave negative results (SZW, 1991).

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

For the oral route limited toxicity data are available. The most relevant study with repeated exposure is an adequate 90-day gavage study in rats performed in 1986 with dosing on 7 days/week. The NOAEL in this study is 900 mg/kg bw/day. At the LOAEL of 3600 mg/kg bw/day significant toxic effects were observed resulting in depressed body and organ weights and depressed food consumption. No effects on mortality, opthalmology, blood and urine chemistry, macroscopy and microscopy were seen (US EPA 1986 (unpublished), as cited in US-EPA, 1988). No further adequate oral toxicity studies are available.

The inhalation toxicity of ethyl acetate has been reviewed in 1991 by the Dutch Expert Comittee on Occupational Standards (SZW, 1991). The following data were selected from this review. The critical effects are mucous membrane irritation and central nervous system effects. For humans (occupational exposures, n=7) it has been reported that long-term exposure to about 5600 mg/m^3 with peaks of 10000 mg/m^3, caused bronchial constriction and EEG abnormalities, as well as more common CNS effects such as irritation, giddiness, nausea and headache (Corradini et al., 1973 as cited in SZW, 1991). Short-term exposure to about 1440 mg/m^3 caused irritation of the eyes and respiratory tract, CNS effects and possibly metabolic disturbances of the liver (Nelson et al., 1943 as cited in SZW,

1991). Long-term exposure to 1100 mg ethyl acetaat/m^3, accompanied by exposure to unknown levels of ethanol and isopropanol, caused central nervous symptoms such as complaints of increased fatigue, failing memory, difficulty in concentration and lack of initiative (Bonde et al., 1987 as cited in SZW, 1991). No information on effects in man at lower concentrations of ethyl acetate is available. The level of 1100 mg/m^3 was conluded to be a minimal-adverse-effect level in man. (SZW, 1991)
The SZW (1991) review shows the number of available animal studies with repeated inhalation exposure to be very limited. No animal studies that could be used in limit value derivation are available. In an acute behavioural inhalation study in mice 2140 mg/m^3 caused a 50% reduction in schedule-controlled responding (Glowa et al., 1987 as cited in SZW, 1991).
In a further animal inhalation study (of more recent date than the SZW review), performed by Yamada (1993), male Wistar rats were exposed twice daily for 7 days to ethyl acetate. Each exposure was continued until disappearance of righting reflex occurred (4-6 minutes). Test concentrations in the air are not reported but probably exposure was to saturated vapour (9.6% in the air at 20°C). The observed effects were: growth retardation, decreased weights of testes and prostate, reduced acid phosphatase activity in prostate, decreased serum testosterone levels and decreased numbers of spermatozoa (Yamada, 1993).

Concerning dermal exposure there are some data concerning local effect. Repeated dermal contact with the undiluted compound caused drying and defatting of the skin. (SZW, 1991) A concentration of 10% ethyl acetate in petrolatum produced no skin irritation in humans (n=26, 48 h closed-patch test). A maximization test according to Kligman with 10% ethyl acetate in petrolatum in 25 volunteers revealed no sensitization. (Opdyke, 1974)

From the above data a TDI and TCA are derived as follows. Based on the NOAEL of 900 mg/kg bw/day from the 90-day gavage study in rats (as cited in US-EPA, 1988) a TDI is calculated using an uncertainty factor of 1000 (10 for interspecies variation, 10 for intraspecies variation and an extra factor 10 for using a subchronic study instead of chronic study). The result is a TDI of 900 µg/kg bw. In the absence of adequate inhalation studies *route-to-route* extrapolation from the figure for the TDI is applied, yielding a provisional TCA (PTCA), because this procedure involves considerable uncertainty. Using the standard assumptions for this procedure (adult daily ventilation volume 20 m^3, absorption after inhalation 75% of oral absorption) (RIVM, 1996) the route-to-route calculation gives a PTCA of 4200 µg/m^3. Since this PTCA was extrapolated from the TDI the local effect in the lungs after inhalation (portal-of-entry effect) as demonstrated in humans is not taken into account in this PTCA. In the MAC-value derivation as presented in SZW (1991), this effect *was* taken into consideration and it was concluded that the level of 1100 mg/m^3 represents a minimal-adverse-effect-level in man. The margin between this level and the PTCA as derived above (4.2 mg/m^3) is considered sufficiently wide to regard the PTCA as protective for the portal-of-entry effects in the respiratory tract.[28]

[28] This conclusion may be supported as follows. From the minimal-adverse-effect-level for humans of 1100 mg/m^3 a MAC value was derived of 550 mg/m^3 (SZW, 1991). A safety factor 2 was used since exposure to much higher concentrations did not cause more severe effects. From the MAC value using an uncertainty factor 75, for compensation of intermittent exposure in the working area to

BACKGROUND EXPOSURE

No data are available

MISCELLANEOUS DATA

Absorption factors:

No data on oral, dermal or inhalational absorption are available. The high volatility of ethyl acetate decreases the likelyhood that significant amounts are taken up through the exposed skin (SZW, 1991)

Guideline values:

-MAC value (limit for occupational exposure): 550 mg/m^3 (SZW, 1995).

Odour threshold concentration: 14 mg/m^3 (SZW, 1991).

CONCLUSION

TDI:	900 µg/kg bw
Background exposure:	unknown
Provisional TCA:	4200 µg/m^3

COMPILATION RECORD:

Database determination based on: - the review documents as included in the reference list below;
- additional literature search: ToxLine Plus 1990-1996

Profile compilation by: M.E. van Apeldoorn & M.F.A. Wouters

Profile review by: G.J.A. Speijers, M.N. Pieters & J.v. Benthem (Toxicology Advisory Group,13-08-1996)

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RIVM-Centre for Substances and Risk Assessment

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continuous exposure (7/5 x 24/8), for compensation of exposure of a worker during 40 yrs to lifetime exposure (70/40) and for intraspecies variation (10), a PTCA of 7.3 mg/m^3 can be calculated.

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APPENDIX 13: TRIBROMOMETHANE

INTRODUCTION

Tribromomethane (bromoform) is released to the environment by industrial activities involving bromine and is formed during the chlorination of drinking-water (hypochlorous acid oxidises bromide-ions to form hypobromous acid which reacts with endogenous organic materials).

RELEVANT ROUTE

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

TOXICITY

IARC classified tribromomethane in Group 3 *(not classifiable as to its carcinogenicity)*, based on *inadequate evidence* for carcinogenicity in humans and *limited evidence* in experimental animals. (IARC, 1991). Tribromomethane was tested for carcinogenicity in 2-year NTP studies by oral gavage in Fisher 344 rats and B6C3F1 mice at dose levels of 0, 100 or 200 mg/kg bw/day (rats and female mice) or 0, 50 or 100 mg/kg bw/day (male mice). No treatment-related tumours were observed in mice at either dose level. Neoplastic lesions (adenomatous polyps or adenocarcinomas) were found in the large intestine of male rats (sum-incidences 0/50, 0/50, 3/50; adenocarcinomas: 0/50, 0/50, 1/50) and female rats (sum-incidences: 0/50, 1/50, 8/50; adenocarcinomas: 0/50, 0/50, 2/50). The occurrence of this type of neoplastic lesion is very rare in control animals (historical control range in all NTP laboratories 0.3% in males and 0% in females). In this study there were severe toxic effects at the highest dose level (increased mortality, marked growth retardation, toxic effects in liver including inflammation and necrosis, inflammation also in many other organs). (NTP, 1989; IARC, 1991; US-EPA, 1991) A further oral study is an unpublished feeding study in rats (Tobe et al., 1982 as cited in WHO-WQG, 1996). In this study Wistar rats (n=40/sex/group) were given diets containing 0, 400, 1600 or 6500 mg microencapsulated tribromomethane/kg diet for 2 years. No increase in tumour incidence was observed. It should be noted that in this study the dose levels (as mg/kg bw/day) exceeded those used in the NTP rat study above. Yet a further carcinogenicity study was a screening test by intraperitoneal injection (male A/St mice, dose levels 4, 48 or 100 mg/kg bw, 3 times/week for 8 weeks), in which a slightly increased incidence of lung tumours was seen at the mid dose only. (IARC, 1991)

Tribromomethane has been shown to be positive in both *in vitro* and *in vivo* mutagenicity assays. Positive results were obtained in the Ames test using *Salmonella typhimurium* (when tested in closed containers results were consistently positive). A test in mouse lymphoma L5178Y cells *in vitro* was positive, as was a test for chromosome aberrations in CHO-cells *in vitro*. SCEs were found in *in vitro* studies in human lymphocytes and CHO cells. (NTP, 1989; IARC, 1991) In addition, in a recent study tribromomethane gave positive results *in vitro* in the SOS chromotest and the Ames-fluctuation test (Le Curieux et al., 1995). In *in vivo* mutagenicity studies, tribromomethane caused mutations in *Drosophila melanogaster* (sex-linked recessive lethal test). A reciprocal translocation test in the same species was negative. (IARC, 1991) SCEs were induced in mouse bone marrow (NTP, 1989). Bone marrow micronucleus tests were negative in two studies in mice (Ishidate et al., 1982, as cited in

Fawell et al., 1992; Hayashi et al., 1988, as cited in IARC, 1991), but weakly positive in another study (NTP, 1989). An *in vivo* cytogenetic test for chromosome aberrations in mouse bone marrow showed no effect (NTP, 1989). For the same endpoint in rats, however, Fujie et al. (1990) found a positive response (effect present at 118 mg/kg bw/day, administered orally for 5 days, effect not present at 11.8 and 1.18 mg/kg bw).
A newt micronucleus test (demonstrating chromosomal aberrations on peripheral blood erythrocytes of the amphibian *Pleurodeles waltl* larvae) was positive (Le Curieux et al., 1995).

From the data on genotoxicity and carcinogenicity the following conclusions are drawn. The results of the *in vitro* genotoxicity assays show that tribromomethane is genotoxic, producing clastogenic effects (chromosome breakage) and gene mutations. The positive results in several *in vivo* studies (notably the cytogenetic assays in rats) have confirmed the clastogenic activity. As to the gene mutations observed *in vitro,* there is no confirmation that tribromomethane produces this kind of genotoxicty *in vivo* also, no valid *in vivo* assay for this endpoint being available. The increased incidences of adenomatous polyps or adenocarcinomas in the large intestine as observed in the rat NTP study, were seen *only* at a dose level at which there were severe toxic effects such as markedly reduced body weight gain and obvious hepatotoxicity. Thus, the Maximum Tolerated Dose was clearly exceeded in this study and consequently the biological significance of these neoplastic changes is questionable. This leads to the conclusion that there is only equivocal evidence that tribromomethane is carcinogenic in experimental animals. Based on the carcinogenicity and genotoxicity data available at present, derivation of a limit value via a threshold approach is the only option feasible in the health evaluation for tribromomethane.

The data for noncarcinogenic effects may be summarised as follows. For the oral route studies of 14-90 days duration in rats and mice exposed by gavage have shown liver, kidney and thyroid as target organs (US-EPA, 1991). In a 13-week NTP study, rats and mice were administered tribromomethane by gavage, 5 days a week, at dose levels of 0, 12, 25, 50, 100 or 200 mg/kg bw/day (rats) and 0, 25, 50, 100, 200 or 400 mg/kg bw/day (mice). Male mice at the two highest dose levels showed minimal to moderate cytoplasmatic vacuolization of hepatocytes. Male rats showed a dose-related increase in hepatocellular vacuolization, which effect was significant at ≥50 mg/kg bw/day. In conclusion, the NOAELs for hepatocellular vacuolization were 25 and 100 mg/kg bw/day for rats and mice, respectively. (WHO-WQG, 1996; NTP, 1989)

Very limited information is available on the effects of tribromomethane after exposure via inhalation. Qualitatively it is known that in experimental animals, exposure to tribromomethane by inhalation produces effects on the central nervous system, liver and kidneys (ATSDR, 1990). In humans, it was reported that inhalation of low levels of tribromomethane (levels not specified, however) causes irritation, provokes the flow of tears and saliva, and reddening of the face (Lewis, 1992).

No studies are available regarding the dermal uptake of tribromomethane. Based on the analogy with another halomethane, chloroform, that is readily absorbed through the skin (IPCS, 1994), it is expected that tribromomethane also is well absorbed dermally. Quantitative data for tribromomethane on this aspect are lacking, however.

Based on the hepatic lesions observed in the 13-week study in rats, US-EPA derived a Reference Dose (RfD)[29] of 20 µg/kg bw/day from the NOAEL of 25 mg/kg bw/day. This NOAEL was adjusted for intermittent exposure to 17.9 mg/kg bw/day (adjustment from 5 days/week to 7 days/week). An uncertainty factor of 1000 was applied (factor 10 for use of a subchronic assay, factor 10 for extrapolation from animal data to humans and a factor 10 for protection of the sensitive human subpopulation). (US-EPA, 1991) This value (20 µg/kg bw/day) is adopted here as the TDI.

US-EPA (1993) considered the data base for tribromomethane inadequate for derivation of a RfC[30]. No chronic or subchronic inhalation studies on tribromomethane, and no reproductive or developmental studies that employed an inhalation regimen were found in literature.
Route-to-route extrapolation for noncarcinogenic effects has limited validity since there are indications that portal-of-entry effects might be critical for the inhalation route (qualitatively it is known that in humans tribromomethane is a strong irritant after inhalation - see above). Adequate studies on these effects are lacking, however. To only account for *systemic* effects after exposure to tribromomethane by inhalation, a provisional TCA (PTCA) may be derived from the oral TDI. Using the standard assumptions for such a calculation (adult daily ventilation volume 20 m^3, absorption after inhalation 75% of oral absorption) the resulting PTCA is 100 µg tribromomethane/m^3. Again, it is stressed that this PTCA does not take into account portal-of-entry effects.

BACKGROUND EXPOSURE

Tribromomethane may be present in drinking-water. For the Netherlands a maximum concentration of 2 µg/litre is given by Fawell et al. (1992). A series of measurements carried out in Amsterdam in 1993, where occasionally drinking water chlorination is performed, showed concentrations of tribromomethane ranging from 0.5 to 3.6 µg/litre (Versteegh et al., 1995). For the USA mean concentrations from 0.1 to 12 µg/litre have been reported (ATSDR, 1990). Like the other trihalomethanes tribromomethane can be found in chlorinated swimming-pool water. Levels in freshwater pools are relatively low (1-2 µg/litre). In swimming-pools with saline water much higher levels are present (mean concentrations up to 650 µg/litre) due to the higher bromine levels in this water. (ATSDR, 1990) The reported concentrations in ambient air are low. For urban areas average levels of up to 37 ng/m^3 (USA) or 100 ng/m^3 (Canada) are given (Fawell et al., 1992). Use of drinking-water in the home for showering and bathing may lead to some additional exposure via air.
No data on levels of tribromomethane in food were found in literature.
From the above data the general population background exposure is estimated at <1 µg/kg bw/day.

[29] The RfD is the acronym that was introduced by the US-EPA in the early 1980's to replace the TDI or ADI. The status and toxicological significance of the RfD is equal to TDI or ADI.
[30] Analogously to the RfD (see previous footnote) the US-EPA uses the acronym RfC to denote the long-term toxicological limit value for inhalation exposure. The status and toxicological significance of the RfC is equal to that of the TCA.

MISCELLANEOUS DATA

- Absorption:
  - oral: 60-90% (ATSDR 1990);
  - inhalation: no data;
  - dermal; no data.

Odour threshold:

13.45 mg/m^3 (ATSDR, 1990)

-Guideline values:

- TLV (occupational exposure limit): 5 mg/m^3 (SZW, 1995)
- WHO-drinking water guideline value: 100 µg/L (WHO-WQG, 1996)

CONCLUSION

TDI: 20 µg/kg bw/day

Background exposure: <1 µg/kg bw/day

PTCA: 100 µg/m^3 (for evaluating systemic effects only)

COMPILATION RECORD:

Database determination based on: - the review documents as included in the reference list below;
- additional literature search (Toxline Plus, 1990-1996)

Profile compilation by: J.G.M. van Engelen & P.J.C.M. Janssen

Advisers: J. van Benthem (genotoxicity) & E. D. Kroese (carcinogenicity)

Profile review by: J. van Benthem, A.G.A.C. Knaap & G.J.A. Speijers (Toxicology Advisory Group 13-9-1996)

September1996

RIVM-Centre for Substances and Risk ssessment

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