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# Guidance on the Derivation of *Maximum Permissible Risk* Levels for Human Intake of Soil Contaminants

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**ABBREVIATIONS**

| | |
|---|---|
| ADI | Acceptable Daily Intake |
| ATSDR | Agency for Toxic Substances and Disease Registry (USA) |
| CEPA | Canadian Environmental Protection Act |
| ECOTOX SCC | Ecotoxicological Serious Soil Contamination Concentration |
| FAO | Food and Agriculture Organisation (UN) |
| FDA | Food and Drug Administration (USA) |
| HEC | Human Equivalent Concentration |
| 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) |
| JMPR | Joint Meeting on Pesticide Residues (FAO/WHO) |
| LMS | Linearised Multistage (model) |
| $LD_{50}$ | median Lethal Dose |
| MAC | Maximum Allowable Concentration |
| MPR | Maximum Permissible Risk (in Dutch: MTR) |
| MTR | Maximum Toelaatbaar Risico |
| LOAEL | Lowest Observed Adverse Effect Level |
| NOAEL | No Observed Adverse Effect Level |
| OECD | Organisation for Economic Co-operation and Development |
| PBPK | Physiologically Based Pharmacokinetic (model) |
| QCRA | Quantitative Cancer Risk Assessment |
| RfC | Reference Concentration |
| 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 |
| UF | Uncertainty Factor |
| US-EPA | United States Environmental Protection Agency |
| WHO | World Health Organisation |
| WHO-AQG | World Health Organisation Air Quality Guidelines |
| WHO-EURO | World Health Organisation Regional Office for Europe |
| WHO-WQG | World Health Organisation Water Quality Guidelines |

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**SUMMARY**

This report contains a basic step-to-step description of the procedure followed in the derivation of the human-toxicological Maximum Permissible Risk (MPR; in Dutch: Maximum Toelaatbaar Risico, MTR) for soil contaminants. In recent years this method has been applied for a large number of compounds (the results have been published as separate RIVM reports). This work is carried out at the RIVM Centre for Substances and Risk Assessment (former name: RIVM Toxicology Advisory Centre) in the scope of the RIVM project on soil intervention values. In the present report the different steps in the procedure are discussed briefly and an outline of the kind of problems to be dealt with, is provided. General issues of regulatory risk assessment aimed at the derivation of health-based limit values are addressed and reference is made to some basic background literature.
For soil contaminants frequently large (but not necessarily complete) toxicological data bases are available. Overall, the approach for MPR-derivation as described here, is a pragmatic one in that use is made of existing toxicological evaluations by national and international bodies. Thus, it is attempted to avoid unwanted duplication of work. Existing evaluations are to be used in a critical fashion: on a case-by-case basis their adequacy for use in the present scope is judged and it is determined whether or not additional literature search to supplement the data base is warranted. In case no adequate review is available for a particular compound, a complete literature search for orginal publications is done. The results of such a complete search are used selectively: it is attempted to spot the problem areas and to limit full evaluation of orginal publications to key studies. The MPR-derivation as a whole proceeding in a structured manner, it is nevertheless stressed throughout the report that, unavoidably, for an adequate evaluation of the data on the different toxicological endpoints some professional judgement is needed.

## SAMENVATTING

Dit rapport bevat een basale beschrijving van de achtereenvolgende stappen in de gevolgde procedure bij de afleiding van het humaan-toxicologische Maximum Toelaatbaar Risico (MTR) voor bodemcontaminanten. In de afgelopen jaren is deze methode toegepast voor een groot aantal chemische stoffen (deze resultaten zijn gepubliceerd als aparte RIVM-rapporten). Dit werk vindt plaats bij het Centrum voor Stoffen en Riscobeoordeling (voorheen: Adviescentrum Toxicologie) van het RIVM in het kader van het RIVM-project voor bodeminterventiewaarden. In het huidige rapport worden de verschillende stappen in de afleidingsprocedure kort besproken en wordt een omschrijving gegeven van de aard van de problemen die zich hierbij voordoen. Op de meer algemene issues van de risicoschatting gericht op het afleiden van grenswaarden voor chemische stoffen wordt ingegaan en verwijzingen naar enige elementaire achtergrondliteratuur worden gegeven.
Voor bodemcontaminanten zijn vaak grote (maar niet noodzakelijkerwijs complete) toxicologische gegevenspakketten beschikbaar. De aanpak bij de afleiding van MTR's zoals hier beschreven is pragmatisch omdat gebruik wordt gemaakt van reeds bestaande toxicologische evaluaties zoals opgesteld door nationale en internationale instanties. Op deze manier wordt gepoogd ongewenste duplicering van werk te vermijden. De bestaande evaluaties worden niet automatisch overgenomen: van geval tot geval wordt getoetst of ze bruikbaar zijn in het huidige kader en wordt bepaald of verder literatuuronderzoek om de dataset aan te vullen, geboden is. In geval dat geen adequate *review* voorhanden is, wordt een complete literatuurrecherche uitgevoerd om alle relevante originele publicaties op te sporen. De verwerking van het resultaat van een dergelijke uitputtende zoekactie is zo selectief mogelijk: geprobeerd wordt de probleempunten te vinden en de beoordeling van originele literatuur te beperken tot de cruciale studies. De afleiding van de MTR zoals hier beschreven verloopt via een vastliggende werkwijze maar niettemin is het een onvermijdelijk en regelmatig in het rapport terugkerend punt dat voor een adequate beoordeling van de verschillende toxicologische eindpunten enige vakinhoudelijke expertise nodig is.

## 1. INTRODUCTION

In the framework of the revision of the Soil Protection Guidelines in the Netherlands, and the incorporation of the Interim Soil Clean-Up Act in the Soil Protection Act of the Netherlands, toxicologically based intervention values (formerly called C-values) have been derived. In the past few years a large number of soil contaminants have been evaluated in this programme. These evaluations involve the use of ecotoxicological criteria and of human-toxicological 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 past few years and is described in a number of RIVM-reports. These reports are listed in section 5 below. The following block diagram schematically depicts the different steps in the procedure towards proposed Intervention Values for clean-up of soil and groundwater.

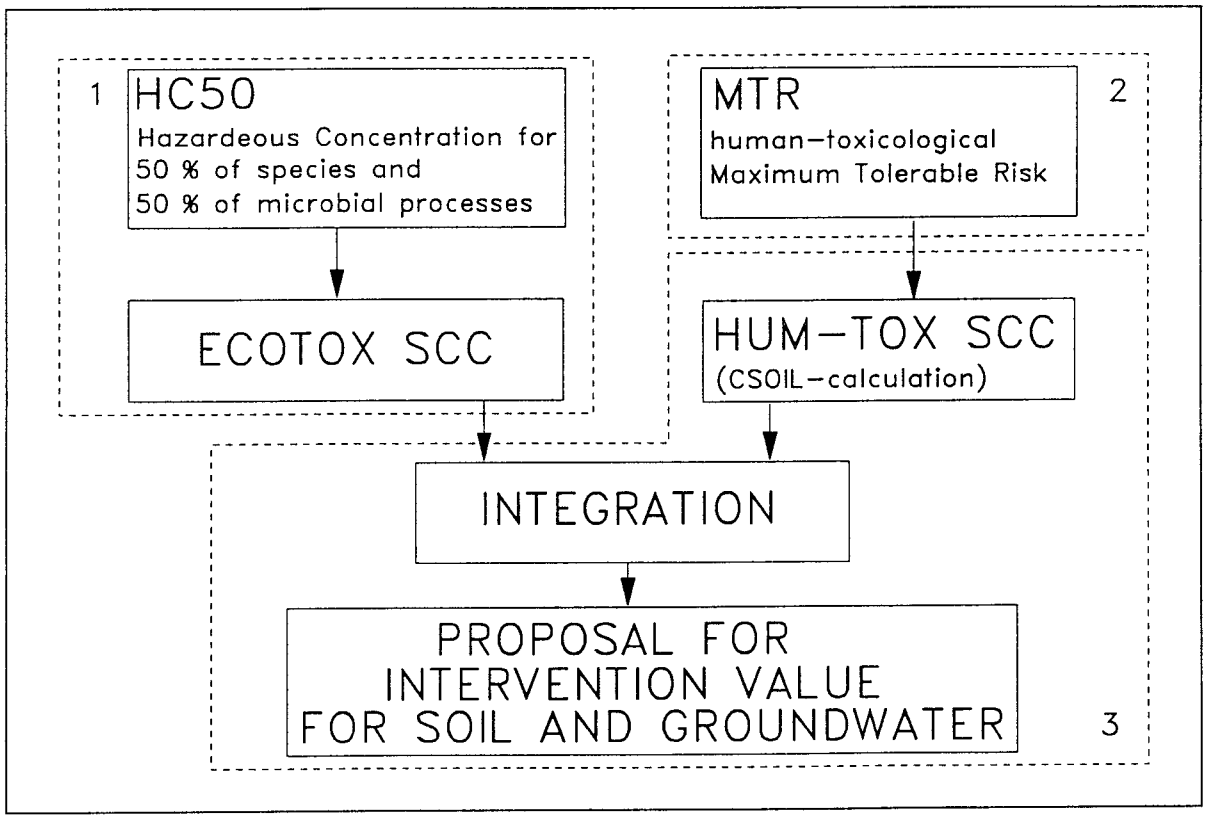


*Figure 1. Diagram of pathways leading to the derivation of proposals for Intervention Values for soil and groundwater*

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: the present report;

step 3: Kreule et al. (1995)[1] - RIVM report no. 715810010 (third series of compounds) & van den Berg et al. (1994)[1] - RIVM report no. 715810004 (second series of compounds).

The present report gives a general description of the method used to derive human-toxicological criteria for the individual compounds. The method has previously been described in the RIVM-report by Vermeire et al. (1991) and, apart from some minor deviations, that description is still applicable. The present guidance document provides a somewhat more detailed presentation of the method[2]. 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*[3] (MPR). This approach was introduced in the brochure *Premises for Risk Management*[4] of the Ministry of Housing, Spatial Planning & Environment of the Netherlands (VROM, 1988).

In general, in the toxicological evaluation of chemical substances, distinction must be made between two standard approaches, 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[5]) 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[6]. 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 chnace 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 of levels of general population exposure to environmental contaminants as encountered in

[1] The two reports given for this step present the *integration* for the second and third series of compounds, respectively (these are the compounds evaluated in the years 1993 and 1994). The integration procedure has not been described in a separate guidance report.

[2] Additionally, it makes the description available in English (the Vermeire et al.-report being written in Dutch).

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

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

[5] 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).

[6] 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 (this point is also discussed in section 3.4.2.1).

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).[7] 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 9 below).

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, inhalational) for humans living on the site of soil contamination (standard situation, all exposure routes operative). The 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 air as calculated by CSOIL at the HUM-TOX SCC, is compared to the toxicological limit value[8] 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 inhalational route, of the TDI. For genotoxic compounds the inhalational $10^{-4}$ excess lifetime cancer risk is used instead of the TCA.[9] 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 $10^{-4}$ inhalational cancer risk level. A detailed description of the CSOIL model is provided by the RIVM report of van de Berg (1995).

As an extension of the procedure for evaluating soil contamination, the human-toxicological MPRs are also used for site-specific risk determination[10]. For these assessments CSOIL-derived models are used. Different *types* of sites or exposure situations are distinguished; in these non-standard situations not all potential exposure routes are operative. For discussion of site-specific assessments see Bockting et al. (1994 & 1996), Swartjes et al. (1994) and Waitz et al. (1996).

In the human-toxicological evaluation aimed at deriving MPRs, toxicity data for all three routes (oral, dermal, inhalational) are considered. This full data set is needed to get a complete picture of the toxicological properties of the compound. Limit value derivation is done for each of the three routes if there are sufficient data. In practice, however, dermal limit values can be derived in exceptional cases only because of lack of data on the dose-response relation for this route. Where oral data are

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[7] 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).
[8] 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, RfC, $10^{-4}$ excess lifetime cancer risks, MPR, as well as MAC.
[9] Additional clarifaction: the MPR also covers these inhalational limit values and in the report text below the term *inhalational MPR* is sometimes used. Thus, the MPR is the umbrella term covering both oral and inhalational limit values.
[10] In Dutch: "bepaling actuele risico's".

insufficient for derivation of a TDI, *route-to-route extrapolation* is done, based on the inhalation data. *Vice versa*, if a TCA is required in view of expected inhalational exposure, oral data may be used if inhalation data are insufficient for derivation of a TCA. Route-to-route extrapolation is discussed in section 3.5. below.

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 has been, and 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 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 inhalational 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 method used for MPR derivation.

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 section 5.

## 2. SCHEMATIC PRESENTATION

Figure 2 on the next page gives the general scheme that is followed in the derivation of the human-toxicological MPRs. As already explained above, the derivation makes use of existing evaluations wherever this is possible. For compounds for which the RIVM has performed an in-depth evaluation in the recent past, this evaluation is used as such and the toxicity profile can be compiled directly from it. The scheme in figure 2 is valid for all compound evaluations, including the cases where existing RIVM evaluations are used without further adjustments being made to them. Where up-to-date evaluations by the RIVM are lacking, as is more usually the case, the steps in the scheme in figure 2 should be followed more closely and more critical evaluation is needed to prepare the toxicity profile. In section 3 the main steps from the scheme are explained in more detail and the relevant information on general issues of toxicological risk assessment is given. The discussion of these general issues highlights the main points only; where relevant, references are given of background texts where the reader can find a more detailed discussion of the topics concerned.

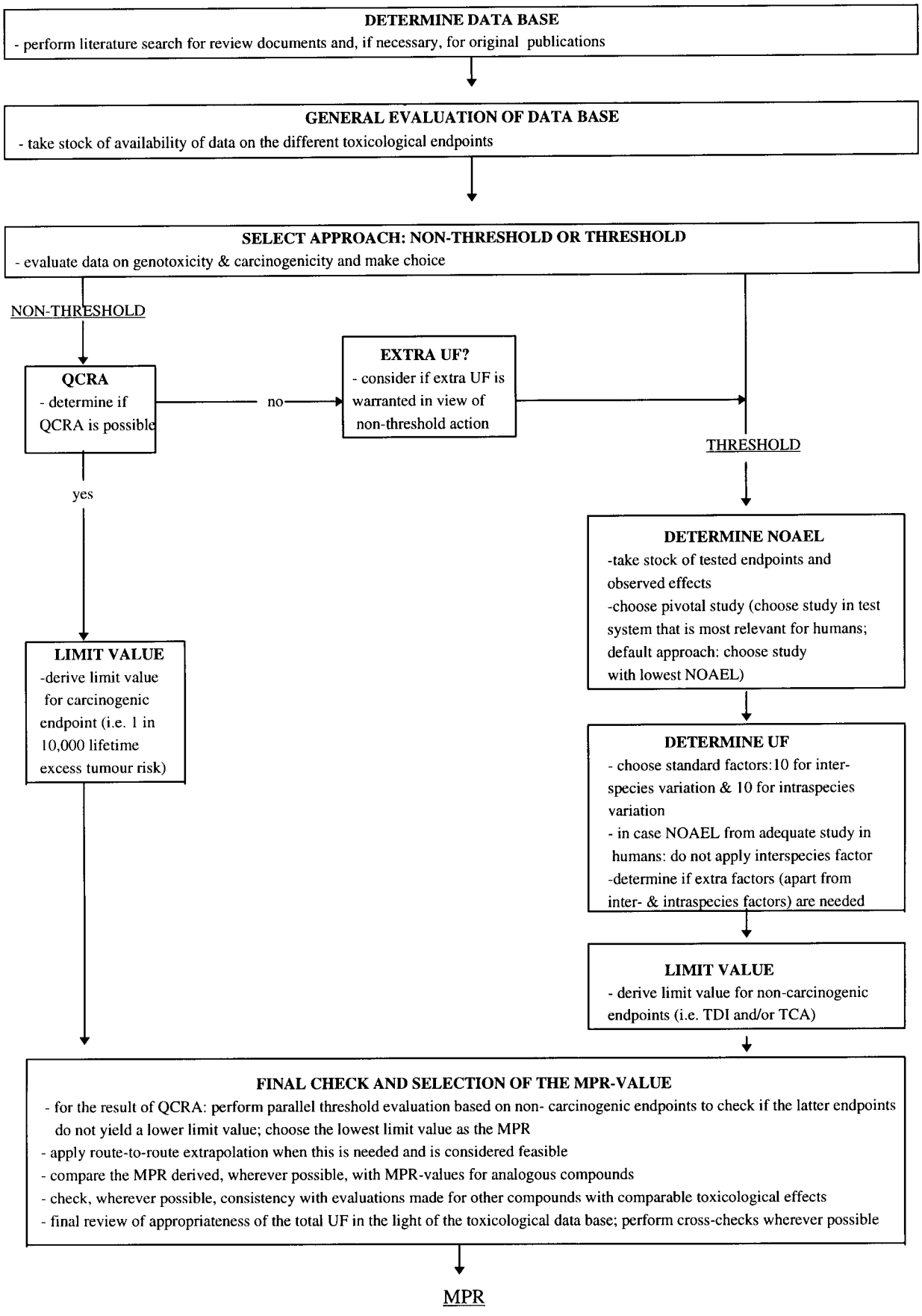


***Figure 2: General scheme for derivation of human-toxicological MPR-values***

## 3. STEP-TO-STEP IN THE HUMAN-TOXICOLOGICAL MPR-DERIVATION

Based on the scheme in figure 2 the following major steps in the MPR-derivation are distinguished:

1. Determination of data base;
2. General evaluation of the data base;
3. Selection of approach: threshold or non-threshold;
4. Selection of pivotal study or studies and derivation of limit value;
   4.1 Non-threshold evaluation (QCRA);
   4.2 Threshold evaluations (application UF to NOAEL);
6. Final check and selection of MPR-value;
7. Report of results as *toxicity profiles*.

In the following paragraphs the different steps will be explained and, where needed, the more general issues discussed.

### 3.1. Determination of data base

As already remarked in the previous sections the general approach is pragmatic in that use is made of existing compound evaluations. For this reason in the first instance the literature search is directed primarily to existing review documents by the RIVM or other national or international bodies. In table 1 a list of frequently used series of reviews is given (for the abbreviations used see page 7).

**Table 1. Series of easy-to-use, comprehensive review documents**

| name of series (& publisher) | description of contents |
|---|---|
| Integrated Criteria Documents (RIVM) | Complete summary of available toxicity data for all exposure routes with evaluation & conclusion for all relevant exposure routes; limit values are derived wherever data allow this. |
| IRIS-files (US-EPA) | Summary presentations of Oral RfD Assessment, Inhalation RfC Assessment, Carcinogenicity Assessment & Drinking Water Health Advisories; concise presentation of principal and supporting studies; is available on-line. |
| ATSDR Toxicological Profiles (ATSDR) | Complete summary of available toxicity data for all exposure routes; limit values (MRLs) are derived for various exposure periods. |
| CEPA Priority Substances Assessments (Environment- & Health-Canada) | Concise & complete summary of toxicity data for all exposure routes; carcinogenicity evaluation included (general approach similar to Dutch approach); limit values are derived. |
| Environmental Health Criteria (WHO/IPCS) | Complete summary of available toxicity data for all exposure routes with evaluation & conclusion but as a rule no limit values are allocated. |
| JMPR Monographs (WHO/FAO) | Complete summary & evaluation of toxicological data of selected pesticides; predominantly oral data considered; oral limit values, i.e. ADIs are derived. |
| JECFA Monographs (WHO) | Series of monographs for food additives and food contaminants; framework & contents similar to JMPR pestides series (previous item); oral limit values are derived: ADIs for additives, TDIs for contaminants. |

| name of series (& publisher) | description of contents |
|---|---|
| WHO Drinking-Water Guidelines (WHO) | Concise summary of key studies per endpoint; wide range of contaminants dealt with; only oral route considered; oral limit values, i.e. TDIs, are derived where possible. |
| WHO Air Quality Guidelines (WHO) | Framework and contents similar to previous item (WHO drinking-water); inhalational limit value derived. |
| IARC Monographs (WHO) | Evaluation of all evidence on carcinogenicity leading to conclusion & classification as to carcinogenic potential. Monographs include review of genotoxicity assays and also limited information on other toxicological endpoints; no limit values are derived. |

As a rule, the conclusions and limit values from the RIVM Integrated Criteria Documents can be adopted as such since these documents represent in-depth reviews of all available experimental data and the conclusions drawn are based on extensive review of the evidence by experts from the laboratories of the RIVM. In addition, as a routine procedure, RIVM Criteria Documents are submitted to a re-evaluation by the Health Council of the Netherlands[11]. The latter re-evaluations should accordingly also be consulted in the preparation of the toxicity profiles from the RIVM Criteria Documents. A further step yet, may be comparing the RIVM evaluation with existing evaluations from other national or international bodies. This comparison may show additional relevant data to exist that may have impact on the MPR derivation.
The other documents listed in table 1 (US-EPA, ATSDR, WHO, CEPA) also represent well-validated data sources because these are evaluations carried out by (inter)national committees of experts.
In all cases where the comprehensive review documents from table 1 are used, the limit value derivation as given should be critically reviewed and it must be decided whether or not the derivation is appropriate for use as MPR in the present scope.

Any other toxicity reviews that are available probably also are of use as providing an overview of the available data base, and for the selection of key studies or publications that may serve as basis for the derivation of limit values.

Where for a particular compound, one or more of the existing evaluations as listed in table1 are available, it should be decided whether or not it is appropriate to perform a limited additional literature search to supplement the data base. In case the reviews are not fully up-to-date such a supplementation probably is warranted. This depends in part on the amount of data and the variety of toxicological endpoints that are the basis for the review document: in case the review already covers a large and fairly complete data set (complete: studies available for each of the items listed in section 3.2.), the urgency for supplementation is less than when only limited data were available for the existing review.

A *complete* literature search for original publications is warranted in case:
- no review documents are available, or:

[11] In Dutch: "Gezondheidsraad".

- the available review documents are an insufficient basis for determining the data base (e.g. in case they are not sufficiently up to date).

The results of such a complete search is used selectively in that it is attempted to spot the problem areas and to limit full evaluation of original publications to key studies.

## 3.2. General evaluation of the data base

This step involves the taking stock of the studies carried out with the compound in question and determining the completeness of the data base. The following check points are important:

- availability of studies on the effects of the compound in humans and their adequacy in giving information on the dose response relation of the compound;
- variety of toxicological endpoints that have been examined in animal experiments;
- amount of data per exposure route.

If adequate human studies exist (adequate epidemiological studies, controlled clinical studies) these studies can be used as the direct basis in the limit value derivation with the animal toxicity data serving as supporting evidence. Adequate human data, however, at present, are available for very few chemicals only. In most cases where there is evidence on the effects in humans this is of a limited nature. Occupational studies, the only kind of human data available usually, have such limitations in that exposure levels are mostly known insufficiently and in that in most cases there is simultaneous exposure to other toxicants. This kind of study usually may give *some* evidence on the exposure levels that lead to adverse effects in humans, but it does not provide an adequate basis for a limit value. Nevertheless these studies should be taken into consideration because they can be used to cross-check the limit value derived from animal data.

There is a variety of relevant endpoints in experimental animals that should be considered in the toxicological evaluation. For these endpoints standard test systems are available. For the performance of these tests, guidelines have been developed by the OECD, the *OECD Guidelines for Testing of Chemicals*. This is an ongoing programme in which international groups of experts participate. The requirements are updated regularly and for new test systems guidelines are developed. These OECD guidelines are very useful where evaluation of individual studies is required.

The standard toxicity studies include:

- acute toxicity ($LD_{50}$-determination): single-dose studies;
- subacute toxicity: repeated administration for 14-28 days;
- semichronic toxicity: administration during 1/10 of the lifetime of test animals (usually 90-day studies);
- chronic studies: administration during whole lifetime (≥90%) of test animals;
- carcinogenicity studies: administration during whole lifetime, combination with chronic toxicity is possible;
- teratogenicity studies: administration during pregnancy (to detect adverse effects on embryo/foetus);

- reproduction studies: continuous administration during 1-3 generations (to detect adverse effects on male & female reproduction);
- genotoxicity studies: variety of test systems, both *in vitro* & *in vivo* (to detect adverse effects on genetic material).

In addition standard protocols are available for studies concerning toxicokinetics, sensitisation, skin & eye irritation and neurotoxicity. An OECD guideline for immunotoxicity testing is being developed. In addition to the standard studies, special toxicity studies focussing on specific adverse effects (and using a non-standard protocol) may also give relevant evidence that should enter into the limit value derivation. The animal species commonly used in toxicity testing are mice and rats. Less frequently used species are hamsters, dogs and monkeys. Guinea pigs are primarily used for irritation and sensitisation testing.

On the animal toxicity studies as listed above, a large literature exists, providing detailed discussion concerning their inherent limitations and the problems relating to the interpretation of results. Only a few points from these elaborations are addressed in the present report. Within the RIVM specialists from the Laboratory of Health Effects Research and of the Laboratory of Pathology and Immunobiology participate in the evaluation of animal toxicity studies.

In the course of performing this second step in the MPR derivation, a general (integral) picture of the toxicological properties of the compound should be obtained and problem areas should be spotted. Having such a general picture makes it easier to take the further steps in the procedure.

### 3.3. Select approach: non-threshold or threshold

This step involves careful consideration of all evidence on carcinogenicity (including data for humans) and genotoxicity. In the evaluation of carcinogenicity data IARC-monographs should be used as back-up check. These monographs provide evaluation of all published data on individual chemical compounds or exposure situations and, as the conclusion of the evaluation, classification for carcinogenic potential for the compound or process in question. The classification system as used by IARC is purely qualitative[12] and is exclusively based on carcinogenicity data only. Data on genotoxicity and other data on interaction with genetic material are presented in the monographs but these are not combined with the evidence from the carcinogenicity studies. Where tumour incidences show increases, such combination of data is required when it is attempted to establish the kind of mechanism through which the compound produces the tumours. The latter approach, i.e. using genotoxicity data to determine the kind of mechanism through which a tumorigenic response arises, has been used in the Netherlands since 1978 (see Health Council of the Netherlands, 1994). The general rule followed is: where the available evidence (i.e. genotoxicity test results and any other

[12] The degree of evidence for carcinogenicity is qualitatively characterised as either *no evidence*, *inadequate evidence*, *limited evidence* or *sufficient evidence*. This kind of conclusion is drawn separately for humans (based on the available human data) and for experimental animals. Similar weight-of-evidence classification systems have been developed by the EU, US-EPA, and other bodies.

relevant data on the mechanism of action) indicate that observed tumours are likely to be the result of a direct interaction with DNA (genotoxic mechanism) a non-threshold approach is warranted. The theoretical assumption for this kind of interaction is that the action of a single molecule of the compound on DNA may ultimately contribute to the formation of a tumour ("one-hit"). Where the experimental data indicate that observed tumours arise through an indirect mechanism of action for which a threshold can be assumed to exist (nongenotoxic mechanism), the theoretical one-hit assumption does not apply and a non-threshold approach is not used.

A carcinogenic response occurs where tumour incidences in groups exposed to the test compound are increased above the control incidences. On the significance and interpretation of the results of carcinogenicity studies there exists a large literature. Guidance for the evaluation on individual animal experiments is given in IARC (1986). The use of human data is discussed in Shore et al. (1992).

Epidemiological studies can be used not only for the qualititative determination of the carcinogenic potency in humans (hazard identification) but also for the quantitative determination of the carcinogenic potency (*quantitative cancer risk assessment* or QCRA[13]). A brief discussion on the use of epidemiological data for QCRA is given by WHO-AQG (1987). If the epidemiological findings give sufficient information on the dose response relation they can serve as the sole basis for the QCRA. Where epidemiological studies give less-detailed information they may be used as a check on risk estimates derived from animal data. It should be noted that the application of epidemiological data, especially when used quantitatively, requires considerable professional judgement. Within the RIVM, epidemiologists from the Department of Chronic Diseases and Environmental Epidemiology are available for support in the evaluation of this kind of studies. As is the case for human data in general, adequate epidemiological data from which unequivocal conclusions can be drawn are comparatively rare. Epidemiological results (studies on workplace exposures mostly) from which QCRA can be performed are available for very few compounds only. For most compounds the carcinogenicity evaluation is based primarily on animal studies and where QCRA is warranted, this is based on the tumour incidences from the animal experiments.

Animal carcinogenicity experiments are performed almost exclusively in rats and mice. Some practical points to be considered in the evaluation of test results are:
- statistical significance of observed increases in tumour incidences & dose response relations;
- dose range tested, presence/absence of toxic response at highest dose levels tested;
- survival rate at test end;
- presence/absence of pre-neoplastic lesions in tumour development;
- route of exposure in relation to observed tumours (relevance of response for other routes);

[13] Terminological clarification: in the toxicological literature the general denomination *quantitative risk assessment* or *quantitative risk estimation* is frequently used so as to refer exclusively to the estimation of cancer risks from tumour incidence data. This qualified usage is potentially confusing, especially so since there is a trend in regulatory toxicology to increasingly use methods for quantitative assessment of noncancer effects (see section 3.4.1.2. for some brief discussion on these methods). To avoid confusion, in the present document the term *quantitative cancer risk assessment* (QCRA) is used.

- historical control tumour data;
- consistency in observed results across different bioassays;
- relevance for humans of tumours observed in animals.

Again, it should be noted that the evaluation of carcinogenicity studies requires considerable professional judgement. Within the RIVM experts from the department of Carcinogenesis, Mutagenesis & Genetics (Laboratory of Health Effects Research) participate in the evaluation of these studies.

Genotoxicity testing, that is determination of the effect on genetic material, is carried out in a wide variety of standard test systems. On the development, application and interpretation of this kind of experiments a large literature exists. A convenient overview of the field is supplied by the *Introduction to the OECD Guidelines on Genetic Toxicology Testing and Guidance on the Selection and Application of Assays*. A more detailed introduction is given in Carere et al. (1995).
Broadly speaking genotoxicity testing is aimed at:

- providing evidence for the putative carcinogenic potential of a compound (screening & detection of direct interaction with DNA);
- determination of the potential of a compound to induce mutations in man that may be transmitted via germ cells to future generations.

The link with carcinogenic activity rests on the consideration that cancer is considered to be the result of the accumulation of genetic damage (genotoxic action, mutation) in somatic cells.

The different genotoxicity test systems that have been developed, each detect a specific genetic endpoint (mostly only one single endpoint per assay). Thus, the results of the different tests supplement each other and a combination of results in different systems is required for full determination of genotoxic potential. The following table gives a general classification of standard genotoxicity tests as to detected genetic endpoint.

**Table 2. General classification of genotoxicity tests**

| test system | OECD guideline no. |
|---|---|
| **Assays for gene mutations** | |
| *Salmonella typimurium* reverse mutation assay | 471 |
| *Escherichia coli* reverse mutation assay | 472 |
| Gene mutation in mammalian cells in culture | 476 |
| Drosophila sex-linked recessive lethal assay | 477 |
| Gene mutation in *Saccharomyces cerevisiae* | 480 |
| Mouse spot test | 484 |
| **Assays for chromosomal aberrations** | |
| *In vitro* cytogenetic assay | 473 |
| *In vivo* cytogenetic assay | 475 |
| Micronucleus assay | 474 |
| Dominant lethal assay | 478 |
| Heritable translocation assay | 485 |
| Mammalian germ cell cytogenetic assay | 483 |
| **Assays for DNA effects** | |
| DNA damage and repair; unscheduled DNA synthesis (UDS) *in vitro* | 482 |
| Mitotic recombination in *Saccharomyces cerevisiae* | 481 |
| *In vitro* sister chromatid exchange (SCE) assay | 479 |

from: Introduction to the OECD Guidelines on Genetic Toxicology Testing of Assays

The relative value of the different assays in predicting possible human effects depends on many factors, but, in general the more closely the system resembles the human the greater the predictive weight placed on the system. Thus, in general, *in vivo* tests have greater weight than *in vitro* tests, test in eukaryotes have greater weight than those in prokaryotes and tests in mammalian species have greater weight than tests using non-mammalian species. As to the utility and application of the various assays the following categorisation is given by the OECD:

- screening assays (mutagen screening & initial screening for carcinogenic potential): the *S. typimurium* and *E. coli* reverse mutation assays, gene mutations in mammalian cells in culture and *S. cerevisiae*, *in vitro* cytogenetic assay, unscheduled DNA synthesis (UDS) *in vitro*, sister chromatid exchanges (SCE) *in vitro*, mitotic recombination in *S. cerevisiae*, *in vivo* cytogenetic assay, micronucleus assay, Drosophila sex-linked recessive lethal assay;
- assays that confirm *in vitro* activity: *in vivo* cytogenetic assay, *in vivo* micronucleus assay, mouse spot test, Drosophila sex-linked recessive lethal assay;
- assays that assess effects on germ cells and that are applicable for estimating genetic effects: dominant lethal assay, heritable translocation assay, mammalian germ cell cytogenetic assay.

For individual compounds the level of genotoxicity evaluation that is possible depends on the assay systems tested with the compound. A single test in prokaryotes provides only a limited indication of genotoxic potential. A meaningful evaluation requires more elaborate data sets. In the context of compound toxicity evaluation for regulatory purposes (registrations for use as pesticides, food additives etc.) international and national bodies have recommended a variety of approaches to the application of genetic toxicology assays and *batteries* comprising from two to five test systems have been suggested. Within some other regulatory programmes tiered systems for genotoxicity testing are used.

For the contaminants dealt with in the present scope, in the usual case, results in several assay systems are available. As will be evident from the foregoing discussion, for the evaluation and interpretation of this kind of sets of results considerable professional judgement is needed. Within the RIVM experts from the department of Carcinogenesis, Mutagenesis & Genetics (Laboratory of Health Effects Research) participate in the evaluation of the genotoxicity studies.

The present step in the evaluation involves the determination of whether or not a non-threshold is appropriate. As explained above, a non-threshold approach is warranted for genotoxic carcinogens because of the theoretical one-hit premise that is assumed for these compounds. The identical assumption also applies to the estimation of the genetic risk for compounds that induce mutations in germ cells *in vivo*. Such an estimation can then be based on the *in vivo* genotoxicity test results. In practice this latter kind of QCRA is carried out very infrequently due to lack of data.

The most usual practical application of genotoxicity test results is in conjunction with carcinogenicity data, i.e. for the determination of whether or not a compound is a genotoxic carcinogen. Any other experimental results (than those obtained in standard assays) that may provide information on the

mechanism of tumour formation should also enter into this determination of yes/no genotoxic carcinogen. All available evidence that could elucidate the mechanism through which tumours could develop should be taken into consideration. This weight-of-evidence approach also involves taking into account of data from other toxicity tests and toxicokinetic studies.

In case a compound is concluded to be a genotoxic carcinogen it must be determined if the data are sufficient to allow a quantitative estimate of the carcinogenic risk (QCRA). This step is discussed in the next section. In case the data on carcinogenicity and genotoxicity do not warrant the conclusion that the compound under review is a genotoxic carcinogen, then a threshold approach is applicable. Threshold evaluations are discussed in section 3.4.2.

## 3.4. Selection of pivotal study or studies and derivation of limit value

### 3.4.1. Non-threshold evaluations

For genotoxic carcinogens quantitative risk assessment is done if data permit. This involves estimating the excess lifetime cancer risks based on observed tumour incidences in, usually, animal carcinogenicity studies. QCRA can also be done from observed tumour incidences in humans but in practice this is done infrequently due to lack of appropriate data. QCRA is carried out using extrapolation models. A number of such models are available, convenient overviews of which are presented by Johannsen (1990) and Park & Hawkins (1993). Performance of QCRA using mathematical extrapolation models is the subject of continuing discussion in the toxicological literature. A recent international comparison of methods used in the carcinogenicity evaluation (Moolenaar, 1994) showed that many countries do not routinely use the method of QCRA through mathematical extrapolation. Thus, there is no international consensus regarding this kind of extrapolation. The IARC (WHO) does not include *quantitative* estimates of cancer risks in its compound evaluations (monographs). The rationale given for this by the IARC is that QCRA entails a large judgemental component and that the understanding of the mechanism of carcinogenesis is still incomplete (IARC, 1994). In the Netherlands QCRA has been applied since about 1980. A linear extrapolation method is used. This linear extrapolation is performed for genotoxic carcinogens only[14]. The WHO in its derivation of Air Quality Guidelines uses a similar approach applying QCRA as the default derivation for genotoxic carcinogens (see WHO-EURO, 1987).

For its QCRA the RIVM has been using a simple linear extrapolation model. The general formula used for this extrapolation is as follows:

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

[14]Note the difference with the US-EPA approach, where QCRA is practiced for all compounds producing increased tumour incidences (including those compounds that in the Netherlands would be considered non-genotoxic carcinogens). The US-EPA is moving towards an approach in which default QCRA is no longer applied automatically and more use is made of data on the mechanism of tumour formation (see NRC, 1994).

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. It uses the lowest tumorigenic dose only: the dose response relation is not taken into account. This latter objection can be met by using a model that does take the entire dose response relation into consideration. The best-known of the latter kind of model is the linearised multistage model (LMS) as developed within the US-EPA (US-EPA, 1987). For estimates of cancer risks as found in literature, in many cases the LMS model was the tool used in QCRA. For this reason some further information on this model may be given here. The multistage model, originally developed by Armitage & Doll in 1961, is based on the consideration that a normal cell must progress through a series of biological events or stages (e.g. mutations) before it can become malignant. Mathematically the multistage model is an exponential polynomial function. The multistage model in its non-linearised form, is very sensitive to minor changes in observed tumour incidences: changes by a few tumours in the observed incidence lead to large changes in estimated cancer risk levels. To account for this statistical instability of the estimated risk a bounding procedure was introduced, yielding the linearised multistage model. This linearised form of the multistage (LMS) model fits the general multistage model and then iteratively increases the linear term ($q_1$) of the polynomial until its upper 95% confidence limit, $q_1^*$, is found. Excess low-dose cancer risk is then calculated from the linear equation:

$$\text{risk} = q_1^* \times \text{dose}$$

Thus, the LMS model gives the *95% upper confidence limit of risk*; a best estimate of the risk is not considered an acceptable estimate due to statistical instability. (US-EPA, 1987)
Very useful analyses of the LMS model in its application as the tool for quantitative risk assessment from tumour incidence data are given by Lovell & Thomas (1996) and Crump (1996).

As already stated, a number of other mathematical models (than the LMS and the RIVM model) is available for the extrapolation of cancer risks. The choice of model is arbitrary. The different models usually fit the experimental data equally well but predict different cancer risks in the low dose region. Model properties are such that choosing the "right" model for a particular extrapolation on the basis of biological considerations, is not possible. The predicted cancer risks for the different mathematical models may well differ by several orders of magnitude. Thus, there is considerable uncertainty in the result of the extrapolation with the available mathematical models. To improve the quantitative carcinogenicity assessment some models have been developed that have a more thorough biological basis, usually referred to as the *biologically-based models*. The model of Moolgavkar-Venzon-Knudson (MVK model) is widely considered the most promising model in this area. In this biologically-based model, species specific biological data on the interaction of the compound with

the organism enter into the extrapolation. The aim of these efforts is a better extrapolation that makes more use of relevant data on the mechanism of action of the compound under investigation. The improvement that this kind of models represent for extrapolation (relative to the statistical/probability-based mathematical models such as the LMS), is that if such a model captures the dose response data in a biological meaningful way, its extrapolation to the low dose area probably is more reliable (more realistic biologically). Application of the biologically-based models requires the generation of appropriate experimental data for the compound under scrutiny. As yet these approaches are under development. At the present time it is not clear whether the biologically-based models at a further stage of their development and application, have potential for use on a more or less routine basis.

The default extrapolation model used by the RIVM is linear in the low-dose region and given that feature may be considered conservative (most likely overestimating the real risk). The LMS model used by the US-EPA produces the linear upper bound on the risk which means that the real risk will be lower in 95% of the cases (it may even be zero). The application of these models constitutes a kind of fall-back approach: they provide an estimate that is (probably) conservative and is inherently uncertain. The tendency of the models as used to overestimate the risk is a deliberate choice given the uncertainty in model prediction. The mathematical models (including the linear model used by the RIVM) lack a real biological basis (i.e. compound-specific experimental data concerning the low-dose mechanism of action); where an alternative approach is possible that is more directly based on biological data for the compound in question, that approach is preferable in principle.

QCRA is done from tumour incidences as observed in experiments, usually animal experiments. Such tumour incidences are selected from the studies in the data base as available for the compound in question. The selection and use of the tumour incidences for QCRA requires professional judgement. The tumour types taken into consideration must be decided upon. Some points for consideration are for instance:

- is the observed tumour type common in the animal strain used in the test;
- if the results indicate that observed benign tumours will progress to carcinomas then these pre-malignant lesions are included in the risk estimate;
- benign tumours that have been demonstrated not to become malign are not included.

In conclusion, for genotoxic carcinogens QCRA is done if there are sufficient data for this. The RIVM uses a simple linear extrapolation method (formula given above) as the default approach. Within the RIVM QCRA is carried out in cooperation with experts from the department of Carcinogenesis, Mutagenesis & Genetics (Laboratory of Health Effects Research).

A case sometimes occurring in practice is that there is sufficient reason to consider a compound as a genotoxic carcinogen but that no reliable tumour incidences that could serve as a basis for QCRA, are available for that compound. For instance a compound shown to be genotoxic *in vivo* and for which carcinogenicity data are inadequate for QCRA, or a compound with a very limited data set that shows the compound to produce similar effects as a closely-related compound that has been demonstrated to be a genotoxic carcinogen. In such cases a threshold evaluation with an extra uncertainty factor is a fall-back option (on the use of such an extra factor see however the discussion by Renwick, 1995).

For QCRA dose conversions may be needed to compensate for limited daily or weekly exposure periods. For the oral route in case of application on less than 7 days/week, dose levels are adjusted downwards to the equivalent level for 7 days/week. For inhalation data, the exposure concentration as used in the experiment (x hours/ day, y days/week) is adjusted downwards to the equivalent level for 24 hours/day, 7 days/week.[15] For the oral route scaling is done based on body weight (not on surface area). The end-result of the QCRA is the human dose in mg/kg body weight (oral route) or in $mg/m^3$ (inhalation) that entails an extra cancer risk of 1 in $10^4$ in case of lifelong exposure.

### 3.4.2. Threshold evaluations

If a compound is not concluded to be a genotoxic carcinogen a threshold approach can be used. The threshold evaluation proceeds on the basic notion that there exists a range of exposures from zero to some finite value that can be tolerated by the organism without adverse effects because protective mechanisms exist that must be overcome before the adverse effect is manifested.

#### *3.4.2.1 The use of uncertainty factors*

The threshold evaluation involves application of uncertainty factors (UFs) or safety factors[16] to a NOAEL selected from the available toxicity studies. This method of toxicological limit value derivation has been practised for several decades. Lehman & Fitzhugh (1954) of the US-FDA originally suggested the use of a safety factor of 100 to be applied to the chronic no-effect levels (as mg/kg diet) from animal studies with the result giving the safe levels of food additives or contaminants. In a slightly modified form this proposal was adopted by the expert committees on food additives and pesticides of the WHO/FAO in the early sixties: the safe level was called the Acceptable Daily Intake (ADI) and was expressed in mg/kg body weight/day. This approach has since been widely used throughout the world. For contaminants the term ADI has been replaced by TDI, the Tolerable Daily Intake. This change is purely terminological; the rationale for it was that

[15] Some further discussion on the dose adjustments as outlined here, is given in section 3.4.2.2.

[16] The term *uncertainty factor* was introduced by the US-EPA at the introduction of the concept of the Reference Dose. *Uncertainty factors* replaced *safety factors*. This was done because the term safety factors was thought to carry an unwarranted suggestion of absolute safety. The name of uncertainty factor was considered more descriptive in that these factors represent scientific uncertainties and it avoids the risk management connotation of "safety". A further factor introduced by the US-EPA is the so-called *modifying factor*. This is an extra factor that is applied, based on professional judgement, for uncertainties in the data base or the pivotal study that have not been adequately addressed by the other uncertainty factors. Another term sometimes used to denote the factors applied in threshold evaluations is *extrapolation factors* (Health Council of the Netherlands, 1985). To solve these terminological points the term *uncertainty factor* is preferred in the present report (replacing "safety factors" and also covering the "modifying factors").

since contaminants are not deliberately used in the production process of foods, their presence cannot be qualified as acceptable given their advantage-of-use, but a certain level of contamination may be *tolerated* because it will not have an adverse effect on human health. For the inhalation route an analogous approach has been adopted involving the application of uncertainty factors to the NOAEL in $mg/m^3$ yielding the Tolerable Concentration in Air (TCA). Exclusively used by the US-EPA are the acronyms RfD and RfC referring to the Reference Dose and the Reference Concentration, respectively. The RfD was introduced by the US-EPA in the early 1980's to replace the ADI/TDI[17]. For the inhalational route the EPA now uses the Reference Concentration (RfC). Strictly speaking the concept of the RfD and RfC are wider in that subchronic and chronic RfDs/RfCs are distinguished but in practice the acronyms RfD and RfC are used without further specification and then stand for the chronic RfD/RfC. Thus, RfD and RfC are synonymous for ADI/TDI and TCA, respectively.

The derivation of the ADI/TDI or TCA involves simply dividing the NOAEL by the total uncertainty factor. This total uncertainty factor is the product of several uncertainty factors. The magnitude of the total uncertainty factor is determined on a case-by-case basis. This determination proceeds in a structured fashion in which there are standard magnitudes for the individual factors that compose the total uncertainty factor. 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

[17] The rationale given for this change in terminology was that "acceptable" as in ADI may suggest a strict demarcation between what is acceptable and what is unacceptable in that any exposure greater than the ADI is unacceptable. The ADI however, is a relatively crude estimate of a chronic level of exposure not likely to result in adverse effects to humans, and its bounds of uncertainty can span perhaps an order of magnitude. Thus, it was that the more neutral name of Reference Dose was preferred by the EPA.

10) are used. For a complete set of animal toxicity data (i.e. studies available for each of the items listed in section 3.2.) 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 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.

Using uncertainty or safety factors for deriving limit values is common practice in many countries and several studies have been carried out to investigate whether available toxicity data can lend some support to the magnitude of the uncertainty factors as commonly used (and specified in table 3). Concerning interspecies differences, allometric considerations and the limited number of experimental data on individual compounds that were analysed, indicate that on average interspecies variation is between factors 3 and 10. In individual cases however, experimental data indicate interspecies variation markedly exceeding a factor of 10. (Dourson & Stara, 1983; Hassauer et al., 1993) Limited observations in humans concerning enzymatic response to xenobiotics, binding to macromolecules and differential risk to disease within populations indicate that interindividual variability is within a factor of 10 in most cases but exceeding a factor of 10 is not uncommon (Calabrese, 1985; Hassauer et al., 1993). Acute laboratory animal data for a number of compounds indicate intraspecies variation within a factor of 3 for 92% of the compounds (Dourson & Stara, 1983). This latter kind of toxicity data however, is of limited value for predicting variability in human populations because genetically homogeneous laboratory animals presumably are poor indicators of differences in susceptibility in human populations that are genetically and physiologically much more heterogeneous.
The data analysis by Dourson & Stara (1983) included a comparison of chronic and subchronic NOAELs to review the adequacy of the extra uncertainty factor that is introduced in case only semichronic studies are available. In 50% of the cases examined (n=52) the ratio between semichronic NOAEL and chronic NOAEL was within a factor of 2; in 96% of the cases the ratio was ≤10. The LOAEL to NOAEL extra uncertainty factor was evaluated in a similar way (number of cases studied: 52) by the same authors. They obtained LOAEL/NOAEL ratios of ≤5 in 96% of the cases; the maximum factor found was 10. (Dourson & Stara, 1993) Two similar analyses of more recent date are available. Kadry et al. (1995) examined data sets for six chlorinated chemicals and found semichronic/chronic ratios of ≤3.5. The ratio between LOAEL and NOAEL was ≤6 in 90% of the cases (maximum 10). Kramer et al. (1995) found a conversion factor (defined as the upper 95% confidence limit of the 95th percentile of the distribution of the ratios) of 46 between the semichronic NOAEL and the chronic NOAEL (number of cases analysed: 149). Between the chronic LOAEL and the chronic NOAEL they found a conversion factor of 12 (n=175).

The above data provide some limited support for the magnitude of the different uncertainty factors as presented in table 3. As is also stressed by the various authors cited, additional studies in this field are needed to allow better evaluation of the default uncertainty factors.

As already stated above, the uncertainty factor application is not automatic and superimposition of all default factors is unwanted. The possibility of reductions on individual factors should be considered. In the current practice of regulatory toxicology such reductions are made in the relatively few cases where there are sufficient data to indicate that it is justified to do so. The reduction most frequently encountered in toxicological evaluations is to the LOAEL-to-NOAEL uncertainty factor. In case the effect at the LOAEL for a particular compound is judged to be less-serious a lower factor than 10 may be applied (for examples see Pohl & Abadin, 1995). The severity-of-effect determination requires professional judgement. In table 4 in the next section a classification system for effect severity is given.

A refinement on the use of the standard default uncertainty factors for inter- and intraspecies variability has been proposed by Renwick (1993). The scheme as proposed by Renwick retains the two 10-fold factors as the cornerstone for extrapolating from animals to humans but the scheme allows subdivision of each of the factors of 10 to incorporate appropriate data on toxicodynamics or toxicokinetics where these are available. In this approach the default factor of 10 for interspecies differences is subdivided in default factors for toxicodynamics (factor 2.5) and toxicokinetics (factor 4.0). The standard factor of 10 for interindividual differences in the human population is similarly subdivided in default factors for toxicodynamics (factor 3.2) and toxicokinetics (factor 3.2). Where appropriate actual data on toxicokinetics and toxicodynamics are available they should allow replacing the default factors in the scheme. The method proposed by Renwick has already been submitted to some review and has been applied on an experimental basis for a number of compounds (see Kroes et al., 1993). The IPCS (1994) has included the Renwick proposal in its procedure for derivation of uncertainty factors. The IPCS Task Group noted that the data base examined with reference to the Renwick method, is limited and recommended that the subdivision of default factors as proposed by Renwick be adopted on an interim basis. The Task Group felt that adoption of the approach should encourage the development and generation of appropriate data, which could then contribute to any future revision of the default values, and further improve the scientific basis for the use of uncertainty factors. (IPCS, 1994)

#### *3.4.2.2 Selection of the appropriate NOAEL from the data base*

Regarding the selection of the appropriate NOAEL[18] from the data base the rule followed is that thát test system is chosen as pivotal study that is most relevant to humans. Thus, studies in primates are in principle more relevant than studies in rodents. The study quality and scope, however, must be taken into account and may warrant the selection of a study in a non-primate system as the pivotal study.

[18] To avoid terminological confusion: this NOAEL is the one that is to serve as the direct basis for the limit value and it is "overall" to the entire data base. Each study in the data set yields a NOAEL and from these NOAELs the one that will be divided by the total UF (giving the limit value) is chosen. In the text the term NOAEL is used generically, as is the usual practice in the toxicological literature; where the "overall-NOAEL" is meant this will be evident from the context.

From the set of standard animal studies as given in section 3.2., it is not possible to a priori give a detailed ranking order as to relevance for humans. Since the TDI or ADI is the limit value for chronic human exposure, a chronic animal study is the most obvious choice or the pivotal study. Nevertheless, in case another test system yields a lower NOAEL the latter study should be chosen. In view of this it is crucial to obtain a detailed overview of the observed LOAELs and NOAELs in the various studies that have been carried out with the compound.

In practice, particular study results may sometimes be excluded from the evaluation. This is warranted in case it has been adequately shown that certain results for a particular compound (or group of compounds) are not relevant for humans. A well-known example of this are the kidney tumours in male rats due to the accumulation of $\alpha_{2u}$-globulin conjugate in the renal proximal tubules. This effect, observed for a number of hydrocarbons, is known to be a species- and gender-specific effect to male rats. Because humans do not possess the high levels of $\alpha_{2u}$-globulin that are required for the formation of the globulin conjugate in significant amounts, this effect is not considerded relevant for humans. Wherever such exclusion of observed effects is decided upon, this should be explicitly stated in the evaluation report and the justification should be given.[19]

In the evaluation aimed at selecting the pivotal study it is important to review the effects observed in the various toxicity studies. Dose response relations and the severity of the observed effects should be noted when the uncertainty factors are chosen. The ranking of effect-severity as used by the US-EPA may provide some helpful guidance on this point. In table 4 below this classification system is given. As detection methods become increasingly more sophisticated the notion that not all changes that are detectable should be interpreted as toxic effects deserves due attention. With very sensitive detection methods changes may be detected already at very low dose levels. Professional judgement is needed to determine if these changes are really toxic effects that must be counted in the determination of the NOAEL.

**Table 4. US-EPA Classification of severity of toxicological effects (non-carcinogenic effects)**

| rating | effect |
|---|---|
| 1 | -Enzyme induction or other biochemical change with no pathological changes and no change in organ weight |
| 2 | -Enzyme induction and subcellular proliferation or other changes in organelles, but no other apparent effects |
| 3 | -Hyperplasia, hypertrophy, or atrophy, but no changes in organ weights |
| 4 | -Hyperplasia, hypertrophy, or atrophy, and changes in organ weights |
| 5 | -Reversible cellular changes: cloudy swelling, hydropic changes, or fatty changes |
| 6 | -Necrosis or metaplasia with no apparent behavioural, sensory or physiological changes |
| 7 | -Necrosis, atrophy, hypertrophy, or metaplasia with a detectable decrement of organ functions<br>-Any neuropathy with a measurable change in behaviour, sensory, or physiological activity |

[19] Where a limit value derivation from an existing evaluation is adopted this may not be necessary because the relevant discussion on this point will already be provided by the review document in question and need not be duplicated.

| rating | effect |
|---|---|
| 8 | -Necrosis, atrophy, hypertrophy, or metaplasia with definite organ dysfunction<br>-Any neuropathy with gross changes in behaviour, sensory, or motor performance<br>-Any decrease in reproductive capacity<br>-Any evidence of foetotoxicity |
| 9 | -Pronounced pathological changes with severe organ dysfunction<br>-Any neuropathy with loss of behavioural or motor control or loss of sensory ability<br>-Reproductive dysfunction<br>-Any teratogenic effect with maternal toxicity |
| 10 | -Death or pronounced life shortening<br>-Any teratogenic effect without signs of maternal toxicity |

from: Stara et al. (1987)

In the threshold evaluation as described above (NOAEL/UF = limit value), the weighing of the severity of observed effects is possible to a limited extent only, i.e. as a factor that may be qualititively taken into account in the determination of the uncertainty factor (for some examples see for instance Pohl & Abadin, 1995). Quantitative incorporation of effect-adversity in the evaluation process is not possible within the NOAEL/UF method. Application of alternative methods that have been developed (notably Crump et al., 1984, Gaylor, 1988, Hoekstra & van Ewijk 1993)[20] should allow such quantitative use of experimental data. These methods have as yet not been used for regulatory purposes and their usefulness is still under investigation, also at the RIVM (see Zeilmaker et al., 1995). Especially the Benchmark Dose approach, proposed by Crump et al. (1984), is being tested for its applicability to actual data sets (see Barnes et al., 1995 and Haag-Grönlund et al., 1995). It may reasonably be expected that in the future more use will be made of the alternative methods. It has been proposed that the NOAEL/UF method could provide the default option to be used when the data set is too limited to allow use of, for instance, the Benchmark Dose method.

A further limitation inherent to the use of the NOAEL/UF approach is the "relativity" of the NOAEL. The value of the NOAEL is an observed value that depends on the protocol and design of the study. Applying one of the alternative methods as mentioned in the previous paragraph, is a possible improvement on this point also, since these methods are aimed at using the dose response curve instead of the single data point that is the NOAEL.

Based on an overview of the relevant NOAELs and LOAELs in the toxicological data set available for the compound under evaluation, the appropriate NOAEL or LOAEL that will serve as the immediate basis for the MPR, is chosen. Before applying the UFs adjustments to the NOAEL/LOAEL may be necessary to compensate for limited duration of exposure in the study from which the NOAEL/LOAEL is taken. The rationale for this adjustment is that the MPR is the limit value for continuous exposure (24 hours/day, 7 days/week) for an entire lifetime and using an unadjusted NOAEL or LOAEL would mean underestimating the risk. The duration-adjusted NOAEL/LOAEL is calculated by dividing the numerical value of the exposure level from the

[20]Zeilmaker et al. (1995) provide a review of these methods.

experiment by a factor to give the equivalent exposure level on a 24-hours/day-7-days/week basis. This back-calculation is done linearly based on the - simplifying - consideration that a shorter duration of exposure to a higher dose level will produce a similar toxic effect as a longer exposure to a proportionally lower dose level (Concentration x Time = constant-effect). Thus, for oral studies in case the dosing schedule involves compound adminstration for 5 days/week only, the NOAEL from such a study is adjusted downwards (by factor 5/7) to the average level over 7 days/week. Similarly for inhalation studies: a NOAEL/NOAEL obtained for instance from a study with exposure to the test compound for 6 hours/day on 5 days/week is adjusted downwards (factor 30/168) to the equivalent level for 24 hours/day, 7 days/week. It should be noted that where existing toxicological limit values as derived in the past by other national or international bodies are adopted, duration adjustments may have been applied in another way or not at all.
Specifically for the inhalational NOAELs derived from animal studies the US-EPA has developed an additional adjustment step in that the *Human Equivalent Concentration* (HEC) is calculated from the animal NOAEL. This calculation takes into account the type of agent under consideration (gas or particle), the type of target effect (respiratory or extrarespiratory) and whether or not periodicity has been attained. Some physiological, parameters of humans and animals such as breathing frequency, tidal volume and alveolar ventilation rate are used in the equations for the HEC calculation. Much of the HEC methodology evolved from the use of PBPK models and mathematical dosimetry models. The impact of applying the step of HEC calculation on the numerical outcome of the limit value derivation is considerable. The extra step of HEC calculation is a refinement in the limit value derivation and it may be expected to be used increasingly by national and international bodies

Although the NOAEL from the pivotal study is the proximal basis of the limit value, the other studies in the data set do nevertheless contribute to the derivation as supporting evidence. In this indirect way the limit value derivation rests on the entire data set that is available and for this reason it is important to adequately take review the different items in the data base for the compound under scrutiny.

## 3.5. Final check and selection of the MPR-value

This step involves critical evaluation of the limit value that would follow from the choices made in the previous steps. NOAELs/LOAELs from supporting studies (the studies not chosen for actual limit value derivation) in the data set may be used to evaluate the limit value. For instance an LOAEL from a study in humans that was not suitable for use as the pivotal study, may nevertheless be used to check the limit value: between the LOAEL and the limit value a sufficiently wide margin of safety should exist. NOAELs/LOAELs from the supporting animal studies may be used in a similar fashion. This is especially important where animal studies have shown up severe effects (e.g. teratogenicity).

For the genotoxic carcinogens the present step involves the development of a parallel threshold evaluation based on non-carcinogenic endpoints in order to check whether or not such a threshold evaluation gives a lower limit value than the non-threshold evaluation for the genotoxic-*cum*-carcinogenic effect. Given 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), there is a distinct 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. An example of this is benzene where the threshold evaluation based on haematotoxic effects yielded a TCA of 30 $\mu g/m^3$ whereas the estimated $10^{-4}$ lifetime excess cancer risk was 1200 $\mu g/m^3$ (see Vermeire et al., 1991 & Vermeire, 1993). Thus, for genotoxic carcinogens for which QCRA has proved possible, the procedure as depicted in figure 2 above should be re-entered at the *threshold* pathway and an alternative limit value should be derived using the appropriate UFs. The necessity for this extra step for genotoxic carcinogens is a consequence of the choice made in the definition of the MPR[21], i.e. using the TDI/ADI or TCA as a cut-off point alongside the $10^{-4}$ excess lifetime cancer risk. As with benzene, the end-result may be that the MPR for a genotoxic carcinogen is not based on the carcinogenicity endpoint as most plausibly would have been the case, but on the other toxicological effects (threshold effects) produced by the compound.

An important point of attention throughout the evaluation is the sufficiency of data for the different exposure routes (oral, inhalational, dermal). The determination of which routes are relevant is done qualitatively on a case-by-case basis (see the discussion in the next section). If the data base is incomplete in that for a route for which an MPR is needed there are insufficient toxicological data, whereas for another route the data do allow MPR-derivation, the feasibility of *route-to-route extrapolation* must be determined. Route-to-route extrapolation is discussed in Gerrity & Henry (1990). The extrapolation involves using the toxicity data for one route to derive the limit value for another route. In practice this cross-route extrapolation is done only for the oral and inhalational routes because almost always adequate toxicity data are available for one of these routes only. The premise for this kind of extrapolation is the consideration that once a chemical penetrates the systemic circulation, its kinetic behaviour is in principle independent of exposure route. Thus, the extrapolation relies on the *internal dose* (the dose measurable as for instance circulating blood levels or area-under-the curve). The relation between the internal dose and the externally applied dose may be complex and route-specific factors may be involved. Oral intake, for instance, presents the compound to the liver, where it is available for first-pass metabolism prior to entry into the systemic blood. In contrast, after inhalational and dermal absorption the compound does not encounter the liver before entering the systemic circulation. The different nature of the barriers, for the different routes, across which absorption takes places mostly will produce dose-rate variations across routes.

The preferred method for performing a route-to-route extrapolation is by using an appropriate PBPK model of the absorption, distribution, metabolism and elimination of the compound under investigation. As pointed out in Gerrity & Henry (1990), the development of a full pharmacokinetic model can involve considerable time and effort but it provides clearly the most reliable way of extrapolation across routes. The use of an existing model structure for an analogous compound can reduce the effort required for model development. As yet, PBPK-model development has not evolved so far as to make possible their use, for route-to-route extrapolation, on a more-or-less routine basis.

[21] MPR-definition as introduced in 1988 in the brochure *Premises for Risk Management* (title in Dutch: *Omgaan met Risico's*) of the Ministry of Public Housing and Spatial Planning & Environment of the Netherlands.

Internationally PBPK-models are becoming available for an increasing number of chemicals and classes of chemicals, and the increased understanding of the principles involved should be of use in developing models that can be applied more routinely.

The current default approach for route-to-route extrapolation is very simple. It consists of the use of default absorption factors for the routes considered. In conformity with the *Uniform System for the Evaluation of Substances* (USES) as developed in the Netherlands (RIVM, VROM, WVC, 1994) it is assumed that absorption via the inhalational route is 75% of that for the oral route. Thus, using the standard values for adult body weight (70 kg) and daily ventilation volume (20 $m^3$/day) as included in USES, from the TDI (oral MPR) as derived from toxicity data, a TCA (inhalational MPR) is calculated using the formula:

$$\frac{\text{TDI} \times 70\,(\text{kg})}{20\,(\text{m}^3)} \times \frac{100}{75} = \text{TCA}$$

Conversely, from a TCA as derived from toxicity data a TDI can be calculated using:

$$\frac{\text{TCA} \times 20\,(\text{m}^3/\text{day})}{70\,(\text{kg})} \times \frac{75}{100} = \text{TDI}$$

Exactly the same calculations can be made in case the MPR is a cancer risk estimate for either the oral or the inhalational route. It should be noted that the result of the default route-to-route extrapolation is inherently uncertain. The two formulas above represent very crude estimates. Because of this low reliability of the result of the default route-to-route extrapolation, all limit values derived using it, are tagged as being *provisional* values only. One option to be considered at this point is to replace the default oral/inhalation absorption ratio (100/75) by reliable absorption percentages from literature.
An important restriction concerning route-to-route extrapolation is that it should not be used if there are portal-of-entry effects (local effects at the site of entry of the body). A TCA based on respiratory effects (for instance irritation) in an inhalation study cannot plausibly be used for calculating an oral limit value. For a genotoxic carcinogen for which the cancer risk estimate is based on tumours that developed at the site of entry of the body, this estimate is of questionable significance for other exposure routes. Thus, the default route-to-route extrapolation should not be applied automatically: a critical look is needed.

A useful final check is comparing the MPR with values for structurally analogous compounds. Compounds that are closely related to the compound under scrutiny will frequently exert similar toxicological actions and taking into consideration the available evidence for such a structural analogue may allow a better-informed choice as to the appropriate MPR-derivation. A possible check on the consistency of the choices made in the derivation of MPRs is comparing the derivation for the

compound under investigation with that of another agent producing similar toxicological effects. One option to be considered in this context is the allocation of a common limit value for a group of compounds that are closely related chemically and that produce the same or a very similar toxicological effect (or plausibly may be expected to produce such an effect). Examples of such group-MPRs are the TDI as derived for the sum of aldrin, dieldrin, endrin, isodrin & telodrin and the TDI for the sum of ethylene glycol and diethylene glycol (see Vermeire et al., 1991 & Janssen et al., 1995).

The evaluations prepared are reported in a concise form as *toxicity profiles*. Before publication the draft profiles are submitted to final review. The latter activity takes place within the Quality Assurance framework of the Centre for Substances and Risk Assessment. The general working procedures, as maintained for the advisory work (human-toxicological and ecotoxicological) as carried out within the Centre for Substances and Risk Assessment are outlined in Standard Operating Procedures. For reasons of traceability and responsibility the names of all persons participating in profile compilation and profile review are recorded in the profile in question. Profile outline is further discussed in the next section.

### 3.6. Report of results as *Toxicity Profiles*

The profile is a narrative statement of the crucial points to be noted concerning the toxicological properties of the compound under review. The main elements of the profile are: a general indication of the size of the data base, a short summary of the evidence on genotoxicity and carcinogenicity (including the IARC qualitative weight-of-evidence classification), description of the pivotal study or studies, where relevant a short outline of supporting studies or other relevant considerations, derivation of the MPR.

The first item to appear in the profile is the determination of which routes are relevant for the compound dealt with. This is determined qualitatively on a case-by-case basis. The oral route is relevant in all cases since the calculation with CSOIL (the model used for quantifying total human exposure within the three-step procedure for deriving proposed soil intervention values - see figure 1 in section 1 above) is based on the oral MPR. The inhalational route is relevant (*ergo* an inhalational MPR is needed) in case, for the compound in question, exposure via that route at a contaminated soil site is to be expected. This will apply for all volatile compounds (see the analysis of van den Berg , 1995). In addition the inhalational route will be relevant for compounds that are less-volatile but must be expected to produce toxic effects already at low concentrations. The inhalational route is not relevant for compounds with a very low volatility. In principle the dermal route should be considered in all cases but the scarcity of toxicological data for this route, quantitative data being absent in almost all cases, precludes any detailed evaluation. For this reason this route is often omitted from the profile.

Apart from the main elements as already mentioned above, the profile contains some figures on general population *background exposure* and some *miscellaneous data*. Information on background

exposure of the general population primarily in the Netherlands is included but because such information is frequently lacking, data from other countries are often given instead. The *miscellaneous data* include relevant regulatory guideline values for the compound in question. These values (for instance residue limits for vegetables, drinking-water guidelines) may be used to check if the concentrations as calculated by CSOIL are not above the maximum allowed in the contact-medium in question. Further items under this heading are odour thresholds and the Maximum Allowable Concentration (MAC-value) for occupational exposure.

As already stated in the previous section the final draft of the profile is submitted to final review before publication.

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

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

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

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

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

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

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

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

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

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

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

Contains: re-evaluation of 9 (groups of) compounds from the set dealt with in the Vermeire et al.-report from 1991.

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

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.

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

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

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

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

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

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

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

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

Crommentuyn, G.H, Posthumus, R. & Kalf, D.F. Derivation of the Ecotoxicological Serious Soil Contamination Concentration - substances evaluated in 1993 and 1994. RIVM-report no. 715810003, dated August 1995.

Contains: ecotoxicological criteria (MPR-values) for 2nd & 3rd series of chemicals (26 chemicals).

Janssen, P.J.C.M., M.E. van Apeldoorn, J.E.M. van Koten & W.C. Mennes (1995) Human-toxicological criteria for serious soil contamination: compounds evaluated in 1993 & 1994. RIVM-rapport 715810 009 d.d. augustus 1995.

Contains: human-toxicological criteria (MPR-values) for 2nd & 3rd series of chemicals (26 chemicals).

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

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

Bockting, G.J.M., Swartjes, F.A., Koolenbrander, L.G.M. & Berg, R. van den (1996) SEDISOIL: Model ter berekening van humane blootstelling ten gevolge van verontreinigde waterbodems. [In Dutch] RIVM-report no. 715810011, dated May 1996.

Contains: extension of CSOIL for use in the assesement of risks for humans in case of contamination of sediments; this method may be used for determination of the urgency for clean-up for polluted sites (in Dutch: " bepaling saneringsurgentie"); model should preferably be used in combination with concentration measurements in water and fish.

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.

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

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. (1997) Human-toxicological Maximium Permissible Risk levels for use in the determination of *Serious Soil Contamination*: fourth series of compounds. RIVM report 711701 004 (in preparation).

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

Kreule, P. & Swartjes, F.A. (1997) 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 003 (in preparation).

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 13 compounds.

Swartjes, F.A. (1997) Criteria voor selectie stoffen voor afleiding interventiewaarden. Inventarisatie stoffen voor eventuele afleiding van interventiewaarden. Selectie stoffen afleiding van interventiewaarden vierde tranche [in Dutch]. RIVM report 715810 016 (in preparation).

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.