Toxicology-based recommended exposure limits
Toxicology-based recommended exposure limits

Health Council of the Netherlands:
Committee on Health-based Recommended Exposure Limits

to

the Minister of Health, Welfare and Sports

the Minister of Housing, Physical Planning and Environment

the State Secretary of Social Affairs and Employment

No 1996/12E, Rijswijk, 29 August 1996
# Contents

- Executive summary 71

1  Introduction 77
1.1  Composition, remit and methodology of the Committee 77
1.2  Structure of the report 78
1.3  Background 78

2  Terminology 83
2.1  Exposure, effect and response 83
2.2  Health and adverse effects on health 84
2.3  Functional mechanisms 87
2.4  Formulation of toxicology-based recommended exposure limits 88

3  Information on the toxicity of a substance 91
3.1  Integrated toxicity profiles 91
3.2  Human data 92
3.3  Animal experiments 94
3.4  In vitro experiments 94
3.5  Biokinetics and biodynamics 95
3.6  Structure-activity relationships (SARs) 95
3.7  Chemical mixtures 96
3.8  Conclusions and recommendations 97
4 Toxicology-based recommended exposure limits and predicting the consequences of exposure 99
4.1 Exposure-response relationships 99
4.2 Health-based recommended exposure limits 101
4.3 The prediction of possible adverse effects on health 102
4.4 Conclusion and recommendation 103

References 105

Annexes 109

A Mission 111
B Membership of the Committee 113
C Methods for formulating health-based recommended exposure limits 115
Executive summary

New concept

This report introduces a new term: *toxicology-based recommended exposure limit*. It refers to the dose or concentration of a substance that induces a certain health effect in an exposed population. In formulating a toxicology-based recommended exposure limit only toxicity data and the interpretation of that data by experts are taken into account. The *health-based* recommended exposure limit, aims at preventing health effects, and is considered to be a special case of a toxicology-based recommended exposure limit.

Toxicology-based recommended exposure limits

The Dutch government’s policy on the control of substances is intended to protect human health against the possible adverse effects of substances released into the environment as a result of human activity. To this end, limits are set on substance concentrations in soil, water, air, food and so on. The limits imposed by the government are in their turn based on *health-based recommended exposure limits* formulated by experts. Exposure to the concentration of a substance equal to or lower than that limit, even for long periods, may reasonably be expected to prevent damage to the health of exposed individuals and their offspring. For some substances, with the framework of the substances policy of the government, *toxicology-based recommended exposure limits* are derived, instead of health-based recommended exposure limits; given continued exposure at a level equal to such a limit, the chance of an individual
suffering a certain effect may reasonably be expected not to be greater than specified in the limit. The chances specified in the limits are small. It is standard practice in the Netherlands to set toxicology-based recommended exposure limits for genotoxic carcinogenic substances; this policy is designed to ensure that the additional chance of an individual contracting cancer may reasonably be expected not to exceed one in a million, given lifelong exposure. (Such additional risk is considered by the government to be negligible.) A health-based recommended exposure limit may be regarded as a particular form of toxicology-based recommended exposure limit, namely a form which specifies a level of exposure at or below which the chance of any adverse health effect may reasonably be expected to be nil.

In addition to prescribing concentration limits, the government sets various other standards, including intervention levels. An intervention level specifies the concentration of a substance at which the government considers it appropriate to intervene (or for others to be obliged to intervene) to protect public health. Intervention levels too are based upon toxicology-based recommended exposure limits; exposure under the specified conditions at a level corresponding to that specified in the limit may reasonably be expected to adversely affect the health only to a certain - specified - extent. Intervention levels are set for periods of increased atmospheric pollution, for example.

This report

In this report, the Health Council’s Committee on Health-based recommended exposure (further on: the Committee) limits provides a general description of the way in which toxicity data and the results of epidemiological research can be used to formulate toxicology-based recommended limits for exposure to substances. The report marks the first step towards the revision and extension of what is widely known as the Van Genderen Report, published by the Health Council in 1985. A review of the Van Genderen Report was felt to be desirable in the light of subsequent scientific debate regarding the formulation of health-based recommended exposure limits. Another consideration was the government’s increasing need for information regarding the effects associated with certain, often unavoidable, levels of exposure and regarding the incidence of such effects – i.e. the response level – within the exposed population.

This report is not intended as an exhaustive treatise on the subject of exposure limit formulation. In keeping with the wishes of the Health Council’s President, the Committee has endeavoured to indicate the respects in which the Van Genderen Report would benefit from revision or expansion, and to highlight areas warranting the Health Council’s further attention.
The critical nature of the exposure-response relationship

At present, toxicity research tends to concentrate on identifying levels of exposure at which adverse health effects are unlikely. The Committee wishes to see the emphasis shifted to increasing insight into the link between exposure and response. If enough is known about the exposure-response relationship for a given substance, a toxicology-based recommended exposure limit may be formulated on a systematic basis. The approach advocated by the Committee is illustrated below.

The formulation of a toxicology-based recommended exposure limit involves a number of stages. First, the available animal experiment data and epidemiological data are analysed with a view to deriving exposure-response functions for those effects which may be considered adverse in relation to human health. Uncertainty factors are then applied to produce an exposure-response function which will form the basis of the toxicology-based recommended exposure limit. The uncertainty factors take account of the uncertainty associated with, for instance, the extrapolation of conclusions regarding human exposure from animal data and sensitivity differences within the population to which the limit will relate. This procedure is intended to exclude any reasonable possibility of the health implications of exposure being underestimated.

Integrated toxicity profiles

Data on the health implications of exposure to a substance is derived from various sources. The Committee recommends that data from these sources be studied on an integrated basis as far as possible. In this context, models of the absorption, distribution, metabolism and excretion of a substance in the body (biokinetic models)
and the effects of a substance or its metabolites in a target organ (biodynamic models) can be very valuable. Analysis will also benefit from general insight into the link between a substance’s chemical structure and its effects. This approach, referred to in this report as the construction of an integrated toxicity profile, is felt by the Committee to be the best way of ensuring optimal utilization of available data and effective and efficient control of toxicity research. Greater efficiency can in turn reduce the need to conduct experiments on laboratory animals. The data basis of an integrated toxicity profile is illustrated below.

### Recommendations

The Committee makes the following recommendations regarding the construction of integrated toxicity profiles:

- The development of improved exposure estimation methods for use in epidemiological research and the use of biomarkers in the measurement of exposure and the early detection of effects should be encouraged.
- Greater importance should be attached to the use of data on substance biokinetics and biodynamics in the extrapolation of conclusions regarding human exposure from animal data and in predicting the outcome of exposure via one route from information regarding another.
- More detailed information should be gathered regarding the reliability of the present biokinetic and biodynamic models.
- The use of such models in protocol toxicity research should be encouraged so that such research may be guided by decision trees and efficiency thereby improved.
The development of methods and procedures for research using volunteer subjects into the biokinetics and metabolism of substances in the body should be encouraged.

The scope for using structure-activity relationships in the assessment of exposure-related human health risks should be investigated, since such models could increase the efficiency of toxicity research.

The formulation of health-based recommended exposure limits

In the Netherlands and elsewhere, health-based recommended exposure limits are normally formulated using the NOAEL/UF* method. (This method is the foundation of the approach advocated by the Van Genderen Committee.) A health-based recommended exposure limit is calculated by dividing the NOAEL for the substance in question by a factor which takes account of uncertainties in the available data and in the extrapolation from that data of findings pertinent to the population group to which the limit is to apply. No other methods are in widespread use. The Committee believes that limits should be formulated using a method which makes systematic use of data on the relationship between exposure and response; the so-called ‘benchmark dose’ (BMD) method is felt by the Committee to be particularly promising. However, before this method can be regarded as a viable alternative to the established method, further practical evaluation is required. The Committee therefore recommends that new health-based recommended exposure limits be formulated using the BMD method for various substances which have already been assessed for occupational health and safety and environmental protection purposes. In this way, it would be possible to identify the data required to apply the method in practice and the issues relevant to the extrapolation of health-based recommended exposure limits from BMDs.

Subjects requiring further attention

The Committee believes that more detailed Health Council reports on the following subjects would be valuable:

- The interpretation of epidemiological research findings.
- Integrated toxicity profile construction methodologies and the way in which the various types of toxicity research are interrelated.
- Techniques for taking account of the toxicology of (complex) chemical mixtures and of substances in combination with co-factors such as noise, odour, heat,

* NOAEL stands for ‘no observed adverse effect level’ and UF for uncertainty factor. The NOAEL is the highest level of exposure to a given substance at which no adverse effect on the health of humans or laboratory animals is observed.
vibration and psychosocial factors when formulating toxicology-based recommended exposure limits.

- The application of response data in the formulation of health-based recommended exposure limits, perhaps once the scope for using the ‘benchmark-dose’ method has been investigated (in which case particular attention should be given to the extrapolation of exposure-response curves into the exposure regions for which data is not available).

The Committee believes that the recommendations contained in the Van Genderen Report remain valid. The desirability of formulating health-based recommended exposure limits in accordance with a transparent procedure is currently widely acknowledged; such a procedure is no less desirable in relation to other types of toxicology-based recommended exposure limit. Nevertheless, the report’s findings do require expansion in some areas, as the Committee has indicated. If, as advocated by the Committee, the emphasis of toxicity research were shifted onto the exposure-response relationship, all types of substance could be brought within a single assessment framework.
Chapter 1

Introduction

1.1 Composition, remit and methodology of the Committee

In 1985, the Health Council of the Netherlands published a report entitled ‘Principles for the formulation of recommended exposure limits’ 1. Produced by the Van Genderen Committee*, the report described a transparent method for setting recommended human exposure limits on the basis of toxicological data. The report was restricted to non-mutagenic, non-carcinogenic and non-immunotoxic substances.

In 1993, the President of the Health Council set up the Steering Committee on Health-based recommended exposure limits. The Steering Committee’s task was to review the Van Genderen Report, decide whether it was in need of revision and, if so, to propose appropriate amendments. A review of this kind was felt to be necessary because in the intervening years there had been a great deal of debate on the use of toxicological data to set recommended exposure limits for government policy purposes, and various alternatives to the Van Genderen method had been put forward. Another consideration was the increasing frequency with which the government was asked to comment on the nature and incidence of the effects associated with certain levels of exposure; extension of the Van Genderen method was felt desirable to provide the authorities with a scientific basis for addressing such queries.

In July 1995, the Steering Committee became a fully fledged Committee of the Health Council (as referred to in Sections 27 and 30.1 of the Health Act) and was asked

* The committee was known by this name because Professor H van Genderen was its chairman.
by the Council’s President to produce a ‘programme document’ as soon as possible, identifying the issues associated with recommended exposure limit development which warranted closer study by the Council. The relevant sections of the President’s letter commissioning the document are reproduced as Annex A to this report, while the members of the Committee are listed in Annex B.

The present report has been produced in response to the Council President’s request. Draft versions were prepared by Dr RA Woutersen of TNO’s* Nutrition Division in Zeist, in consultation with Dr WF Passchier of the Health Council secretariat.

1.2 Structure of the report

Chapter 1 concludes by outlining the background against which the Committee’s recommendations should be viewed; this background is described in more detail in Chapter 2. Chapter 3 deals with the data used in estimating the risks associated with exposure to a given substance. The actual formulation of recommended exposure limits is considered in Chapter 4. The conclusions and recommendations are listed in the Executive Summary at the beginning of the report.

1.3 Background

Risk assessment and risk management

Human activities can adversely affect the environment and human health, for instance, as a consequence of exposure to substances released during the course of the activity in question. The assessment of the risks associated with a given activity and the management of those risks form a structured process (see, for instance, Figure 1 in the report entitled ‘Not all risks are equal’ produced by another Health Council committee 2). The risk assessment phase of this process involves identifying the ways in which health can be adversely affected and the relationship between exposure to stressors (including substances) and adverse effects. Risk assessment is followed by risk management**, during which the tolerability of the risk is evaluated and ways of (further) controlling the risk are identified. Risk management is the responsibility of the

---

* TNO is the Netherlands Organization for Applied Scientific Research.
** In academic literature, the term ‘risk management’ is used in various ways. In this report, its meaning is as defined by the US Environmental Protection Agency. Occupational health and safety professionals tend to apply the term ‘risk management’ only to the last stage illustrated in Figure 1, i.e. the implementation and maintenance of appropriate measures. Others use ‘risk management’ to refer to the whole process of assessing and analysing risk and taking appropriate action to control it.
Substance-induced effects

The toxicological analysis of a substance, *i.e.* identification of its toxic properties and determination of the relationship between exposure and toxic effect, is one element of risk analysis. The Committee believes that such assessment should be left largely to experts in the field. As Figure 1 shows, such experts consult the policy-makers regarding the presentation of their findings (risk characterization), particularly with regard to the object of the analysis. The outcome of this consultation influences the way uncertainties and factual lacunae are addressed.

Standards

The risk management phase of the process illustrated in Figure 1 involves making a judgement regarding the acceptability of a given risk. To this end, the level of risk associated with exposure to a substance is compared to standards which specify the boundary between tolerable and intolerable exposure. Examples of such standards are Maximum Accepted Concentrations (MACs) of airborne substances at the workplace, the concentrations which correspond to the maximum permissible risk levels specified for environmental protection purposes, and maximum daily intake values for substances in foodstuffs. These standards are based on scientific assessments of the toxicity of the substances in question, expressed as ‘toxicology-based recommended exposure limits’. The latter are set during the risk assessment phase of the process (risk analysis and risk characterization).
Toxicology-based recommended exposure limits

The report ‘Principles for the formulation of recommended exposure limits’ concentrates on the development of recommended exposure limits for non-mutagenic, non-carcinogenic and non-immunotoxic substances. The Van Genderen Committee defined a ‘recommended exposure limit’ as follows:

*an estimation of the highest level of exposure to a substance believed to be medically responsible*

From the definition and explanatory note, it follows that if the recommended exposure limit** is exceeded, the possibility of exposed individuals suffering adverse health effects cannot confidently be excluded. However, at the level of exposure specified in the limit and at lower levels of exposure, health effect can be confidently excluded, even if such exposure continues for years on end.

The Van Genderen Committee’s definition is based upon an implicit assumption regarding substance toxicity, namely that for a given substance there is an exposure threshold, at or beneath which that substance is not harmful. However, for certain types of mutagenic, carcinogenic and immunotoxic substances, it does not appear to be theoretically or experimentally possible to identify such a threshold. The Van Genderen Committee therefore excluded the formulation of recommended exposure limits for such substances from its report.

The present Committee decided to take a broader approach with a view to producing recommendations that would apply to all types of substance and all types of effect, at least in principle. The report is accordingly concerned primarily with how the relationship between exposure and adverse health effects can best be determined. Once the exposure-effect relationship for a given substance is properly understood, a toxicology-based recommended exposure limit can be formulated. The meaning of the phrase ‘toxicology-based recommended exposure limit’ is as follows:

*the level of exposure to a substance that, taking due account of factual lacunae and uncertainties regarding the interpretation of toxicity data, may reasonably be believed not to have more than a specified chance of affecting the health of a specified population group in a specified way.*

---

* The Van Genderen Committee attached the following explanatory note to the quoted definition: “The recommended exposure limit is expressed as the maximum daily dose or maximum concentration in one or more environmental compartments, including drinking water and foodstuffs. The limit should be arrived at by an objective expert assessment of the toxicological data as possible and should include a safety margin. Where possible, recommended exposure limits should be accompanied by notes on their use and limitations.”

** A ‘recommended exposure limit’ of the type defined by the Van Genderen Committee is referred to in this report as a “health-based recommended exposure limit”. See below.
Thus, a toxicology-based recommended exposure limit must always specify the following:

- The health effect concerned
- The population group concerned
- The maximum chance of the substance having the specified effect on the specified group, if exposure is limited to the level indicated.

It is also necessary to clarify the nature of ‘the level of exposure’: whether the exposure concerned is short-term or chronic, occurs only once or is intermittent, etc. To prevent the toxicity of a substance being underestimated, the Committee has endeavoured to frame a definition which is intended to ensure that proper account is taken of the inherent uncertainties.

A recommended exposure limit of the type defined by the Van Genderen Committee is in fact a particular form of toxicology-based recommended exposure limit – a form which in this report is referred to as a ‘health-based recommended exposure limit’. A health-based recommended exposure limit specifies the level of exposure at or below which the chance of any adverse health effect may reasonably be expected to be nil.
Chapter 2

Terminology

2.1 Exposure, effect and response

Contact with a substance can lead to local toxic effects and to absorption of the substance by the body. Having been absorbed, a substance and its metabolites are liable to be conveyed to the organs by transport and metabolic mechanisms, and thus to become involved in or affect local biochemical processes. If these processes are disturbed, the individual’s health may be adversely affected. In the most serious cases, death can result.

![Figure 2 Principal means of exposure to a substance.](image)

In this report, the term *exposure* is used to refer to contact between an organism and a substance, such that the substance may affect functions of the organism. The main exposure routes are illustrated in Figure 2. Absorption by the organism may follow inhalation, ingestion or skin contact. To quantify the level of exposure, it is
necessary to specify the duration and frequency of the exposure and the concentration of the substance in the air, water, food or whatever, to which the individual is exposed.

Reference is sometimes made to internal exposure. The Committee follows the Van Genderen Report in equating such exposure to the quantity of a substance present in the body. However, the Committee prefers to use the term ‘body burden’ in this context. The effect of the substance on bodily organs is influenced by the degree to which the body burden is biologically available*. The amount of a substance present in the body depends not only upon the amount absorbed or administered, but also upon the speed with which it is metabolized, broken down and excreted.

The Committee does not distinguish between the terms ‘dose’ and ‘dosage’, and prefers to use the former. The term ‘dose’ is used to refer to the amount of a substance absorbed or administered per unit body mass. Although this variable is therefore dimensionless**, the Committee advises suffixing ‘units’ such as g/kg or mg/kg to expressions of dose.

The consequences of exposure are described using the terms ‘effect’ and ‘response’; the meanings of these terms as used in this report are as follows:

- **effect**
  The reaction of an organism (human or animal) over the short or long term induced by exposure to a substance. Effects may include changes in morphology, physiology, blood pressure, growth, development or lifespan.

- **response**
  The proportion of an exposed population group or group of animals in whom a given effect is induced by exposure to a given substance.

### 2.2 Health and adverse effects on health

**Health determinants**

The authors of the Public Health Forecast Survey identify five key features of health:

- Good health involves functioning optimally or adapting to given circumstances optimally.
- Good health involves dynamic equilibrium or interaction between endogenic and environmental factors.
- Health has physical, psychological and social aspects.
- Health has organic, functional and social implications.
- Health has both subjective and objective aspects.

---

* i.e. may interact with cells or biologically important molecules.
** In toxicology, the amount of a substance is generally expressed in units of mass.

---

84 Toxicology-based recommended exposure limits
On this basis, any definition of a healthy situation must cover not only empirically observable matters, but also subjective and socially and culturally determined matters. An individual’s state of health is, therefore, the product of interaction between exogenic factors or determinants, endogenic determinants and health care (Table 1; 5 6). Exogenic determinants include physical environmental factors, such as substances in the air, water or food, as well as radiation, noise, bacteria and other microorganisms, individual behaviour (e.g. eating and drinking habits, smoking and medicine use) and social environmental factors.

The health implications of exposure to a given substance cannot therefore be determined in isolation, since other influences will always be at work; these may include other physical environmental factors (e.g. exposure to other substances), other exogenic factors, hereditary factors, acquired characteristics and the quality of health care. This does not mean that there is no point in collecting data on the toxic properties of a substance or identifying levels of exposure which, on the basis of such data, may be deemed hazardous, acceptable or desirable. On the contrary, such data and such levels have proved valuable in the protection of public health. What it does mean, however, is that when limits are set for the protection of public health, account must be taken of other influences which may be at work.

Determining adverse effects on health

To be useful in the formulation of toxicology-based recommended exposure limits, data on the relationship between exposure to a given substance and the occurrence of health effects must meet certain conditions. The Committee shares the view expressed in the report on the formulation of air quality objectives 7, namely that such data must meet the following criteria:

---

**Table 1** Factors which contribute to a person’s state of health

<table>
<thead>
<tr>
<th>Exogenic factors</th>
<th>Endogenic factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical environmental factors</td>
<td>Hereditary factors</td>
</tr>
<tr>
<td>Lifestyle</td>
<td>Acquired characteristics</td>
</tr>
<tr>
<td>Social environmental factors</td>
<td></td>
</tr>
</tbody>
</table>

---

85 Terminology
Quantitative data on the effects of measurable and measured concentrations, which takes account of the duration of exposure, must be included. The effects in question must be measurable (e.g. changes in morphology, function or biochemistry, or objectively discernable undesirable psychological changes). A causal relationship must definitely or very probably exist between the reported adverse effects on health and the intensity, frequency and duration of exposure to the agent. The effects must be relevant to general health.

Pathological effects, such as death or a recognized illness, are obviously relevant to general health, as are carcinogenic or congenital effects. By contrast, reflex reactions to the stimulation of chemosensors (even if potentially unpleasant) and other temporary physiological reactions of the organism cannot automatically be classed as adverse effects on health. The issue is complicated by the fact that sensitive biochemical and molecular biological techniques now make it possible to measure effects which would previously have gone unnoticed. Such ‘new’ effects take place at a low biological level (often a cellular level) and the extent to which they are precursors of dysfunction in an organ or the organism as a whole is frequently debatable.

The Committee endorses the conclusion of the Van Genderen Report, that it must be left to suitably qualified experts to decide whether an observed effect is relevant to the general health of an individual in the short or long term. In reaching a decision, such experts will need to consider various questions, including the following:

- Are dysfunctions or morphological defects in the organism involved?
- Is the effect irreversible or too severe to be dealt with by the organism’s repair and compensation mechanisms?
- Could exposure result in overload of the organism’s repair and compensation mechanisms and thus in ill health or reduced resistance in the long term?
- Could the effect, if not directly associated with ill health, serve as a biomarker for subsequent effects which may be relevant to general health?

If the answer to one or more of these questions is ‘Yes’, it is more likely that exposure to the substance will be considered to have an adverse effect on health.

Generally speaking, the body tries to prevent or compensate for the adverse effects of exposure to a given substance. However, it is not always entirely successful. All sorts of other factors are also involved in this process. For example, temperature and humidity can influence the ease with which a substance enters and is absorbed by the body; simultaneous exposure to other substances can affect processing mechanisms, and pre-existing illnesses and disabilities will influence the seriousness of any adverse effect which exposure to a given substance may have on health.
The modifying factors referred to, which can vary from individual to individual and from situation to situation, will contribute to an inherent degree of uncertainty in all substance toxicity data. When such data is used in the formulation of toxicology-based recommended exposure limits, the degree of this inherent uncertainty must be taken into account.

### 2.3 Functional mechanisms

Exposure to substances is associated with a variety of bodily dysfunctions which have health implications; these dysfunctions may relate to cell division, protein synthesis, enzyme systems, membranes or cellular energy supply, or involve irreversible DNA damage, disturbance of the DNA repair processes, reduced availability of essential nutrients or changes in the water and electrolyte balances. Numerous process abnormalities can result, including increased or reduced cell mortality, information transfer problems between cells, reduced biosynthesis, tissue-building problems and abnormal tissue structures, leading eventually to pathological effects. The mechanisms of action concerned can be divided into a few general groups*.

With a **non-stochastic or deterministic mechanism of action**, an adverse effect only takes place once the dose of the substance in question exceeds a certain threshold level; above that level, the seriousness of the effect will increase as the dose increases. The distinguishing characteristic of this type of mechanism is that at doses up to and including the threshold, the substance will be satisfactorily dealt with by the body and no pathological effect will result. In principle, the threshold dose for a given effect varies from one individual to another, and the variation can be considerable. The critical adverse effects** of nearly all the substances studied are based on deterministic functional mechanisms.

With a **stochastic mechanism of action**, within a certain dose range, the chance of a given effect occurring increases as the dose of the substance in question increases; it is not generally possible to discern a threshold dose at or beneath which the chance of the effect taking place is zero***.

Distinction between stochastic and deterministic effects has been promoted since the seventies by the International Commission on Radiological Protection (ICRP) through its recommendations regarding protection against ionizing radiation 8. It is not,

---

* The definitions provided are of a theoretical nature and intended for use in the formulation of toxicology-based recommended exposure limits.

** In this report, the phrase ‘critical adverse effect’ is used to refer to the first adverse effect on health to manifest itself as the dose of a substance is increased from zero.

*** Mechanisms of this type are generally associated with irreversible molecular-scale effects such as irreversible DNA changes.
however, an approach which has met with universal approval; effects on the nervous system, for example, are apparently not easily categorized in this way. One Canadian report on toxicological risk assessment therefore refers to ‘traditional deterministic’ and ‘traditional non-deterministic’ effects. Within the second category, ‘chronic, cumulative’ effects form an important subgroup. A committee of air pollution experts set up by the WHO suggested that it was no longer appropriate to speak of threshold substance doses (the key concept in the deterministic model), and that attention should focus on the nature of the dose-effect relationship. The WHO committee’s comments were based in part on the finding that no threshold value could readily be identified for particulate matter in air or ozone. In addition, various authors reported that exposure to relatively low levels of substances not essential for life appeared to have positive effects on health or to increase the resistance of the exposed organism.

Thus, the categorization of substances on the basis of the types of effect they are liable to induce, or on the basis of the mechanisms action which form the basis of such effects, is often far from straightforward. Matters are complicated by the fact that there is insufficient data on certain types of effect to enable a conclusion to be drawn regarding the mechanisms of action associated with them. In spite of these drawbacks, the Committee believes that distinction between effects associated with stochastic mechanisms and those associated with deterministic mechanisms, while not always strictly applicable, remains valid for toxicological analysis purposes.

2.4 Formulation of toxicology-based recommended exposure limits

Process

The process of formulating toxicology-based recommended exposure limits is illustrated in Figure 3. The first step is to collate the available toxicity data on the substance under examination to produce an ‘integrated toxicity profile’ (see Chapter 3). Once this has been done, the data has to be assessed to determine whether it is capable of shedding light on the consequences of exposure for people in the population group to which the limit is to apply. If so, that data which is relevant to the link between exposure and response for a given effect is selected. From this data, conclusions regarding the link between exposure and response in humans have to be

* To illustrate: if the effect in question was the development of a particular form of cancer, one would have to decide whether humans were susceptible to that cancer or whether it was specific to the species of animal used in the experiment or to the experiment. (So, for instance, certain Health Council committees recently concluded that the results of experiments in which man-made mineral fibres were injected into the windpipe, thorax and abdomen of laboratory animals were not relevant to the assessment of the risk associated with inhalation of such fibres.) Alternatively, it might be necessary to decide whether the results of a particular epidemiological survey were transferable to the population group under consideration.
extrapolated. The process of extrapolation must take account of the uncertainties associated with matters such as the incompleteness and inaccuracy of the original data and the differences between laboratory animals and humans or between the studied population group (e.g. workers) and the population group to which the limit is to apply (e.g. the population at large). Such uncertainties are accounted for by allowing safety margins or, better, by building uncertainty factors into the calculation. The size of an uncertainty factor depends on the purpose of the limit being calculated. Thus, consideration is given to matters such as

- the population group to which the toxicology-based recommended exposure limit is to apply; and
- the purpose of the toxicology-based recommended exposure limit and the margin of safety appropriate in view of, for instance, differences in sensitivity between members of the population group in question*.

**Standards**

Toxicology-based recommended exposure limits form the scientific basis for the regulatory standards used in the protection of public health. Such standards include maximum permissible or acceptable concentration levels as well as intervention levels (the concentrations which trigger, for instance, further research into the effectiveness of control measures, medical surveys of the exposed population, etc).

---

* One of the considerations the Committee would wish to see taken into account is the possibility of a link between age and susceptibility.

---

---

---

---

---

---

---
Generally speaking, the development of regulatory standards is a three-stage process. First, toxicology-based recommended exposure limits are formulated by experts. Second, interested parties in the wider community are given the opportunity to comment on the practicality and desirability of using the toxicology-based recommended exposure limits as the basis for the proposed standard. Finally, the policy-makers (in the Netherlands: the relevant minister(s), the government or the government and parliament collectively) produce the standards.

For environmental protection purposes, the government works on the basis that the maximum tolerable concentration of a substance which has an effect only above a certain threshold should be equal to the health-based recommended exposure limit, while the maximum tolerable concentration of a substance for which no such threshold exists should be equal to the toxicology-based recommended exposure limit corresponding to a response rate of one in a million per year of exposure* 17. A similar approach is taken with food. In the field of occupational health and safety, health-based recommended exposure limits for ‘threshold-substances’ and certain toxicology-based recommended exposure limits for other substances** are submitted to the Social and Economic Council (SER), which is asked to consider whether they can be used for the development of MACs*** for airborne substances in the workplace. The national government then sets MACs on the basis of the SER’s response.

* This rule applies to chronic exposure to genotoxic carcinogenic substances. The government would, incidentally, like to see exposure limited to one hundredth of this level.

** For genotoxic carcinogens the Health Council formulates toxicology-based recommend exposure limits that correspond to an additional chance of cancer of 4 per 1000, respectively 4 per 100 000, due to continuous occupational exposure to the substance.

*** MAC stands for Maximum Accepted Concentration.
3

Information on the toxicity of a substance

3.1 Integrated toxicity profiles

The first step in the formulation of a toxicology-based recommended exposure limit is the collation of data on the toxicity of the substance in question (see Figure 3). Such data is obtained mainly from epidemiological surveys, research using volunteers, individual case reports (casuistics), animal experiments and in vitro toxicological research (i.e. experiments using cells, tissues and organs). These data sources are illustrated in Figure 4. It is not often that a toxicology-based recommended exposure limit can be based entirely on data from research involving human subjects, since there is not normally enough data of this kind available. In most cases, certainly those concerning substances not yet on the market, limits have to be based on data from animal experiments, in vitro tests, structure-activity relationships and similar sources.

Toxicity research generally proceeds along two tracks. The first line of research involves studying the adverse effects of the substance in question; the second is concerned with the associated mechanisms of action. Data from both is required in order to be able to draw reliable conclusions regarding the toxicity of the substance to humans. An structured dataset on the toxicity of a substance, which is sufficiently comprehensive for use in the formulation of toxicology-based recommended exposure limits is referred to in this report as an ‘integrated toxicity profile’. Such a profile should contain information regarding:

- the physical and chemical properties of the substance;
Construction of an integrated toxicity profile involves bringing together various types of data. To this end, use is made where possible of research findings regarding other substances (e.g. via structure-activity relationships), as well as models of the transport and metabolism of the substance in the body and of its effect on the target organ (biokinetic and biodynamic models). See Figure 4.

The various types of research which provide data on the effects of exposure to a substance are considered in turn in the following paragraphs.

### 3.2 Human data

The Committee believes that data on the health implications of exposure to a substance obtained from research using human subjects is extremely important in the formulation of a toxicology-based recommended exposure limit for that substance. The use of such data can substantially reduce the uncertainty inherent in the calculations. However, for many substances there is a paucity or complete lack of data obtained from:
- epidemiological surveys
- research with volunteers
reports on cases of accidental exposure.

Certain notable exceptions do nevertheless exist; a great deal of epidemiological information has been published on the consequences of exposure to air pollution and certain air pollutants, and to metals such as lead and cadmium, for instance.

**Epidemiological studies**

As indicated earlier, the characterization of human exposure to substances in the environment has improved since the Van Genderen Report was published. For example, the influence of an individual’s behaviour on his or her exposure to substances (and other agents) is now better understood and new techniques have made the measurement of individual exposure levels much more accurate. Molecular-biological test methods also enable epidemiologists to gather body burden data. The development of geographical information systems (GISs) has meanwhile increased the scope for modelling the exposure of large population groups.

Present-day scientists can, moreover, estimate historical exposure more accurately than their predecessors. Job exposure matrices are now well established in occupational epidemiology, for instance, and environmental epidemiologists are starting to use similar techniques. The exposure estimates used in retrospective research such as case-control and cross-sectional studies utilizing historical exposure data are consequently more accurate than in the past. Time series analyses of temporally fluctuating variables such as daily mortality rates and the use of so-called auto-regression models in longitudinal research have also yielded new data for quantitative risk estimation.

Finally, there have been developments in interventional research (into allergen reduction, for example) in which exposure to the agent under study is manipulated. Studies of this kind is, however, something of an exception, since most work on the long-term health implications of exposure is non-experimental. One drawback of such research is that it is always possible that the chance of ill health within the exposed group was different from the chance of ill health in the general population even before exposure. It is difficult to correct the research results to allow for this eventuality.

Because epidemiological research is observational, when an association is discerned the critical question is always whether this indicates the existence of a causal relationship between exposure to the substance (or other agent) and the effect concerned. To assist in addressing this question, guidelines are available, based directly or indirectly on a paper published by Hill in 1967. The Committee would draw attention to a recent WHO publication 19, which summarizes the checks which must be made before an observed association may be interpreted as a causal relationship.
Epidemiological data is not usually available on new substances (medicinal drugs excepted). Nevertheless, epidemiological data on the effects of exposure to similar substances can shed light on the toxicity of a new substance.

Research with volunteers

The Van Genderen Report refers to research with volunteers in relation to the establishment of a link between the dose of a substance and the associated physiological effects. The Committee believes that in the ten years since the Van Genderen Report appeared, the importance of using volunteers has increased, especially for investigating the metabolism and bodily distribution of a substance. However, the involvement of volunteers must satisfy strict ethical criteria.

3.3 Animal experiments

Most data on the toxic effects of substances (still) comes from in vivo experiments on laboratory animals. Mammals, and in particular rodents such as rats and mice, are most commonly used. The aims of such experiments are as follows:
- To identify the toxic effects of the substance under investigation.
- To obtain information regarding the mechanisms involved.
- To determine exposure-response relationships for the observed effects.

The organization, extent and quality of toxicity research using laboratory animals are covered by internationally accepted guidelines (produced by organizations such as the OECD, the EU and the US federal government agencies the EPA and FDA)*. The drawback with any animal experiment is the uncertainty inherent in extrapolating conclusions regarding human exposure. Data from animal experiments nevertheless often underpins exposure-related risk estimates for humans.

3.4 In vitro experiments

Great advances have been made in the field of in vitro toxicity research over the last ten years. Genotoxicity tests using bacterial and mammal cell systems in the presence or absence of subcellular fractions of mammal organs are nowadays normally among the tests required by law to establish the toxicity of a substance. In vitro model systems have also been shown to be useful tools for the determination of eye and skin toxicity. Other valuable applications of in vitro testing are the study of substance kinetics and

* OECD: Organization for Economic Cooperation and Development; EU: European Union; EPA: Environmental Protection Agency; FDA: Food and Drug Administration.
metabolism and research into the mechanisms by which toxic effects are induced in humans. Possible differences between laboratory animals and humans in terms of substance metabolism and the functional mechanisms associated with substance effects can be investigated if human tissues and cells can additionally be used for comparative in vitro experimentation.

However, in vitro model systems cannot fully simulate all that happens to a substance in vivo, partly because of the absence of the transport and metabolic processes at work in the living organism (in vivo biokinetics). As a result, mistaken conclusions can on occasions be drawn from in vitro test data if, for instance, the concentrations used in the tests are not relevant with regard to the exposure of laboratory animals or humans. A further complication is that in vivo substances can accumulate in certain organs, leading to (toxic) effects which might easily be underestimated on the basis of in vitro experimentation. Computer models which use in vitro data to predict the in vivo kinetics of a substance may be useful in this context*.

3.5 Biokinetics and biodynamics

Exposure to a substance can induce effects in a laboratory animal which differ markedly from those induced in humans. This is one of the sources of the uncertainty inherent in the extrapolation of conclusions regarding human exposure from data obtained using laboratory animals. Such differences are partly attributable to dissimilarities in the proportion of an administered dose which reaches the target organ (biokinetics) and dissimilarities in the way the substance affects the target organ (biodynamics). A better understanding of these phenomena can therefore decrease the uncertainty of the extrapolation process and increase the reliability of any derived toxicology-based recommended exposure limits, as well as reducing the use of laboratory animals. The importance of biokinetic and biodynamic information has received increasingly wide recognition in recent years, as reflected, for example, by growing calls for protocol toxicity research involving laboratory animals to be preceded by ‘ADME’ studies (i.e. absorption, distribution, metabolism and excretion studies) of the substance in question in the bodies of laboratory animals.

The Committee considers models describing the biokinetics and biodynamics of a substance to be of great value in the interpretation of integrated toxicity profile data. Such models have already proved extremely useful in the study of certain substances, including dichloromethane.

* These comments are made partly in the light of conclusions drawn at a recent working conference at which the uses and limitations of in vitro and in vivo research were compared.
3.6 Structure-activity relationships (SARs)

Structure-activity relationships (SARs) predict certain properties of a substance, such as its melting point, vapour pressure or phase distribution, on the basis of its structure. In principle, there seems no reason why such relationships should not be developed to predict the parameters which influence the toxicity of a substance. The use of SARs in the study of a substance’s toxic effects on an ecosystem is now accepted practice. Their use in the analysis of a substance’s toxic effects on humans is still in its infancy, however.

SARs may prove valuable in the assessment of test data reliability and in determining what additional information is necessary to enable a toxicology-based recommended exposure limit to be formulated with confidence. The use of SARs could save time and money, and, moreover, reduce the need to experiment on laboratory animals. On the other hand, it must be borne in mind that even proven SARs can suggest completely mistaken conclusions.

In the Committee’s view, the use of SARs in combination with the results of in vivo and in vitro experiments can contribute to the development of more complete and reliable toxicity profiles of a substance than would otherwise have been possible. Research is being conducted in the Netherlands and elsewhere into the merits of using various SARs in the evaluation of substance-related risks to people and the environment.

3.7 Chemical mixtures

Combination toxicology – the toxicology of chemical mixtures – has come into being because in practice people are normally exposed to numerous substances at once. Risk evaluation and substance authorization, by contrast, are almost always concerned with single substances. The same is true of nearly all toxicological research. However, this situation appears to be changing rapidly; articles on chemical mixtures are appearing with increasing frequency in the scientific press and a number of reference works on the toxicology of such mixtures have recently been published. In November 1994, the US Environmental Protection Agency organized a symposium on the toxicology and risk assessment of chemical mixtures and in October 1995, the Netherlands hosted the European Conference on Combination Toxicology.*

* This conference was organized with financial support from the Netherlands Ministry of Housing, Spatial Planning and the Environment, the European Union, the US Environmental Protection Agency, the German Research Foundation and the international business community.
The Committee does not consider that the combination toxicology research findings published to date have on the whole provided much insight into the possible health implications of exposure to chemical mixtures. The research has tended to involve doses or concentrations which are far too high for the results to shed any real light on any combination effects which might be induced in practice. That research which has focused on realistic exposure levels has produced very different results*.

3.8 Conclusions and recommendations

The Committee recommends that in the formulation of toxicology-based recommended exposure limits, the greatest significance should be attached to data from epidemiological studies and research involving volunteers. Conclusions based on epidemiological data must meet the accepted criteria regarding the assumption of causality in exposure-effect relationships. The Committee views the further development of improved exposure estimation methods and the use of biomarkers in the measurement of exposure and the early detection of effects as desirable.

The existence of considerable international unanimity regarding the conduct of animal experiments has greatly increased the efficiency of such research.

When the Van Genderen Report was produced, in vitro research was used mainly in the identification of genotoxicity. Today, however, such research provides information regarding a wider range of toxic effects and the mechanisms associated with them. Nevertheless, taken on their own, in vitro research findings have little significance for the formulation of toxicology-based recommended exposure limits.

The Committee regards research into the biokinetics and biodynamics of a substance as essential to the construction of an integrated toxicity profile of that substance. Advances in this area could make it possible to develop the present international toxicity research guidelines into decision trees. Biokinetic and biodynamic research can, moreover, be very valuable in the extrapolation from animal data of conclusions regarding human exposure and in predicting the outcome of exposure via one route from information regarding another. The Committee would wish to see further research into the reliability of the present biokinetic and biodynamic models before they were used in the formulation of the toxicology-based recommended exposure limits upon which standards are based. The Committee also advocates the further development of research involving volunteer subjects into substance biokinetics and metabolism, subject to the proviso that the relevant ethical criteria are met.

Structure-activity relationships (SARs) are already being used in the estimation of the substance-related ecotoxicological risks. However, the Committee is not aware of

* Some of the Dutch publications of relevance in this context are: 27 28 29 30 31 32.
any SAR which is sufficiently reliable for use in the formulation of toxicology-based recommended exposure limits (for humans). Nevertheless, by providing information regarding the relative toxicity of a substance within a group of similar compounds, for example, SARs could enhance the efficiency of toxicity research. The Committee therefore recommends that research be conducted into the scope for the use of SARs in the assessment of exposure-related human health risks.

Animal experimentation and *in vitro* research using human and animal material should, in the Committee’s view, be coordinated with one another. SARs could be used in the planning of such research and could assist in the interpretation of the results obtained. Greater understanding of the biokinetics and biodynamics of a substance in both laboratory animals and humans could increase the reliability of conclusions extrapolated from *in vivo* animal research data and *in vitro* research data. The results of research in which volunteer subjects are involved could be used in a similar way.

Another reason for the mutual coordination of toxicity research with animals and *in vitro* toxicity tests is that, by increasing efficiency, the use of laboratory animals could be kept to the minimum. At present it is not possible to construct an integrated toxicity profile of a substance without data from animal experiments. However, the Committee believes that a further reduction in animal use is possible if substance biokinetics and biodynamics, and possibly SAR data, are built into the decision trees which guide research into substance toxicity profiles.

The Committee proposes that the Health Council devote more attention to the methodology of developing integrated toxicity profiles and in particular to the interrelationships between the various types of toxicity research illustrated in Figure 4.

The Committee further proposes that a separate report be prepared on combination toxicology in relation to the formulation of toxicology-based recommended exposure limits, indicating whether and, if so, to what extent the toxicology of (complex) chemical mixtures should be taken into account. Among the questions such a report would need to address are the following:
- What developments are taking place in the field of combination toxicology and combined risk evaluation?
- How important are similarities and dissimilarities between substances in terms of target organs and mechanisms of action?
- To what extent are combination effects dose and time-related?
- How can pertinent information be extrapolated from toxicity data on complex chemical mixtures (e.g. welding smoke, tobacco smoke, sawdust, new foodstuffs) obtained from animal experiments and studies involving high substance doses?
- Should account be taken of the effects of substances, not only in combination with one another, but also in combination with co-factors such as noise, odour, heat, vibration and psychosocial factors? If so, how?
Deduction of a relationship between exposure (dose or concentration) and human response for a given effect, from the data comprising an integrated toxicity profile (an exposure-response curve is fitted to points plotted on the basis of research data; uncertainty factors are then applied to determine the exposure-response relationship for humans).

The formulation of toxicology-based recommended exposure limits at specified response levels on the basis of the exposure-response curve illustrated in figure 5 (the health-based recommended exposure limit corresponds to the highest level of exposure at which effect and response are zero, provided the effect in question is the critical adverse effect; see 2.3)
Toxicology-based recommended exposure limits and predicting the consequences of exposure

4.1 Exposure-response relationships

The possible adverse effects on human health of exposure to a given substance have to be deduced from the data comprising the integrated toxicity profile of that substance. The data is then analysed with a view to identifying any links which may exist between exposure and response for selected effects (see Figure 5). Ideally, a link between exposure and human response will be apparent after appropriate uncertainty factors have been applied (see 2.4 and Figure 3). The selection of the uncertainty factors should exclude any reasonable possibility of the response at a certain level of exposure being underestimated. Figure 5 represents a collation of consistent figures relating to different effect types and exposure regimes.

In most cases, the available data on the relationship between exposure and response for a given effect is limited in its extent and derived from various sources. Nevertheless, a coherent picture can in principle be obtained by applying a mathematical function to the available data point. One example of this is the postulated linear relationship between exposure and response seen with genotoxic carcinogenic substances. Over the last few years, various proposals have been made regarding the functions used in the formulation of recommended exposure limits.

Ideally, uncertainty factors can then be applied and an exposure-response curve for humans drawn. The uncertainty factors are introduced to compensate for experimental uncertainties and deficiencies, differences between humans and laboratory animals and sensitivity differences between members of the population or population group under consideration (see Figure 5). The resulting exposure-response curve indicates sensitivity variations within the exposed population group for the effect in question: the steeper the curve, the smaller the variation.

An exposure-response curve can be used to formulate a toxicology-based recommended exposure limit, as illustrated in Figure 6. The health-based recommended exposure limit corresponds to the highest level of exposure at which the curve indicates effect and response to be zero, provided that the effect in question is the 'critical
adverse effect’, *i.e.* the first adverse effect on health to manifest itself as the dose of a substance is increased from zero.

The process illustrated in Figures 5 and 6 is idealized. In many cases, there is insufficient data to draw exposure-response curves for various effects with any confidence. It should also be appreciated that the section of the curve which is of most interest (certainly for health protection purposes) - *i.e.* the section around the point where the response is zero - is precisely the section for which accurate data tends to be lacking, since in both animal experimentation and epidemiological research, response levels of less than about five or ten per cent are indistinguishable from zero.

### 4.2 Health-based recommended exposure limits

In scientific circles, there has been considerable debate during the last decade regarding methods for formulating *health-based recommended exposure limits* ¹⁰ ³⁵ ³⁶. One of the main points at issue has been the type of substance effect data likely to provide the most reliable basis for such limits.

The most widely established way of formulating a health-based recommended exposure limit is to divide the no-observed-adverse-effect level (NOAEL)* by an uncertainty factor (UF). This method - which is the foundation of the approach advocated by the Van Genderen Committee (see also Annex C) - has proved its worth in practice. It does, however, have its drawbacks, not least that little attention is paid to the shape of the exposure-response curve.

One of the alternative approaches which has received considerable attention ³⁷ is the ‘benchmark dose method’, or BMD method, proposed by Crump in 1984 ³⁵. The BMD method is based upon an assumed link between exposure and response. The benchmark dose is the lowest statistically reliable exposure level corresponding with a specified response level (*e.g.* 1 per cent or 10 per cent; see Figure 8 in Annex C). The health-based recommended exposure limit is calculated by dividing the BMD by a factor to compensate for differences between laboratory animals and humans and experimental deficiencies. It is also necessary to take account of the fact that acceptable response levels are lower than the benchmark level; this is done by also assuming a functional relationship between exposure and response in the exposure region below the BMD, or by applying an additional correction factor.

---

* The no-observed-adverse-effect level is the highest concentration or dose of a substance which is observed to have no adverse effect under the given exposure conditions. When specifying a NOAEL, one must therefore state the exposure quantity to which the NOAEL relates and the associated exposure conditions.

---

¹⁰2 Toxicology-based recommended exposure limits
Use of the BMD method or one of the other alternative approaches to health-based recommended exposure limit formulation depends on the nature and quality of the research data available for analysis. To this end, one needs to decide:

- the extent to which the research data allows quantitative exposure-response analysis; and
- whether the benchmark dose can be deduced directly from the research data or whether extrapolation beyond the field of observation is necessary.

Before the BMD method or one of the other alternative approaches can be widely adopted, further research will be required \(^3^8\) \(^3^9\). The Committee considers that the BMD method warrants closer evaluation because, unlike other approaches, it can be used not only with quantal data (the presence or absence of the effect), but also continuous effect data (the effect is present to a certain degree). If the NOAEL/UF method were superseded by the BMD method, the Committee believes that the uncertainty margins associated with health-based recommended exposure limits could be reduced, since consistent use would be made of exposure-response data in the vicinity of the benchmark response level. Thus, the BMD method is in keeping with the approach illustrated in Figures 5 and 6. This implies that in toxicity testing, doses or concentrations would have to be selected with a view to obtaining good exposure-response curves rather identifying a dose without any adverse effect \(^4^0\).

### 4.3 The prediction of possible adverse effects on health

A curve such as that shown in Figure 5 can also be used to predict the consequences of a certain level of exposure. However, the curve has been deliberately drawn so as to exclude any reasonable possibility of the consequences of exposure being underestimated. This has implications for the interpretation of the predictions (see Figure 7). The response level which would appear from the curve to correspond to a given level of exposure may be interpreted as the maximum response which might reasonably be expected in the exposed population or population group. The possibility of a greater response cannot be excluded altogether, but it is more probable that the response to exposure will be smaller, or even non-existent.
4.4 Conclusion and recommendation

The Committee believes that toxicity studies of a substance should not be concerned purely with identifying the NOAEL associated with that substance. Much more emphasis should be placed on obtaining information regarding the effects of exposure and regarding the levels of response for the observed effects within certain population groups. The formulation of toxicology-based recommended exposure limits outlined in this report warrants further development; in particular, attention should be given to the calculation of uncertainty factors and to selection of the model curves upon which exposure-response curves are based.

In practice, few methods other than the NOAEL/UF method are used to formulate health-based recommended exposure limits, and none is in widespread use. For the reasons outlined in Section 4.2, the Committee regards more detailed evaluation of the BMD method as desirable. The Committee proposes that in the risk assessment process, health-based recommended exposure limits should not be formulated exclusively by the NOAEL/UF method, but that the BMD method should also be used. Moreover, the Committee recommends that health-based recommended exposure limits be formulated using the BMD method for various substances which have already been assessed for occupational health and safety and environmental protection purposes. In this way, it would be possible to identify the data required to apply the method in practice and the issues relevant to the extrapolation of health-based recommended exposure limits from BMDs.
Rijswijk, 29 August 1996,
for the Committee
(signed)
dr WF Passchier prof dr WRF Notten
scientific secretary chairman
References


30 Feron VJ, Groten JP, Zorge JAv et al. Toxicity studies in rats of simple mixtures of chemicals with the same or different target organs. Toxicol Letters 1995;82/83:506-12.


A Mission

B Membership of the Committee

C Methods for formulating health-based recommended exposure limits
Annex

A

Mission

On 26 October 1994, the President of the Health Council wrote as follows to the members of the Steering Committee on Health-based Recommended Exposure Limits:

In January 1993, I established the Steering Committee on Health-based Recommended Exposure Limits, as a working party of the Standing Committee on Toxicology. The Steering Committee’s remit was ‘to supervise the revision and extension of the report Principles for the formulation of recommended exposure limits (1985/31) and to prepare reports on closely related matters’.

Since then, the Steering Committee has made an inventory of recent developments in the field of substance risk evaluation and has set in motion the preparation of several background reports on subsidiary topics.

There is, unfortunately, a problem associated with the way the Health Council has proceeded on this front thus far, namely that interested parties, such as government departments, are not aware of what is being done or the progress that is being made. I have therefore decided that a change of tack is necessary.

I intend to make the Steering Committee a full-blown committee, as referred to in the Health Act; the formal arrangements will be made in due course. The new committee will be given the task of producing a ‘programme document on the points of departure for the formulation of recommended exposure limits’. This will be a (short) report setting out recent developments and addressing matters of relevance in this context. These matters may subsequently be dealt with in more detail in topic reports. Much of the necessary preparatory work has already been done by the Steering Committee. Background reports will continue to be drawn up as usual.
Membership of the Committee

The members of the Committee on Health-based Recommended Exposure Limits involved in the preparation of this report were as follows:

- Professor WRF Notten, chairman
toxicologist, TNO Prevention and Health, Leiden
- Dr WFJPM ten Berge
toxicologist, DSM, Heerlen
- Dr BJ Blauboer
toxicologist, Research Institute of Toxicology (RITOX), University of Utrecht
- Professor VJ Feron
biological toxicologist, TNO Nutrition and Food Research Institute, Zeist
- Professor PHM Lohman
genetic toxicologist, Sylvius Laboratory, University of Leiden
- Dr G de Mik
toxicologist, National Institute of Public Health and Environmental Protection, Bilthoven
- Dr RA Woutersen, advisor
toxicologist/pathologist, TNO Nutrition and Food Research Institute, Zeist
- Dr JA van Zorge, advisor
Ministry of Housing, Spatial Planning, and the Environment, The Hague
- Dr PW van Vliet, scientific secretary
Health Council, The Hague
- Dr WF Passchier, scientific secretary
Health Council, The Hague
Methods for formulating health-based recommended exposure limits

This Annex contains descriptions of the two methods for formulating health-based recommended exposure limits, namely the NOAEL/UF method and the ‘benchmark dose’ method (BMD method) developed by Crump. For further details, see references 10 35 36.

A NOAEL/UF method

In practice, NOAELs are calculated by comparing an exposed group of people or laboratory animals with a control group. A no-observed-adverse-effect level may be deemed to exist if the difference between the exposed group and the control group in terms of the frequency or seriousness of an effect is statistically or biologically insignificant. The NOAEL method involves establishing the highest such level for the critical adverse effect, i.e. the first adverse effect to manifest itself as the dose of the substance in question is increased from zero.

The health-based recommended exposure limit is calculated by dividing the NOAEL by an uncertainty factor (UF), composed of constituent factors. The Van Genderen Committee indicated that constituent factors were necessary to take account of the following 1:

- experimental deficiencies
- uncertainties regarding the differences between the laboratory animals used and humans (interspecies-uncertainty factor)
- sensitivity differences within the exposed population group (intraspecies-uncertainty factor).
Additional constituent factors may have to be included if the data is not considered sufficiently relevant to the situation that the recommended exposure limit is to cover (if, for instance, a chronic exposure limit is being formulated and only sub-chronic data is available).

The Van Genderen Committee indicated that the constituent factors should be combined, e.g., by simple multiplication or by squaring the logarithms, adding the results together and obtaining the square root of the sum (in the latter case the logarithm of the uncertainty factor is obtained). The most common method of calculating the UF 35, in the Netherlands and elsewhere, is to multiply the constituent factors*.

**B  BMD method**

The BMD method is based on an exposure-response curve obtained by fitting a model curve to the experimental data. The fitting process assumes the existence of a particular functional relationship. One also has to determine the lower limit of the curve’s statistical reliability, generally based on the 95 per cent criterion. The benchmark dose or BMD is the lower statistical reliability limit of an exposure level corresponding to a specified response level, say 1 or 10 per cent. Calculation of a BMD is illustrated in Figure 8.

![Figure 8](image-url)

*The second method referred to by the Van Genderen Committee should be used if extrapolation of human data from animal data is performed on the basis of caloric intake as opposed to body weight.*

---

Methods for formulating health-based recommended exposure limits

117
The health-based recommended exposure limit is calculated by dividing the BMD by uncertainty factors. In addition to factors to compensate for interspecies uncertainty and experimental deficiencies, a factor has to be applied reflecting the difference between the BMD response level and the response level that is considered acceptable. To this end, it is desirable to assume a functional; form for the exposure-response curve in the exposure range below the BMD. The latter factor also compensates for sensitivity differences within the exposed population group.