Health Council of the Netherlands

Guideline for the calculation of occupational cancer risk values

2012/16E

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Foreword

You have before you the new guideline for the calculation of occupational cancer risk values. The Dutch Expert Committee on Occupational Safety (DECOS) calculates these cancer risk values, upon request of the Minister for Social Affairs and Employment, for carcinogenic substances for which no safe exposure level exist.

The methodology for deriving cancer risk values was defined by the Health Council of the Netherlands in a guideline published in 1995. Subsequent scientific developments prompted the Committee to update this guideline.

The new guideline describes a method based on epidemiological data, and a method based on toxicological data. In drafting this guideline, the Committee has taken note of the methodologies used by other countries and organisations. An overview of internationally used methods can be found in Annex E.

Henceforth, the Committee will adhere to the updated guideline when preparing advisory reports on carcinogenic substances.

The Hague, 26 October 2012
(signed)
Professor W.A. van Gool
President

Guideline for the calculation of occupational cancer risk values

Guideline for the calculation of risk values for genotoxic carcinogens with a stochastic mechanism of action

to:

the State Secretary of Social Affairs and Employment

No. 2012/16E, The Hague, October 26, 2012

The Health Council of the Netherlands, established in 1902, is an independent scientific advisory body. Its remit is "to advise the government and Parliament on the current level of knowledge with respect to public health issues and health (services) research..." (Section 22, Health Act).

The Health Council receives most requests for advice from the Ministers of Health, Welfare & Sport, Infrastructure & the Environment, Social Affairs & Employment, Economic Affairs, and Education, Culture & Science. The Council can publish advisory reports on its own initiative. It usually does this in order to ask attention for developments or trends that are thought to be relevant to government policy.

Most Health Council reports are prepared by multidisciplinary committees of Dutch or, sometimes, foreign experts, appointed in a personal capacity. The reports are available to the public.

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INAHTA

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Chapter 1

Introduction

Protecting employees from adverse effects of exposure to compounds in the workplace is one of the basic principles of the Dutch working conditions legislation. In general terms, this means that safe occupational exposure levels are determined for a compound, and it is ensured these levels are not exceeded in practice. For a certain group of cancer causing (carcinogenic) compounds, that with a stochastic genotoxic mechanism of action, it is not possible to derive a level of exposure at which no adverse health effects may occur. For this group of compounds it is assumed that each level of exposure, regardless how low, entails a certain risk of cancer.

There is no consistent approach at the international level for evaluating risks of exposure to this group of carcinogens. In the Netherlands, the Health Council calculates for these compounds cancer risk values: exposure levels corresponding to an extra risk of cancer that is predefined by the government. Cancer risk values constitute the scientific basis for determining occupational exposure limits.

The methodology for the derivation of cancer risk values was defined by the Health Council of the Netherlands in 1995 in the Guideline *Calculating cancer risk*.[1] That guideline is focused on the use of animal data, as reliable epidemiological data were scarce at the time. Since then, epidemiological data are more frequently available, as are new methods for analysing data from epidemiological and animal studies. These developments prompted the Dutch Expert Committee on Occupational Safety (DECOS), hereafter called the Committee, to

formulate a new guideline for the calculation of cancer risk values. Details on the members of the Committee can be found in Annex A of this advisory report.

In Chapter 2, the Committee outlines the background for the use of cancer risk values, and briefly describes the methodology used by the Health Council of the Netherlands until now. The updated guideline is presented in Chapters 3 and 4.

Chapter 2

Background

2.1 Occupational exposure limits

Working with carcinogens can have serious health consequences. In the Netherlands, the policy to protect employees from occupational risks is laid down in the Dutch Working Conditions Act. The related Dutch Working Conditions Decree contains explicit regulations on working with carcinogens. This decree states that exposure to dangerous compounds must be prevented or limited, and that carcinogens must be substituted if technically possible. The principle is that exposure must be kept 'as low as reasonable achievable'. This is known as the ALARA principle.

A key measure for managing exposure to dangerous compounds is the application of exposure limits. Occupational exposure limits are legally determined, maximum permitted (time-weighted average) concentrations of compounds in the workplace air, that should protect employees from the adverse health effects of exposure to these compounds.

2.1.1 Health-based recommended occupational exposure limits

An health-based recommended occupational exposure limit is a 'safe' (occupational) exposure level: at exposure levels equal to or below the recommended level, no harmful health effects are to be expected.[2] These health-based recommended occupational exposure levels are derived by the

Health Council of the Netherlands, and are the basis upon which the minister of Social Affairs and Employment sets a legal limit.

Whether an health-based recommended occupational exposure limit can be derived for a carcinogenic compound, depends on the intrinsic properties of the compound in question. In the *Guideline on classification of carcinogenic compounds*, the Health Council described the framework for the classification of carcinogens based on mechanism of action.[3] Four different categories have been distinguished:

- Non-genotoxic carcinogens. These compounds can promote various phases of the cancer process, without directly or indirectly damaging DNA.
- Genotoxic carcinogens with a non-stochastic mechanism of action. These compounds do not directly interact with DNA, but can ultimately result in indirect DNA damage.
- Genotoxic carcinogens with a stochastic mechanism of action. These compounds can directly interact with DNA, thus resulting in DNA damage.
- Genotoxic carcinogens with an unknown mechanism of action.

A carcinogen with a non-genotoxic, or non-stochastic genotoxic mechanism of action is assumed to be able to cause cancer only if exposure exceeds a specific threshold. For these two categories of carcinogens, in principle, an health-based recommended occupational exposure limit can be derived.

For genotoxic carcinogens with a stochastic mechanism of action, current scientific insights do not allow the determination of safe exposure levels below which cancer does not occur; any level of exposure is assumed to entail a certain risk of developing cancer.

For reasons of safety, the same assumption is made for genotoxic carcinogenic compounds with an unclear mechanism of action. The Committee will consider this last group implicitly as ‘stochastic genotoxic carcinogens’ in this guideline.

2.1.2 Cancer risk values

As no health-based recommended occupational exposure limit can be established for carcinogens with a stochastic genotoxic mechanism of action, the Health Council calculates, on request of the Minister for Social Affairs and Employment, so-called cancer risk values (see Figure 1). A cancer risk value is an exposure level (a concentration in the air) corresponding with a (by the government) predefined extra risk of developing cancer.

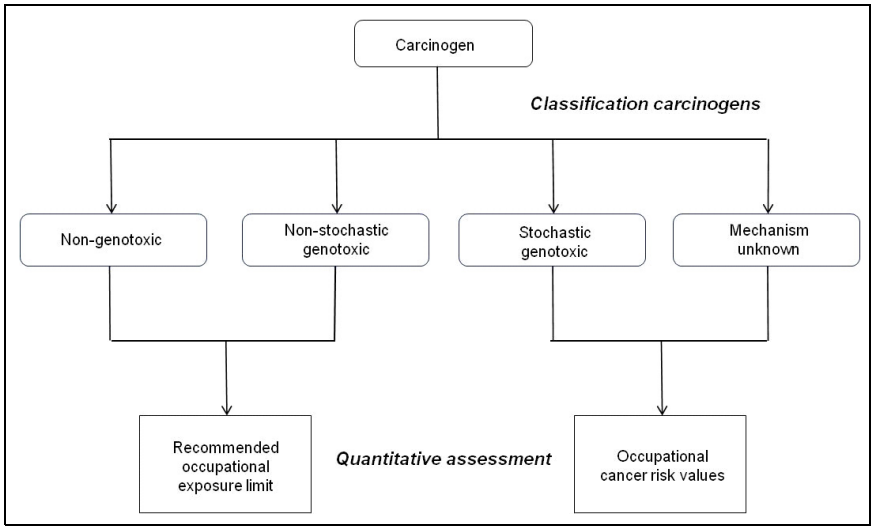

Figure 1 Overview of categories of carcinogenic compounds (based on mechanism of action) and consequences for the choice to derive an occupational health advisory value, or cancer risk values.

There is no univocal approach at the international level, for the risk estimation for carcinogens with a stochastic genotoxic mechanism of action. The approaches described by other international organisations differ in terms of methodology and implementation. The Committee has summarised these approaches in Annex E.

2.2 Determining risk levels

The Minister of Social Affairs and Employment has determined two general reference risk levels for the calculation of cancer risk values: a target risk level and a prohibitive risk level.

These risk levels were proposed in 1992 by the Subcommittee MAC-values of the Dutch Working Environment Council (Arboraad).* The Arboraad based its recommendation on, among others, the risk levels used in other policy frameworks at the time.[4] For example, the maximum tolerable risk for death due to exposure to radiation is 1×10^{-6}.[5] In national environmental policy, exposure limits for carcinogens are applied that correspond to two predefined risk levels:

* In 1993, the Arboraad was succeeded by the Working Conditions Committee of the Social and Economic Council of the Netherlands (SER). The OEL Subcommittee has taken over the tasks of the Subcommittee MAC-values.

- The concentration corresponding with the prohibitive risk level results in an expected (extra) risk of dying of cancer of 1 per million (1 x 10^{-6}) per 1 year of exposure.
- The concentration corresponding with the negligible risk results in an expected (extra) risk of dying of cancer of 1 per 100 million (1 x 10^{-8}) per 1 year of exposure.

Occupational risk levels are expressed as lifetime risks of extra cases of cancer (see tekst box) due to occupational exposure, based on a working period of 40 years (8 hours per day, 40 hours per week).[4] For carcinogens used in the workplace, the Arboraad proposed to strive for an extra individual risk level of 1 x 10^{-6} (one per million) for each year of exposure. This relates to a target risk of 4 x 10^{-5} for 40 years of occupational exposure.[4]

Below the level of exposure corresponding to the target risk level, no additional protective measures need to be taken. In addition to the target risk level, a prohibitive risk level has been introduced which is a 100-fold higher (i.e. a risk of 4 x 10^{-3}). The prohibitive risk level implies that this level may not be exceeded.

The risk levels used in legislation for limiting exposure to genotoxic carcinogenic compounds with a stochastic mode of action are specified in Table 1.

Table 1 Risk levels used for limiting exposure to carcinogenic compounds in the workplace and in the environment.

		Risk period	Exposure period [a]	Risk level
Occupational Health and Safety	Prohibitive risk	Life	Working life	4 x 10^{-3}
			One year	1 x 10^{-4}
	Target risk	Life	Working life	4 x 10^{-5}
			One year	1 x 10^{-6}
Environment	Maximum tolerable risk	Life	Lifetime	1 x 10^{-4}
			One year	1 x 10^{-6}
	Negligible risk	Life	Lifetime	1 x 10^{-6}
			One year	1 x 10^{-8}

[a] For the calculation of the risk related to the exposure during a full (working) lifetime, a period of 40 years for workplace exposure and a period of 100 years for environmental exposure is taken into account.

Risk: extra risk of cancer

An extra risk of cancer due to exposure to a compound is expressed as an estimated number of additional cases of cancer, regardless of overall mortality in the population. This extra risk of cancer may be expressed as an additional number of deaths (mortality) or diseased (incidence). The Committee illustrates an extra riks of cancer below, for a compound that causes lung cancer.

Extra risk based on mortality

In the Netherlands, of every 100,000 men who will die, about 11,200 will die of lung cancer. The target risk level of 4×10^{-5} expressed as mortality, for a compound that causes lung cancer, corresponds to 4 additional lung cancer deaths due to subsequent exposure (11,200 plus 4, a total of 11,204) per 100,000 general deaths.

Extra risk based on incidence

Of every 100 men who develop lung cancer, about 90 will die of the disease. For every 100,000 deaths, an estimated 12,444 men will have developed lung cancer (100/90 x 11,200). The target risk level of 4×10^{-5} expressed as incidence, for a compound that causes lung cancer, is equivalent to 4 additional cases of lung cancer (12,444 plus 4, a total of 12,448) per 100,000 general deaths.

After the Health Council has published an advisory report on cancer risk values, the OEL Subcommittee of the SER considers the technical feasibility of implementing a legal limit value at the target risk level, and subsequently advises the Minister of Social Affairs and Employment. In this procedure, the OEL Subcommittee involves branch organisations, in addition to the major employer and employee organisations. Finally, the Minister of Social Affairs and Employment sets a new legally binding occupational exposure limit. In practice, the established occupational exposure limits will vary between exposure levels corresponding to the target risk level and the prohibitive risk level.

2.3 Calculation of risk values to date

In 1995, the Health Council published a guideline for the calculation of cancer risk values.[1] In this guideline, the Committee indicated that it preferred to use data obtained from epidemiological studies. These data can be used directly, or with minimal adjustments, to estimate risks for the working population. As reliable epidemiological data were often lacking at that time, the Committee was forced to use carcinogenicity data obtained from animal studies in its previous guideline.

The Committee identified several steps for determining risk values using animal data:

- Selection of data suitable for the calculation of risk values
- Estimation of the carcinogenic activity* of a compound
- Estimation of the daily dose in relation to carcinogenic activity
- Estimation of health risks for humans in an occupational setting
- Calculation of exposure levels relating to the reference risk levels.

The Committee described standard methods for each step. The carcinogenic activity, for example, expressed as incidence per unit of daily dose or per unit of air concentration, was calculated by the Committee based on the lowest dose or air concentration at which a significant increase in the number of animals with tumours was found compared to the control group(s). The Committee subsequently converted the carcinogenic activity in animal models to a lifetime cancer risk for humans due to occupational exposure using default values. Finally, the Committee derived exposure levels corresponding to an extra cancer risk of 4×10^{-3} and 4×10^{-5} by linear extrapolation.

* The carcinogenic activity of a compound is defined as 'the increase in the incidence of tumours in the experimental or study group attributable to exposure during a defined experimental or observation period, compared to the tumour-incidence in a control group'.

Chapter 3

Risk estimation based on human data

The increasing availability of epidemiological and toxicological data, as well as the development of new models for risk estimation, prompted the Committee to update the guideline *Calculating cancer risk.*[1]

The guideline is a general guideline for deriving cancer risk values. In practice, the Committee applies a compound-specific approach, in which the most suitable methodology is determined based on the integration of all available data. The Committee describes this process in its advisory reports on specific compounds.

The Committee prefers the use of epidemiological data for the calculation of cancer risk values, as this type of data does not involve the uncertainties associated with biological differences between animals and humans. Furthermore, the exposure conditions in epidemiological studies, in contrast to those in animal studies, are generally representative for the exposures in current occupational setting.

In this chapter, the Committee describes its approach based on human data. The use of data from animal studies is discussed in Chapter 4.

Cancer risk values for different cancer types

Some compounds can cause multiple types of cancer. As workers should be protected from all types of cancer a compound may cause, a cancer risk value should preferably apply to all types of cancer the compound may cause. In

practice, however, this is rarely the case, as the available data usually relate only to a few specific types of cancer. Therefore, the Committee generally derives a cancer risk value for every form of cancer. The lowest cancer risk value is then used as the basis for an occupational exposure limit.

If different forms of cancer develop at similar levels of exposure, these may, in principle, be analysed jointly by using combined mortality or incidence statistics. This approach however, cannot necessarily be applied as this sets specific requirements for the underlying (exposure) data.

Stepwise approach for deriving cancer risk values

In the derivation of cancer risk values using human data, the Committee distinguishes the following main steps (see Figure 2):

- Evaluation of data and selection of key research
- Determination of relative risk
- Calculation of extra risk and cancer risk values.

3.1 Step 1: Evaluation of data and selection of key research

Various aspects play a role in the evaluation of data for the calculation of cancer risk values, such as the type of study the data are derived from, the quality of the study, and subsequently the reliability of the data.

3.1.1 Types of epidemiological research

The research that is used as the source of information and provides the starting point for calculating cancer risk values is referred to as key research. Where possible, the Committee combines multiple epidemiological studies for its risk estimate (see paragraph ‘Pooled studies and meta-analyses’). Epidemiological studies that are most suited to determine long-term cancer risks are cohort studies and case-control studies.

In a cohort study, a group of people with a common characteristic, e.g. the exposure to a potentially carcinogenic compound, is followed for a long period of time. The risk of cancer due to such exposure can be determined by comparing the occurrence of cancer in this cohort to the occurrence of cancer in a reference cohort. The strength of the association between exposure and the occurrence of the disease is expressed as the relative risk (RR).

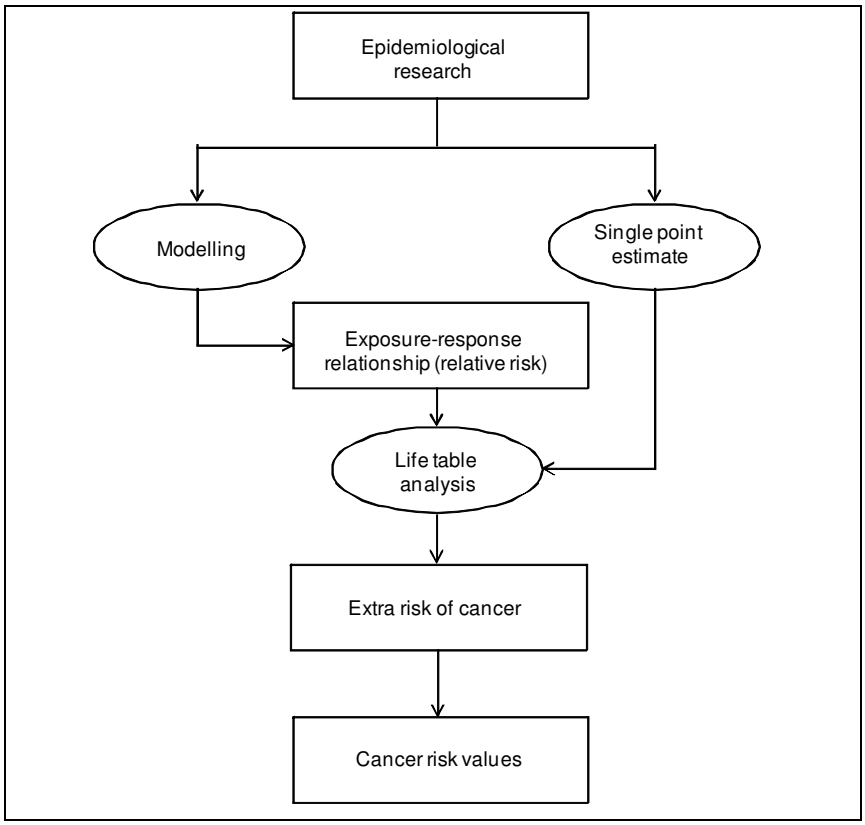

Figure 2 Stepwise approach for the derivation of risk values based on human data.

In another study design, a relative risk is obtained by a comparison with the general population, after correction for age and sex. This results in a Standardised Mortality Ratio (SMR) if mortality statistics are used, or a Standardised Incidence Ratio (SIR) if incidence statistics are used.

In a case-control study, historical exposure is estimated for a group of patients with a specific form of cancer, and compared to a control group without the disease. This type of epidemiological study is generally less accurate, as information is obtained retrospectively. Therefore, strict criteria for the selection of a control group exist. Instead of a relative risk, an odds ratio (OR) is calculated for a case-control study: the ratio of the odds of cancer occurring in an exposed group to the odds of cancer occurring in a non-exposed group. The odds ratio

provides an estimate of the relative risk. Particularly for relatively rare conditions, the calculated odds ratio and relative risk fall within a similar range.

3.1.2 *Guidelines for evaluation of epidemiological research*

The Committee only considers epidemiological research for the calculation of cancer risk values if it is of sufficient quality, and both exposure and related risk have been quantified. The framework that is used by the Committee for the evaluation of epidemiological research is described in Annex B.

It is important that both the data on exposure and the data on health effects are of sufficient quality (limited information bias), that certain methodological criteria related to the population selection are met (minimal selection bias), and that the potential of bias due to other causes of cancer is low (limited confounding bias). The Committee adheres to the CBO guidelines* when evaluating epidemiological studies. These describe general points for attention and criteria regarding the evaluation of the quality of human data. The criteria are consistent with international criteria as described for observational research in the STROBE project**.[6]

The calculation of cancer risk values requires a reliable, quantitative measure of exposure. The manner in which exposure is estimated in an epidemiological study is therefore of great importance. The CBO and STROBE criteria are not specifically focused on the reliability of exposure assessment. Additional criteria were recently formulated for the stepwise assessment of the usability of epidemiological research for quantitative risk assessment, with an emphasis on exposure aspects.[7] Critical aspects for the Committee in the evaluation are the degree to which the estimated exposure reflects the actual exposure of the cohort during the risk period (internal validity), and the degree to which the exposure measurements are representative for the population of the study (external validity). Based on data available, the Committee subsequently selects the most suitable exposure metrics, such as the level of average exposure or cumulative exposure.

In order to determine whether an epidemiological study is ultimately suitable as key research, it must be assessed whether the association between the exposure to a compound and the occurrence of cancer can be interpreted as a

* Dutch institute for healthcare improvement CBO.
** Strengthening the reporting of observational studies in epidemiology; http://www.strobe-statement.org [consulted on 07-09-2012]

causal relationship. For this, nine points of attention are traditionally used.[8] These are summarised in Annex C.

3.1.3 *Pooled studies and meta-analyses*

A single study of sufficient quality may be used for the calculation of cancer risk values. However, the Committee prefers to use a combined analysis of various studies, as this can provide more reliable outcomes. Epidemiological studies may be combined based on individual data (pooled analysis) or aggregated data (meta-analysis).

Epidemiological data that have been combined and analysed at the individual level include several populations (often in different countries). As data must be available for each individual, these can be corrected for confounding variables.

Also in a meta-analysis, data from several studies are combined. However, the underlying individual data are not available in such cases, and the analysis must therefore be performed at the level of aggregated data. This is likely to result in more heterogeneous outcomes, as even studies with a largely similar design differ at certain points. This aspect must be taken under consideration in the evaluation process.

3.1.4 *Incidence statistics versus mortality statistics*

Over time, improved diagnostic and treatment options have increased the difference between the number of new cancer cases and the number of cancer deaths. The majority of epidemiological research is based on mortality statistics, as historically, these are well-documented. However, epidemiological research is increasingly based on cancer incidence (the number of new disease cases per unit of time). Working conditions policy is primarily focused on protecting employees from the occurrence of disease, in this case cancer, regardless of the resulting mortality. Therefore, the Committee prefers to use incidence statistics over mortality statistics for cancer risk values calculation. An additional argument is that registration of incidence data is generally more reliable than registration of mortality data. As the diagnosis of cancer always includes histopathological confirmation, so there is a reduced risk of misclassification.

If no incidence statistics are available, it is possible, in principle, to convert mortality statistics to incidence statistics. The most suitable method for doing so is not predetermined, and will be selected by the Committee on a case-by-case basis. Various factors may play a role, such as life expectancy and mortality after diagnosis.

3.2 Step 2: Determination of relative risk

In epidemiological studies, the risk of cancer following exposure to a compound is generally expressed as a relative risk. Preferentially, the data should describe the relative risk over a range of exposure levels. Using a model, an exposure-response relationship can be determined, making optimal use of the available data.

3.2.1 Modelling individual and aggregate data

From a scientific perspective, the Committee prefers to use data that can be analysed at the individual level. Using parametric models it is possible to determine whether on the basis of individual data, after correction for any confounding variables, a reliable exposure-response relationship can be derived.*

In practice, individual data are rarely available to the Committee. Particularly in the past, individual exposure measurements were often first combined to one or more exposure categories and then analysed at the aggregate level. The Committee therefore has to rely on secondary data** based on published analyses, and on the underlying choices and assumptions made by the authors. If authors did not perform exposure-response analyses, for example using Poisson or linear regression, the Committee will consider doing this post-hoc. The Health Council has done so recently in its advisory report on asbestos.[9] A representative point estimate for an exposure category, such as the geometric average or the median of the exposure, is most appropriate for post-hoc modelling of exposure-response relationships.***

If multiple studies are available, the Committee will consider meta-regression or meta-analysis. A recent example of such an analysis based on published data is the meta-analysis performed for asbestos.[9]

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* Commonly used methods to examine association at the individual level are survival analysis and logistic regression.

** Aggregated data for which in addition to individual exposure data, individual characteristics such as sex and age, are combined.

*** The Committee prefers the use of the median, as it is less sensitive to outliers in the exposure data. If the estimated exposure involves a range with only a upper limit (i.e. < 100 mg/m^3) or an lower limit (i.e. > 0 ppm), the Committee derives a point estimate by dividing the upper limit or multiplying the lower limit by 2, respectively.

The final exposure-response relationship, in the form of a linear regression model or a more complex parametric function, is then used as a starting point for deriving an extra lifetime risk.*

3.2.2 Relative risk based on a single exposure group

Only if no exposure-response relationship can be derived will the Committee consider, given a lack of alternatives, using a point estimate of the relative risk based on a single exposure group to calculate cancer risk values.

3.3 Step 3: Calculation of extra risk and cancer risk values

The quantitative relationship between the exposure to a compound and the relative risk of cancer that is derived from epidemiological data must be converted into a appropriate measure of risk for deriving a cancer risk value. This means that a relative risk for developing cancer must be converted to an extra risk of cancer, regardless of the background risk. Additionally, the risk due to occupational exposure based on the observation period of the epidemiological study must be converted to a lifetime risk.

3.3.1 Use of life tables

The Committee uses life tables to calculate an extra risk of cancer. By using life tables, death due to other causes can be accounted for. In a group of workers exposed to a carcinogenic compound, other causes of death will lead to a reduction of the population at risk, and therefore to a lower number of additional cancer cases by the compound in absolute terms. If this is not corrected for, the probability of overestimating the risk is high.[11]

It is important to extend the life table to an age at which the mortality burden due to occupational exposure to a carcinogenic compound is negligible, compared to the mortality due to other causes. For this purpose, the Committee currently adheres to an age of 100 years.

Furthermore, using life tables it is possible to take into account time and age-dependent factors in the development of cancer. An elevated relative risk of a type of cancer that primarily occurs at old age, for instance, will not contribute

* More background information on the analysis of epidemiological research is described in, inter alia, the epidemiological manuals by Rothman & Greenland and, specifically with regarding to working environments, Checkoway et al.[10]

substantially to the number of additional cancer cases in young employees who are exposed, but will contribute significantly to the additional cancer cases in later life. Furthermore, the background risk of cancer may increase (such as leukaemia in children) or decrease during a specific period in life. The use of life tables also allows to take into account risks that increase (due to latency, for example for asbestos in relation to mesothelioma), as well as risks that decrease after a certain period following exposure (for example for ionising radiation).

Ultimately, analysis of a life table results in a cumulative exposure level corresponding to a specific extra risk, based on a working period of 40 years. The cancer risk values are calculated at the level of cumulative, inhalatory exposure for which the risk of extra cancer cases is 4×10^{-3} and 4×10^{-5} (expressed in an exposure unit, such as [mg/m^3]).

The Committee has included a calculated life table as Annex D for illustrative purposes.

Chapter 4

Risk estimation based on data from animal studies

If no suitable epidemiological data are available, the Committee will base its calculations of cancer risk values on animal studies. In practice, the use of a cancer risk value based on an animal study does not differ from the use of one based on human data. However, the Committee emphasizes that, in addition to the obvious difference in species, there is a fundamental difference in the background of both types of cancer risk values. In animal studies, all tumours that can be detected microscopically are analysed, while in a human population, the only tumours registered are usually those that lead to clinical symptoms (unless screening is involved).

Stepwise approach for calculating cancer risk values

Similar to the approach based on human data, does the Committee apply a stepwise approach when using animal data for the calculation of cancer risk values. An additional extrapolation step from animals to humans is required, however. The steps are (see Figure 3):

- Evaluation of data and selection of the key research
- Determination of starting point for estimating carcinogenic activity
- Estimation of carcinogenic activity in animals
- Risk estimation for humans and calculation of cancer risk values.

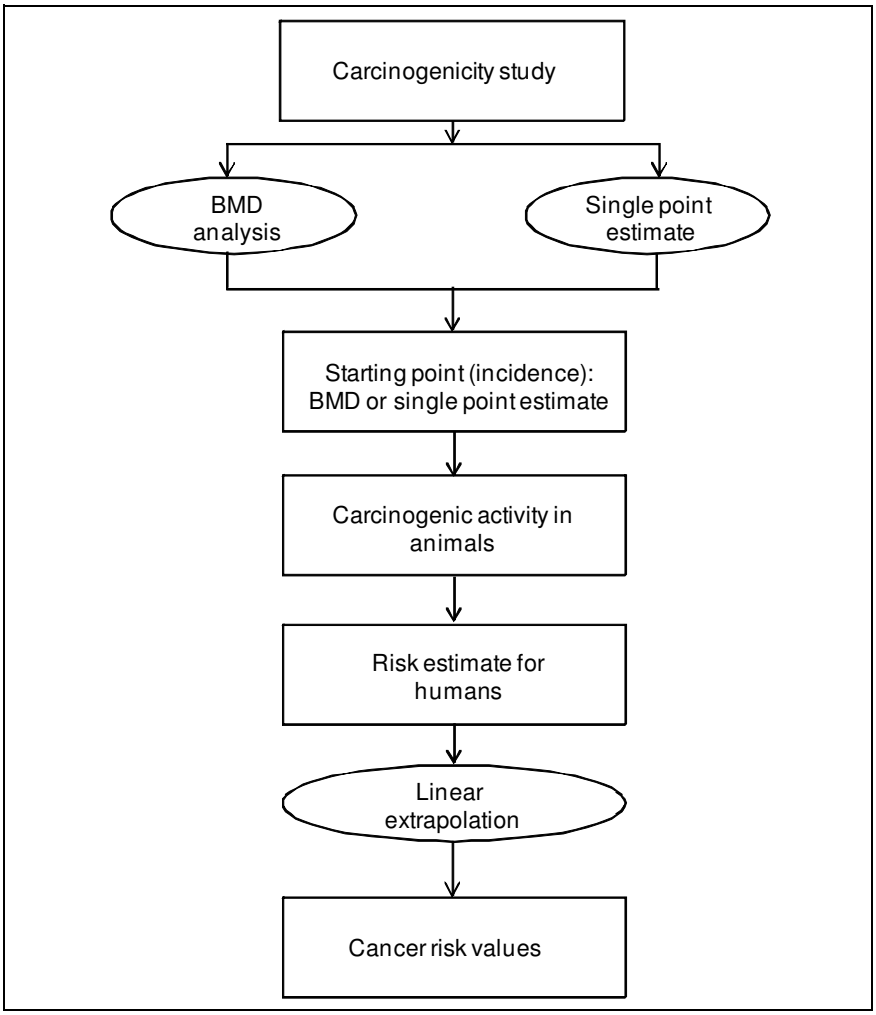

Figure 3 Stepwise approach for the calculation of risk values based on animal study data.

4.1 Step 1: Evaluation of data and selection of key research

The Committee evaluates the animal carcinogenicity studies for their suitability for the calculation of cancer risk values. In addition to the evaluation of quality, the interpretation of the carcinogenic effects observed plays a key role in this process.

4.1.1 *Evaluation of data quality*

General guidelines for evaluating the reliability of animal studies have been described by Klimisch et al. (1997) (see Annex B).[12] Additional specific requirements apply to the use of a carcinogenicity study for the calculation of cancer risk values. The Committee will discuss some in detail below.

Carcinogenicity studies* are conducted on rats (exposed for at least 24 months), mice or (occasionally) hamsters (both species exposed for at least 18 months). A study with a shorter exposure period may also be used if relevant tumours are found, that have developed due to exposure to the compound (what the Committee considers relevant is described below). If data are available for multiple animal species, the Committee will select the most sensitive, i.e. the species for which the lowest cancer risk values are calculated.

If intercurrent mortality is increased due to other causes than the carcinogenic effects of the compound, this may be cause for the Committee to reject the study. Premature loss of animals may lead to a relatively (too) short exposure period and follow-up, possibly leading to carcinogenic effects of a compound or spontaneous tumours being missed. Only if data on individual animals are available, there can (partially) be corrected for.[13]

As cancer risk values represent concentrations in the air, the Committee has a preference for studies in which animals were exposed by inhalation. If no inhalation data are available, the Committee will also consider data from other exposure routes for the derivation of risk values. In such cases, a conversion is required.

4.1.2 *Interpretation of carcinogenic effects in animals*

For the interpretation of an increased tumour incidence in an animal study and establishing the relevance of such finding for humans, no ready-to-use guidelines exist. Various aspects play a role, a few of which the Committee will comment on below.

An elevated incidence of a specific type of tumour in multiple species, and supporting data regarding the carcinogenic mechanism of action, will weigh heavily in the evaluation. Also, the Committee takes into account the background incidence of the tumours in question, in the species and strain concerned. An elevated incidence of a commonly occurring (spontaneous) tumour may,

* Carcinogenicity studies that meet international guidelines (e.g. OECD).

particularly at high doses, relate to indirect toxicity rather than carcinogenic activity of the compound. Examples include renal toxicity of chloroform resulting in renal tumours, and inhalatory particulate overload resulting in lung tumours in rats. A non-statistically significantly elevated incidence of a rare tumour, on the other hand, may indicate a specific carcinogenic effect due to exposure and may not be ignored.[14]

Generally, the Committee will base its cancer risk values on the incidence of malignant tumours in a specific organ. Benign tumours as such are not a basis for the Committee for the derivation of cancer risk values: these tumours apparently do not posses the potential to develop into malignant tumours. Combining numbers of different tumours, to increase statistical power, is only allowed in specific cases. For example, numbers of benign and malignant tumours may be combined if there are indications that the benign tumours can develop into the malignant type (e.g. if both malignant and benign tumours are found concurrently in the liver). Also numbers of histologically related tumours in different organs, or in both sexes, may be analysed jointly. However, the Committee is extremely reserved in such cases, as mechanisms of tumourigenesis in different sexes or organs may vary considerably.

4.1.3 Selecting key research

If multiple studies meet the criteria, the assessment of uncertainties will play a critical role in the Committee's ultimate choice of key research. In general, the study conducted in the species in which carcinogenic effects occur at the lowest exposure will be selected, and the data that result in the lowest cancer risk values will be used.

4.2 Step 2: Determination of starting point for estimating carcinogenic activity

After evaluating the available data and selecting the key study, the Committee determines a representative measure of the carcinogenic activity of a compound. This is referred to as the 'starting point' for risk estimation.

4.2.1 Benchmark dose as starting point

The Committee prefers to use the benchmark dose (BMD) approach for deriving a starting point.[15] The BMD method aims to describe the best possible dose-response relationship* for a set of toxicity data using mathematical models.

A BMD is an exposure level of a compound, that corresponds with a predefined value for an effect (the benchmark response, BMR). For carcinogenicity as an endpoint, a BMR is often the proportion of animals with a tumour, corrected for spontaneous tumours (BMR5 for 5 percent response; BMR10 for 10 percent response, et cetera). The size of the BMR is not predetermined, and depends on the available data. The Committee notes that a BMR preferably falls within the experimental data, and the extrapolation factor is relatively small for a relatively low BMR (see Chapter 4.4). As default, the Committee uses a BMR of 10 percent.

The BMD approach provides a substantiated estimate of carcinogenic activity, as all usable experimental data are used and the related statistical uncertainties are taken into account.[15] These uncertainties are expressed by the BMDL (the lower limit of the 95% confidence interval of the BMD). The Committee prefers the BMD over the use of the BMDL as a starting point for the calculation of cancer risk values, as the BMD provides the best estimate of the carcinogenic response. The Committee considers the linear extrapolation step in deriving cancer risk values (described in 4.4) to be sufficiently conservative, so statistical uncertainties are not further taken into account.

Various software packages are available for performing a BMD analysis. The Committee currently prefers the BMD software from the Environmental Protection Agency (EPA)[16], as it is relatively easy to use, freely accessible and widely accepted.

4.2.2 Single dose as starting point

If insufficient data are available to model a (reliable) dose-response relationship, a reliable BMD cannot be derived.* In such cases, the Committee has no alternative other than to apply the traditional approach.[1] This means that an exposure level and the corresponding tumour incidence are selected, and used as a representative point estimate for the carcinogenic activity of a compound. In general, this will be the lowest level of exposure for which a statistically significant and/or biologically relevant tumour incidence is observed.

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* Dose is generally defined as an administered or ingested amount of a compound per unit of body mass. In this guideline, the Committee uses the term dose, such as *benchmark* dose, dose-response relationship, for both oral and inhalatory exposures.

* In such cases, the BMD and the BMDL will differ greatly (by a factor >10). Criteria for data quality for BMD analysis are described in the BMD guideline published by EFSA.[17]

4.3 Step 3: Estimation of carcinogenic activity in animals

The estimation of the carcinogenic activity in animal studies occurs similar to the method reported in the previous guideline.[1] Here, the Committee will provide a brief description.

The carcinogenic activity in animals is calculated based on the starting point that is selected (i.e. a point estimate based on a single dose group or, preferably, a BMD). The carcinogenic activity is expressed as incidence per unit of the daily dose, or per unit of air concentration (respectively the I_{dose} or $I_{\text{concentration}}$).

Based on a single dose group, carcinogenic activity, per unit of daily dose, is calculated as follows:

$$I_{dose} = \frac{I_e - I_c}{D \times (X_{po}/L) \times (X_{pe}/L) \times \text{exposure days per week}/7}$$

This is essentially the same when a BMD is used as the starting point:

$$I_{dose} = \frac{BMR}{BMD \times (X_{po}/L) \times (X_{pe}/L) \times \text{exposure days per week}/7}$$

in which:

- I_{dose} is the carcinogenic activity that can be ascribed to exposure to the compound per unit of daily dose during the entire life expectancy, assuming a linear dose-response relationship, generally expressed in mg per kg of body weight per day
- *BMR* is the benchmark response, often expressed as a 10 % increase in tumour incidence
- *BMD* is the benchmark dose, the dose corresponding to the BMR
- I_{e} and I_{c} represent tumour incidences in, respectively, the group of exposed animals and the control group
- *D* is the administered daily dose, generally expressed in mg per kg of body weight
- X_{po} and X_{pe} are, respectively, exposure time and duration of the experiment
- *L* is standard life expectancy for the animal species in question.

Similar formulas apply for the calculation of carcinogenic activity, based on the unit of air concentration:

$$I_{concentration} = \frac{I_e - I_c}{C \times (X_{po}/L) \times (X_{pe}/L) \times \text{exposure hours per day}/24 \times \text{exposure days per week}/7}$$

And, for a BMD as starting point:

$$I_{concentration} = \frac{BMR}{BMR \times (X_{po}/L) \times (X_{pe}/L) \times \text{exposure hours per day}/24 \times \text{exposure days per week}/7}$$

in which:

- $I_{concentration}$ is the carcinogenic activity that may be ascribed to exposure to the compound per unit of air concentration, usually expressed in mg per m^3
- *BMR,* the benchmark response, is often expressed as a 10 % increase in tumour incidence
- *BMD* is the benchmark dose, the concentration corresponding to the BMR
- I_e and I_c represent the tumour incidences in, respectively, the group of exposed animals and the control group
- *C* is the concentration the animals are exposed to, usually expressed in mg per m^3
- X_{po} and X_{pe} are, respectively, exposure time and duration of the experiment
- *L* is the standard life expectancy for the animal species in question.

Values for the parameters required for the calculation of carcinogenic activity, such as life expectancy, body weight and daily food and water consumption, are preferably obtained from the selected study. If these data are not available, the Committee uses default values (see Table 2).

Table 2 Default values for dose calculations.

Animal	Sex	Standard life expectancy (days)	Body weight (kg)	Food per day (g) (per kg of body weight)	Water per day (ml) (per kg of body weight)
Rat	Male	1000	0.5	20 (40)	25 (50)
	Female	1000	0.35	17.5 (50)	20 (57)
Mouse	Male	750	0.03	3.6 (120)	5 (167)
	Female	750	0.025	3.25 (130)	5 (200)
Hamster	Male	900	0.130	-	12 (90)
	Female	900	0.150	-	14 (90)

Source: Health Council of the Netherlands, 1995.[1]

4.4 Step 4: Risk estimation for humans and calculation of cancer risk values

Cancer risk values (at risk levels of 4 x 10^{-3} and 4 x 10^{-5}) for the human, occupational situation are calculated using health-based calculated occupational reference values (HBC-OCRV).[1]

Considering the carcinogenic activity per unit of the dose, I_{dose}, and default values (Table 3) the formula is:

$$HBC - OCRV = I_{dose} \times \frac{40\ years}{75\ years} \times \frac{48\ weeks}{52\ weeks} \times \frac{5\ days}{7\ days} \times (10\ m^3) \times (70\ kg)^{-1}$$

Considering the carcinogenic acvity per unit of air concentration, $I_{concentration}$, the formula is:

$$HBC - OCRV = I_{concentration} \times \frac{40\ years}{75\ years} \times \frac{48\ weeks}{52\ weeks} \times \frac{5\ days}{7\ days} \times \frac{10\ m^3}{18\ m^3}$$

In practice, the estimated carcinogenic activity of a compound that is determined in an animal study will be several orders of magnitude greater than the activity that corresponds with a cancer risk value (namely the effect associated with an additional risk of 4 x 10^{-3} or 4 x 10^{-5}). As reliable information is rarely available on the dose-response curve in the lower exposure ranges, the Committee will apply linear extrapolation to calculate cancer risk values.

Only if the relationship between exposure and effect in the lower dose range is found not to be linear, the Committee considers using a different extrapolation method. In that case, there must be supporting (mechanistic) data.

Table 3 Standard values for humans for lifetime exposure and occupational exposure.

Exposure setting	Duration of exposure	Inhalation
Lifetime	75 years, 24 hours per day, 7 days per week, 52 weeks per year	18 m^3 per 24 hours
Workplace	40 years, 8 hours per day, 5 days per week, 48 weeks per year	10 m^3 per 8-hour workday

Source: Health Council of the Netherlands, 1995.[1]

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Annexes

Annex **A**

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The Health Council and interests

Members of Health Council Committees are appointed in a personal capacity because of their special expertise in the matters to be addressed. Nonetheless, it is precisely because of this expertise that they may also have interests. This in itself does not necessarily present an obstacle for membership of a Health Council Committee. Transparency regarding possible conflicts of interest is nonetheless important, both for the chairperson and members of a Committee and for the President of the Health Council. On being invited to join a Committee, members are asked to submit a form detailing the functions they hold and any other material and immaterial interests which could be relevant for the Committee's work. It is the responsibility of the President of the Health Council to assess whether the interests indicated constitute grounds for non-appointment. An advisorship will then sometimes make it possible to exploit the expertise of the specialist involved. During the inaugural meeting the declarations issued are discussed, so that all members of the Committee are aware of each other's possible interests.

Annex **B**

Assessment of research quality

Epidemiological research

In assessing the weight of contribution of epidemiological studies in the risk assessment of carcinogenic substances, it is important to estimate the quality of those studies. This can be done systematically by using a certain set of criteria (see also the guidelines by the Dutch Institute for Healthcare Improvement). These criteria need to cover the essential characteristics of the study. For carcinogenic effects caused by exposure of carcinogens, in practice two study designs are of importance: 1) patient and control study, and 2) cohort study. In exposure-related cancer research most types of studies have a cohort design. Since the design of the case-control and cohort studies significantly differ, the quality criteria differ as well, as shown below.

Quality criteria for cohort studies:

a Is there a clear hypothesis formulated prior to starting the study?

b Is the composition of the exposed group done in such a way that at the beginning of the follow-up the disease risks are comparable between the exposed and the 'non-exposed' reference group? In other words, do both groups have the same cancer incidence pattern if the compound under

investigation would not be a carcinogen (the healthy worker effect is no reason to decline the study)?

c Is the status of the disease assessed in a comparable way regarding the exposed and reference group?

d Is the follow-up done in a reliable way, also regarding completeness?

e Is the statistical analyses performed adequately, and did it include corrections for differences in ages, duration and period of follow-up?

f Is the influence of confounding factors that could add to the observed adverse health effects, adequately controlled?

The criteria a, b, c, d and e must always be met. Regarding criterion f, in case of co-exposure to a known carcinogen, it should be plausible that co-exposure did not influence the observed effects. To fulfill criterion f, it is not necessary to control on potentially strong confounders, such as smoking and alcohol consumption.

Quality criteria for case-control studies:

g Is there a clear hypothesis formulated prior to starting the study?

h Are the patient and control groups composed in such a way that the prevalence of exposure is comparable between them when there is no relationship between disease and exposure?

i Is the exposure assessed in a valid way, independent from and without knowing the disease state?

j Is the statistical analyses performed adequately?

k Is the state of disease assessed in a valid way, independent from the state of exposure?

l Is the influence of confounding factors controlled adequately, either by statistical analysis or by making up the patient groups?

The criteria *g*, *h*, *i,* and *j* must always be met. Beside that it is allowed that one of the criteria *k* or *l* is not met. At least, in case of co-exposure to a known carcinogen, it should be plausible that co-exposure did not influence the observed effects. This additional criterion only holds for co-exposure which is strongly correlated to the exposure under investigation, and not for instance to smoking in case of lung and bladder cancer.The characterisation of exposure can still be assessed by considering a number of specific aspects, such as documentation of measurements (methods, numbers, basic statistical calculations), coverage of the follow-up period with measurements, completeness of the information about the

profession during the entire period employees were ‘at risk’, degree of detail of the categorisation into occupational or exposure categories.[7,18,19]

Animal studies

Klimisch et al. (1997) have set a number of criteria that can be used to systematically evaluate the quality of animal experiments.[12] These criteria have been adopted or processed by various authorities. Studies that are classified in reliability category 1 and 2 appear to be suitable for basing an assessment.

Code of reliability	Category of reliability
1	Reliable without restriction
1a	‘Good laboratory practice’ guideline study (OECD, EC, EPA, FDA, etc.
1b	Comparable to guideline study
1c	Test procedure in accordance with national standard methods (AFNOR, DIN, etc.)
1d	Test procedure in accordance with generally accepted scientific standards and described in sufficient detail
2	Reliable with restrictions
2a	Guideline study without detailed documentation
2b	Guideline study with acceptable restriction
2c	Comparable to guideline study with acceptable restrictions
2d	Test procedure in accordance with national standard methods with acceptable restriction
2e	Study well documented, meets generally accepted scientific principles, acceptable for assessment
2f	Accepted calculation method
2g	Data from handbook or collection of data
3	Not reliable
3a	Documentation insufficient for assessment
3b	Significant methodological deficiencies
3c	Unsuitable test system
4	Not assignable
4a	Abstract
4b	Secondary literature
4c	Original reference not yet available
4d	Original reference not translated
4e	Documentation insufficient for assessment

Source: Klimisch et al. 1997.[12]

Annex **C**

Bradford-Hill guideline for causality

The criteria proposed by English epidemiologist Sir Austin Bradford Hill (1897-1991), also known as Hill's causality criteria, are a group of properties that can be used to assess the strength of a causal relationship, or causality, between an incidence and a consequence.[8] The Committee emphasises that these should not be applied as explicit criteria, but rather as guidelines.

1 *Strength of the association*: The stronger the association (measured using suitable statistical methods), the more likely the relationship is causal.
2 *Consistency:* An association is consistent if results can be reproduced under different circumstances with different methods.
3 *Specificity:* The more specific the relationship between a factor and an effect (to what degree does a factor predict the course of an effect?), the more likely the relationship is causal.
4 *Temporal relationship:* For a causal relationship, it is essential for exposure to precede the effect. Longitudinal studies provide more convincing evidence in this regard than patient-control or cross-sectional research.
5 *Dose-response relationship*: The presence of a dose-response relationship is a strong indicator for causality.
6 *Biological plausibility:* Causality is more likely if a biological, mechanistic foundation exists. The lack hereof does not mean this relationship is irrelevant; it may also result in the re-evaluation of the theoretical foundations.

7 *Coherence:* Causality is more likely if a correlation is consistent with current knowledge and theories. The lack hereof does not mean this relationship is irrelevant; it may also result in the re-evaluation of the theoretical foundations.
8 *Experimental evidence*: In a number of cases, a correlation may be demonstrated experimentally.
9 *Analogy:* If comparable correlations have already been demonstrated, the possibility of causality is more likely.

Annex **D**

Example life table

For illustrative purposes, the Committee has included a calculated life table for a substance that causes leukaemia.

A	B	C	D	E	F	G	H	I	J	K	L	M	N	O
			Not exposed						Exposed					
			Fraction of deaths				Number of deaths		Fraction of deaths				Number of deaths	
Age	Exp	RR	Leukaemia	Other	Total	*At Risk*	Total	Leu-kaemia	Leukaemia	Other	Total	*At Risk*	Total	Leu-kaemia
1	0.0	1.00	0.00001	0.00139	0.00141	100000.0	140.5	1.1	0.00001	0.00139	0.00141	100000.0	140.5	1.1
2	0.0	1.00	0.00001	0.00085	0.00086	99859.5	85.4	1.0	0.00001	0.00085	0.00086	99859.5	85.4	1.0
3	0.0	1.00	0.00001	0.00052	0.00053	99774.1	52.9	1.0	0.00001	0.00052	0.00053	99774.1	52.9	1.0
4	0.0	1.00	0.00001	0.00033	0.00034	99721.3	33.7	0.9	0.00001	0.00033	0.00034	99721.3	33.7	0.9
5	0.0	1.00	0.00001	0.00021	0.00022	99687.6	22.3	0.9	0.00001	0.00021	0.00022	99687.6	22.3	0.9
6	0.0	1.00	0.00001	0.00015	0.00016	99665.3	15.5	0.9	0.00001	0.00015	0.00016	99665.3	15.5	0.9
7	0.0	1.00	0.00001	0.00011	0.00011	99649.8	11.4	0.9	0.00001	0.00011	0.00011	99649.8	11.4	0.9
8	0.0	1.00	0.00001	0.00008	0.00009	99638.4	9.0	0.9	0.00001	0.00008	0.00009	99638.4	9.0	0.9
9	0.0	1.00	0.00001	0.00007	0.00008	99629.4	7.5	0.9	0.00001	0.00007	0.00008	99629.4	7.5	0.9
10	0.0	1.00	0.00001	0.00006	0.00007	99621.9	6.8	0.9	0.00001	0.00006	0.00007	99621.9	6.8	0.9
11	0.0	1.00	0.00001	0.00006	0.00006	99615.1	6.5	0.9	0.00001	0.00006	0.00006	99615.1	6.5	0.9
12	0.0	1.00	0.00001	0.00006	0.00007	99608.6	6.5	1.0	0.00001	0.00006	0.00007	99608.6	6.5	1.0
13	0.0	1.00	0.00001	0.00006	0.00007	99602.1	7.0	1.0	0.00001	0.00006	0.00007	99602.1	7.0	1.0
14	0.0	1.00	0.00001	0.00007	0.00008	99595.1	7.9	1.1	0.00001	0.00007	0.00008	99595.1	7.9	1.1
15	0.0	1.00	0.00001	0.00008	0.00009	99587.1	9.3	1.1	0.00001	0.00008	0.00009	99587.1	9.3	1.1
16	0.0	1.00	0.00001	0.00010	0.00011	99577.9	11.2	1.2	0.00001	0.00010	0.00011	99577.9	11.2	1.2
17	0.0	1.00	0.00001	0.00012	0.00014	99566.7	13.7	1.3	0.00001	0.00012	0.00014	99566.7	13.7	1.3
18	0.0	1.00	0.00001	0.00016	0.00017	99553.1	16.8	1.4	0.00001	0.00016	0.00017	99553.1	16.8	1.4
19	0.0	1.00	0.00001	0.00019	0.00021	99536.2	20.7	1.4	0.00001	0.00019	0.00021	99536.2	20.7	1.4
20	2.1	1.00	0.00002	0.00024	0.00025	99515.5	25.3	1.5	0.00002	0.00024	0.00025	99515.5	25.4	1.5
21	6.4	1.01	0.00002	0.00029	0.00031	99490.2	30.5	1.6	0.00002	0.00029	0.00031	99490.1	30.5	1.6
22	10.7	1.01	0.00002	0.00035	0.00036	99459.6	36.0	1.6	0.00002	0.00035	0.00036	99459.6	36.0	1.6
23	14.9	1.02	0.00002	0.00040	0.00041	99423.6	41.2	1.7	0.00002	0.00040	0.00042	99423.6	41.3	1.7
24	19.2	1.02	0.00002	0.00045	0.00046	99382.4	46.0	1.7	0.00002	0.00045	0.00046	99382.3	46.1	1.7
25	23.4	1.03	0.00002	0.00049	0.00050	99336.4	50.1	1.7	0.00002	0.00049	0.00050	99336.3	50.1	1.7
26	27.7	1.03	0.00002	0.00052	0.00054	99286.3	53.2	1.7	0.00002	0.00052	0.00054	99286.2	53.3	1.8
27	32.0	1.04	0.00002	0.00054	0.00056	99233.1	55.4	1.7	0.00002	0.00054	0.00056	99232.9	55.4	1.8
28	36.2	1.04	0.00002	0.00055	0.00057	99177.7	56.6	1.7	0.00002	0.00055	0.00057	99177.4	56.6	1.8
29	40.5	1.05	0.00002	0.00056	0.00058	99121.1	57.0	1.7	0.00002	0.00056	0.00058	99120.8	57.1	1.8
30	44.8	1.05	0.00002	0.00056	0.00058	99064.2	57.0	1.8	0.00002	0.00056	0.00058	99063.7	57.1	1.8

Example survival table

A	B	C	D	E	F	G	H	I	J	K	L	M	N	O
			Not exposed						Exposed					
			Fraction of deaths				Number of deaths		Fraction of deaths				Number of deaths	
Age	Exp	RR	Leukaemia	Other	Total	*At Risk*	Total	Leu-kaemia	Leukaemia	Other	Total	*At Risk*	Total	Leu-kaemia
31	49.0	1.06	0.00002	0.00056	0.00057	99007.2	56.8	1.8	0.00002	0.00056	0.00058	99006.7	56.9	1.9
32	53.3	1.06	0.00002	0.00056	0.00057	98950.4	56.9	1.8	0.00002	0.00056	0.00058	98949.7	57.0	1.9
33	57.6	1.07	0.00002	0.00056	0.00058	98893.5	57.4	1.9	0.00002	0.00056	0.00058	98892.7	57.6	2.0
34	61.8	1.07	0.00002	0.00057	0.00059	98836.1	58.6	1.9	0.00002	0.00057	0.00059	98835.2	58.8	2.1
35	66.1	1.08	0.00002	0.00059	0.00061	98777.4	60.6	2.0	0.00002	0.00059	0.00062	98776.4	60.8	2.2
36	70.3	1.08	0.00002	0.00062	0.00064	98716.8	63.6	2.1	0.00002	0.00062	0.00065	98715.6	63.8	2.3
37	74.6	1.09	0.00002	0.00067	0.00069	98653.1	67.9	2.3	0.00003	0.00067	0.00069	98651.8	68.1	2.5
38	78.9	1.10	0.00002	0.00072	0.00075	98585.2	73.8	2.5	0.00003	0.00072	0.00075	98583.7	74.0	2.7
39	83.1	1.10	0.00003	0.00080	0.00083	98511.5	81.3	2.7	0.00003	0.00080	0.00083	98509.7	81.6	2.9
40	87.4	1.11	0.00003	0.00089	0.00092	98430.1	90.9	2.9	0.00003	0.00089	0.00093	98428.1	91.2	3.2
41	91.7	1.11	0.00003	0.00101	0.00104	98339.3	102.5	3.2	0.00004	0.00101	0.00105	98336.9	102.9	3.5
42	95.9	1.12	0.00004	0.00115	0.00119	98236.8	116.4	3.5	0.00004	0.00115	0.00119	98234.1	116.8	3.9
43	100.2	1.12	0.00004	0.00131	0.00135	98120.4	132.8	3.9	0.00004	0.00131	0.00136	98117.2	133.3	4.3
44	104.4	1.13	0.00004	0.00151	0.00155	97987.6	151.7	4.3	0.00005	0.00151	0.00155	97984.0	152.2	4.8
45	108.7	1.13	0.00005	0.00172	0.00177	97835.9	173.1	4.7	0.00005	0.00172	0.00178	97831.7	173.7	5.4
46	113.0	1.14	0.00005	0.00196	0.00202	97662.8	196.7	5.2	0.00006	0.00196	0.00202	97658.1	197.4	6.0
47	117.2	1.15	0.00006	0.00222	0.00228	97466.1	222.2	5.8	0.00007	0.00222	0.00229	97460.6	223.0	6.6
48	121.5	1.15	0.00007	0.00250	0.00256	97244.0	248.8	6.4	0.00008	0.00250	0.00257	97237.6	249.8	7.4
49	125.8	1.16	0.00007	0.00278	0.00285	96995.1	276.4	7.1	0.00008	0.00278	0.00286	96987.8	277.5	8.2
50	130.0	1.16	0.00008	0.00307	0.00315	96718.7	304.6	7.8	0.00009	0.00307	0.00317	96710.4	305.8	9.1
51	134.3	1.17	0.00009	0.00337	0.00346	96414.2	333.3	8.6	0.00010	0.00337	0.00348	96404.6	334.7	10.1
52	138.5	1.17	0.00010	0.00368	0.00378	96080.9	362.3	9.5	0.00012	0.00368	0.00379	96069.9	363.9	11.2
53	142.8	1.18	0.00011	0.00399	0.00410	95718.6	391.5	10.5	0.00013	0.00399	0.00412	95706.0	393.4	12.4
54	147.1	1.19	0.00012	0.00431	0.00443	95327.1	421.4	11.7	0.00015	0.00431	0.00445	95312.6	423.5	13.8
55	151.3	1.19	0.00014	0.00464	0.00478	94905.7	452.4	12.9	0.00016	0.00464	0.00480	94889.1	454.8	15.4
56	155.6	1.20	0.00015	0.00500	0.00515	94453.3	485.5	14.3	0.00018	0.00500	0.00518	94434.3	488.2	17.1
57	159.9	1.20	0.00017	0.00540	0.00557	93967.8	521.6	15.8	0.00020	0.00540	0.00560	93946.1	524.6	19.0
58	164.1	1.21	0.00019	0.00584	0.00603	93446.2	561.8	17.5	0.00023	0.00584	0.00607	93421.4	565.3	21.1
59	168.4	1.22	0.00021	0.00635	0.00656	92884.4	607.0	19.4	0.00025	0.00635	0.00660	92856.1	611.0	23.5
60	170.5	1.22	0.00023	0.00692	0.00716	92277.4	658.0	21.5	0.00028	0.00692	0.00721	92245.2	662.5	26.1
61	170.5	1.22	0.00026	0.00758	0.00784	91619.4	715.8	23.7	0.00032	0.00758	0.00790	91582.7	720.7	28.9

A	B	C	D	E	F	G	H	I	J	K	L	M	N	O
			Not exposed						Exposed					
			Fraction of deaths				Number of deaths		Fraction of deaths				Number of deaths	
Age	Exp	RR	Leukaemia	Other	Total	*At Risk*	Total	Leu-kaemia	Leukaemia	Other	Total	*At Risk*	Total	Leu-kaemia
62	170.5	1.22	0.00029	0.00834	0.00863	90903.5	781.5	26.2	0.00035	0.00834	0.00870	90862.0	786.8	31.9
63	170.5	1.22	0.00032	0.00922	0.00955	90122.0	856.2	28.9	0.00039	0.00922	0.00962	90075.1	862.1	35.2
64	170.5	1.22	0.00036	0.01024	0.01059	89265.8	940.7	31.7	0.00043	0.01024	0.01067	89213.0	947.0	38.6
65	170.5	1.22	0.00039	0.01139	0.01179	88325.1	1035.1	34.7	0.00048	0.01139	0.01187	88266.0	1041.9	42.2
66	170.5	1.22	0.00044	0.01270	0.01314	87290.1	1139.5	37.8	0.00053	0.01270	0.01324	87224.2	1146.8	46.0
67	170.5	1.22	0.00048	0.01418	0.01466	86150.6	1253.8	41.0	0.00058	0.01418	0.01476	86077.3	1261.6	49.9
68	170.5	1.22	0.00053	0.01583	0.01636	84896.8	1377.3	44.2	0.00064	0.01583	0.01647	84815.7	1385.6	53.8
69	170.5	1.22	0.00057	0.01767	0.01824	83519.5	1509.9	47.5	0.00070	0.01767	0.01837	83430.1	1518.5	57.8
70	170.5	1.22	0.00062	0.01971	0.02034	82009.6	1651.0	50.7	0.00076	0.01971	0.02047	81911.6	1660.0	61.7
71	170.5	1.22	0.00068	0.02198	0.02265	80358.5	1800.0	53.8	0.00083	0.02198	0.02280	80251.6	1809.2	65.5
72	170.5	1.22	0.00073	0.02448	0.02521	78558.5	1955.7	56.9	0.00089	0.02448	0.02537	78442.3	1965.1	69.2
73	170.5	1.22	0.00079	0.02723	0.02802	76602.8	2116.9	59.9	0.00097	0.02723	0.02820	76477.2	2126.3	72.8
74	170.5	1.22	0.00085	0.03028	0.03113	74485.9	2283.2	62.7	0.00104	0.03028	0.03132	74351.0	2292.5	76.2
75	170.5	1.22	0.00092	0.03367	0.03459	72202.7	2454.5	65.2	0.00112	0.03367	0.03479	72058.5	2463.5	79.3
76	170.5	1.22	0.00099	0.03746	0.03844	69748.3	2630.6	67.6	0.00120	0.03746	0.03866	69594.9	2639.2	82.2
77	170.5	1.22	0.00106	0.04173	0.04279	67117.7	2811.2	69.6	0.00129	0.04173	0.04302	66955.7	2819.3	84.6
78	170.5	1.22	0.00114	0.04657	0.04770	64306.5	2995.5	71.3	0.00138	0.04657	0.04795	64136.4	3002.7	86.6
79	170.5	1.22	0.00121	0.05207	0.05328	61311.0	3181.3	72.5	0.00148	0.05207	0.05355	61133.7	3187.5	88.0
80	170.5	1.22	0.00129	0.05835	0.05964	58129.7	3365.5	73.1	0.00158	0.05835	0.05992	57946.2	3370.3	88.7
81	170.5	1.22	0.00138	0.06552	0.06690	54764.2	3543.9	72.9	0.00168	0.06552	0.06720	54575.9	3547.0	88.5
82	170.5	1.22	0.00146	0.07376	0.07521	51220.3	3711.2	71.9	0.00178	0.07376	0.07553	51028.8	3712.4	87.3
83	170.5	1.22	0.00154	0.08321	0.08475	47509.1	3860.6	70.0	0.00187	0.08321	0.08509	47316.4	3859.5	84.9
84	170.5	1.22	0.00161	0.09405	0.09566	43648.6	3982.1	67.1	0.00196	0.09405	0.09602	43456.9	3978.5	81.3
85	170.5	1.22	0.00168	0.10642	0.10810	39666.5	4064.4	63.1	0.00205	0.10642	0.10847	39478.5	4058.1	76.5
86	170.5	1.22	0.00174	0.12048	0.12222	35602.1	4095.9	58.2	0.00212	0.12048	0.12260	35420.4	4086.8	70.5
87	170.5	1.22	0.00178	0.13638	0.13816	31506.2	4065.7	52.5	0.00217	0.13638	0.13855	31333.5	4054.0	63.6
88	170.5	1.22	0.00181	0.15427	0.15608	27440.6	3965.5	46.1	0.00221	0.15427	0.15648	27279.5	3951.4	55.8
89	170.5	1.22	0.00183	0.17430	0.17613	23475.1	3791.0	39.4	0.00223	0.17430	0.17653	23328.0	3775.1	47.7
90	170.5	1.22	0.00183	0.19664	0.19847	19684.1	3543.4	32.7	0.00223	0.19664	0.19887	19552.9	3526.2	39.6
91	170.5	1.22	0.00182	0.22142	0.22324	16140.6	3229.4	26.4	0.00222	0.22142	0.22364	16026.7	3211.7	31.9
92	170.5	1.22	0.00180	0.24877	0.25057	12911.3	2861.7	20.5	0.00219	0.24877	0.25096	12815.0	2844.2	24.8

A	B	C	D	E	F	G	H	I	J	K	L	M	N	O
			Not exposed						Exposed					
			Fraction of deaths				Number of deaths		Fraction of deaths				Number of deaths	
Age	Exp	RR	Leukaemia	Other	Total	*At Risk*	Total	Leu-kaemia	Leukaemia	Other	Total	*At Risk*	Total	Leu-kaemia
93	170.5	1.22	0.00176	0.27880	0.28057	10049.6	2458.6	15.4	0.00215	0.27880	0.28095	9970.8	2442.2	18.7
94	170.5	1.22	0.00172	0.31169	0.31341	7591.0	2042.3	11.2	0.00209	0.31169	0.31378	7528.6	2027.6	13.5
95	170.5	1.22	0.00167	0.34762	0.34929	5548.7	1635.8	7.8	0.00203	0.34762	0.34965	5501.0	1623.1	9.4
96	170.5	1.22	0.00161	0.38679	0.38840	3912.9	1259.4	5.2	0.00197	0.38679	0.38876	3877.8	1249.0	6.3
97	170.5	1.22	0.00156	0.42940	0.43096	2653.5	929.0	3.4	0.00190	0.42940	0.43131	2628.8	921.0	4.1
98	170.5	1.22	0.00151	0.47565	0.47716	1724.4	654.4	2.1	0.00184	0.47565	0.47749	1707.8	648.4	2.5
99	170.5	1.22	0.00146	0.52568	0.52714	1070.1	438.4	1.2	0.00178	0.52568	0.52746	1059.4	434.3	1.5
100	170.5	1.22	0.00141	0.57958	0.58099	631.7	278.3	0.7	0.00172	0.57958	0.58130	625.2	275.6	0.8
				Total number of deaths due to leukaemia in control population				1941	Total number of deaths due to leukaemia in exposed population					2341

Column A: Age
Column B: Cumulative exposure (mg/m^3), for which the Committee assumes it begins at the age of 20 and ends at the age of 60
Column C: Relative risk due to exposure compared with the unexposed group. The exposure-response relationship is derived based on epidemiological research
Columns DEF: The fraction of deaths in the unexposed group due to leukaemia (D), other causes (E) and total (F)
Column G: Population at risk (unexposed group)
Columns HI: Absolute number of deaths in the unexposed group, in total (column H) and due to leukaemia (column I)
Columns JKL: The fraction of deaths in the exposed group due to leukaemia (J), other causes (K) and total (L)
Column M: Population at risk (exposed group)
Columns NO: Absolute number of deaths in the exposed group, in total (column N) and due to leukaemia (column O)

Clarification

A life table allows the calculation of the cumulative exposure that is associated with a predetermined number of extra cancer deaths. In this example, the Committee calculates the cumulative exposure to a substance that results in 400 extra leukaemia deaths in a population of 100,000 (in other words, the cumulative exposure level corresponding with the prohibitive risk level).

The number of deaths due to leukaemia and other causes is calculated for each life year, by multiplying the respective mortality fractions by the population size. Both the exposed population and unexposed population decrease by the total number of deaths (leukaemia deaths and deaths by other causes) each year.

The Committee assumes that workers are exposed between the ages of 20 and 60. During this period, exposure accumulates gradually each year, and subsequently the relative risk of leukaemia increases, compared with the unexposed group.* In this example, the Committee assumes that the relative risk of leukaemia remains elevated also after the exposure period (> 60 years of age). The fraction of leukaemia deaths in the exposed group increases in proportion with the relative risk.

For both the exposed population and the control population, the total number of leukaemia deaths is calculated by summing leukaemia deaths for each life year. The Committee takes into account the leukaemia deaths until the age at which mortality due to exposure is negligible. For this, the Committee adheres to an age of 100 years.

The additional number of leukaemia deaths is the total number of leukaemia deaths in the exposed population minus the number in the unexposed population. Using an iterating (repeating) algorithm, the Committee calculates the cumulative exposure consistent with a predefined number of additional cancer deaths (in this case 170.5 mg, resulting in 400 deaths due to leukaemia per 100,000 deaths).

* Derivation of the underlying exposure-response relationship is outlined in Chapter 3.2.

Annex **E**

Approaches used by other (international) organisations

There is currently no consistent approach at the international level, for the risk estimation for carcinogens with a stochastic genotoxic mechanisms of action. In this Annex, the Committee summarises a few methods used by other (international) organisations. For a more extensive description of these methods, the Committee refers to the guidance documentation of the organisations in question.

The fundamental differences between the methods are summarised in a table at the end of this Annex.

E.1 ECHA

The european substances legislation on the Registration, Evaluation and Authorisation of Chemical substances (REACH) was enforced in 2007. The European Chemical Agency (ECHA) is an agency of the European Union, which is responsible for the implementation of REACH.

Use of risk levels under REACH

European regulations have not yet defined any binding prohibitive or target risk levels for genotoxic carcinogenic substances under REACH. In its guidance documentation on REACH, ECHA notes that there is some experience with

determining tolerable risks within Europe.[20] Within this context, risks of 1 x 10^{-5} and 1 x 10^{-6} are noted as indicative tolerable risk levels for workers and general population, respectively. The ECHA does not further specify the context for these risk levels, such as the correponding exposure duration or risk period.

Risk assessment under REACH

For non-threshold carcinogens, a derived minimum effect level (DMEL) must be derived under REACH. A DMEL is an exposure level consistent with a risk that is considered a tolerable, but otherwise unspecified risk.

REACH has two methods for deriving a DMEL. In the linearised approach, an exposure level related to a specific carcinogenic effect is extrapolated (linearly) to a level that corresponds with a tolerable risk. A DMEL derived using the linearised approach can therefore be considered as a cancer risk value.
The large assessment approach is based on the margin of exposure principle as is applied by the European Food Safety Authority (EFSA) (see also Paragraph E.2). In this approach, a DMEL is calculated using an exposure level at which a carcinogenic effect is found, and applying an uncertainty margin large enough so that the final risk may be considered negligible. This risk is not further specified in the large assessment approach.

Linearised approach

Human data

If epidemiological data are used, the need for correction for differences in comparability of exposure conditions between studied groups and the target population is first considered. The following uncertainty factors are then considered:

Uncertainty factor	Size
Intraspecies differences	To be determined
Data quality	To be determined

The starting point, usually a relative risk, must be converted to an extra risk, namely the number of additional cancer cases due to exposure. For this, REACH documentation describes a so-called 'direct method'. * The use of the direct method is accepted under REACH if the form of cancer in question is uncommon in the general population, and the substance is not potent or the calculated risk affects a relatively young age (< 70 years). Life table analysis is mentioned as a more accurate alternative to the direct method, but is not discussed further in the REACH documentation.

Extrapolation to a tolerable risk occurs, linearly by default. Only if reliable data indicate the dose-response relationship in the lower dose range is non-linear, a different model may be used.

Animal data

Under REACH, the BMD10 and T25** may be used as starting points for deriving a DMEL. Unlike the BMD10, the T25 is not a modelled value for tumour incidence, but a potency measure based on only one dose group.[21,22] Therefore if available data allow modelling, a BMD analysis should be used.

The starting point is defined for a daily dose and lifetime exposure; if the administration frequency is lower (for example 5 instead of 7 days per week) or exposure duration shorter (for example 18 rather than 24 months), this is corrected for.

The starting point is subsequently corrected for factors that negatively impact the comparability of exposure between humans and animals (such as differences in exposure duration and route, bioavailability and respiratory volume).

In the linearised approach, the BMD10 or T25 is corrected using uncertainty factors, after which standard linear extrapolation is used to determine a DMEL.

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* An additional cancer risk due to occupational exposure can be calculated directly from a relative risk using the formula: [additional lifetime risk = lifetime background risk x (relative risk -1)]. However, the direct method does not account for mortality due to other causes, and results in overestimation of the risk, particularly for cancers with a high background risk.

** The T25 is the dose associated with a tumour incidence of 25%, corrected for spontaneous tumours and, if necessary, interim mortality.

The following uncertainty factors have been considered to correct the starting point, where relevant:

Uncertainty factor	Standard value (systemic tumours)
Interspecies variation	Allometric scaling[a]
Intraspecies differences	Not applied[b]
Nature of carcinogenicity[c]	Not applied [b]
Use of a LOAEL instead of a NOAEL	Not applied[b]
Use of T25 instead of BMD10	2.5
Linear extrapolation of BMD10 to low dose	10,000 (for a risk of 1 x 10^{-5}) 100,000 (for a risk of 1 x 10^{-6})

[a] If applicable. The standard uncertainty factor of 2.5 for other interspecies differences is not applied, as REACH considers a large linear extrapolation factor to be sufficiently conservative.
[b] This uncertainty factor is not applied, as REACH considers a large linear extrapolation factor to be sufficiently conservative.
[c] Uncertainties relating to inter-individual differences in processes involved in the genotoxic mechanism of action.

Large assessment factor approach

The large assessment approach is only described by the ECHA for animal data. In accordance with the EFSA, the ECHA prefers a BMDL as a starting point.* If data do not permit BDM analysis, the T25 should be used as a starting point.

Similar to the linearised approach, the starting point is corrected for factors that result in differences in comparability of exposure between humans and animals. Subsequently, the margin of exposure is determined by the following uncertainty factors:

Uncertainty factor	Standard value (systemic tumours)
Interspecies variation	10
Intraspecies differences	10 (for the general population), or 5 (for the occupational population)
Nature of carcinogenicity[a]	10
Use of a LOAEL instead of a NOAEL	10
Use of T25 instead of BMDL10	2.5

[a] Uncertainties relating to inter-individual differences in processes involved in the genotoxic mechanism of action.

* This may result in the outcome differing significantly from that of the linearised approach, in which the BMD10 is the preferred starting point.

In accordance with the EFSA, the ECHA applies a margin of 10,000 for the calculation of a DMEL for the general population, when a BMDL10 is used as a starting point. A margin of 5,000 is used to calculate a DMEL for workers.

If a T25 value is used as a starting point, REACH applies a (2.5 times) higher uncertainty factor to take into account the effect size, resulting in a margin of 12,500 for workers.

Alternatives under REACH

For many substances, specific carcinogenicity data are not available for the calculation of cancer risks. In such cases, REACH allows the use of data on structurally related substances (read-across), the use of alternative studies (such as sub-chronic studies), or the application of a exposure threshold value below which no significant risk to human health is expected to exist (the so-called threshold of toxicological concern (TTC) concept). The Committee refers to Annex A8-15 of the ECHA Guidance Document for a more detailed description of the above-mentioned concepts.[23]

E.2 EFSA

A scientific committee of the EFSA published an approach for risk assessment of genotoxic carcinogenic substances in food in 2005.[24]

Margin of exposure principle

The EFSA does not apply predetermined risk levels in its approach, and therefore does not calculate cancer risk values. The EFSA considers the uncertainties associated with model-based extrapolation from animal data, to the low dose range, too large. As an alternative, the EFSA uses the margin of exposure principle. This principle is based on the application of a wide margin between an exposure level to a substance that results in a carcinogenic effect in animals (the starting point, referred to as reference point by the EFSA), and the estimated intake of this substance by humans based on a normal consumption pattern. With the use of the margin of exposure approach the discussion about the shape of the dose-response relationship in the low dose range is avoided.[24]

EFSA approach to risk assessment

The EFSA prefers the use of the BMD method for determining a starting point for the calculation of a margin of exposure. The EFSA has a preference for the BMDL10, as in many studies a tumour incidence of 10% is in the range of the lowest effect level within the experimental data, for which a statistical significance can be determined. The derivation of a BMDL10 therefore requires no, or minimal extrapolation beyond the range of the original data. If a BMDL10 cannot be derived, the EFSA uses a T25 as a starting point.

The margin of exposure is calculated by dividing the starting point by the estimated human intake. In general, the EFSA considers the presence of a genotoxic carcinogenic substance in food a low priority if a margin of 10,000 is used between the BMDL10 and the estimated daily intake via diet. This margin is based on the following uncertainty factors:

Uncertainty factor	Standard value
Interspecies variation	10
Intraspecies differences	10
Human variability[a]	10
Use of a LOAEL instead of a NOAEL	10
Use of T25 instead of BMDL10	Not specified

[a] Factors for uncertainties relating to inter-individual differences in processes involved in the genotoxic mechanism of action

E.3 SCOEL

The European Scientific Committee on Occupational Exposure Levels (SCOEL) distinguishes between genotoxic carcinogenic substances with a mechanism of action with a threshold value, and those for which no threshold value can be identified.[25] For the latter group, the SCOEL calculates a number of cancer risk values based on data from human or animal studies. By default, the SCOEL assumes a linear dose-response relationship in the low dose range.[26]

The SCOEL has not published a guideline for derivation of cancer risk values. The SCOEL lets the European Commission decide on the level of a tolerable risk.

E.4 US EPA

In the Guidelines for carcinogen risk assessment, the US Environmental Protection Agency (EPA) bescribe the risk assessment of carcinogens in a broad, general framework, including analysis of carcinogenicity data, assessment of the mechanism of action and derivation of a dose-response relationship.[27] In its guideline, the EPA does not deal with the application of uncertainty factors or the size of a tolerable risk.

General EPA approach to risk assessment

The EPA uses models to derive a starting point for risk assessment. These may have a biological basis, and for example describe a process preceding the development of cancer (toxicodynamic models). In the absence of mechanistic data, models may be used that, by means of a function, purely describe data on a statistical basis (empirical models; curve-fitting).

The EPA recommends the use of the lowest starting point that can still be reliably predicted by the model, often the BMDL10, but in some cases also the BMDL01. When extrapolating to low doses, the EPA states that data on mechanism of action should be used. A non-linear approach is only acceptable if it is supported by (mechanistic) data.

E.5 AGS

In Germany, as in the Netherlands, cancer risk values are determined for the assessment of occupational exposure to genotoxic carcinogenic substances with a mechanism of action without a threshold value.

Use of risk levels

The Ausschuss für Gefahrstoffe (AGS), part of the Bundesanstalt für Arbeitsschutz und Arbeitsmedizin (BAuA), has defined the following risk levels:

- *Akzeptanzrisiko*: This is the risk level that is generally accepted. The AGS has decided to introduce the acceptable risk level in two phases:
  - 4×10^{-4} (interim value)
  - 4×10^{-5} (introduced by 2018 at the latest)
- *Toleranzrisiko*: This is the tolerable risk level
  - 4×10^{-3}.

Like the risk levels used in the Netherlands, these risk levels correspond to a lifetime risk, based on a working life of 40 years and continuous exposure during the working day.

The two risk levels are applied to differentiate between three risk areas (the so-called 'traffic light model'). If the exposure does not exceed the accepted risk, no additional reduction of exposure is required (green light). If the tolerable risk is exceeded in the workplace, risk reducing measures are implemented or use of the substance is prohibited (red light). Exposure with a risk between the accepted risk and the tolerable risk gives also reason for measures to reduce exposure, albeit with less urgency (orange light).

AGS approach to risk assessment

The AGS published a guideline for the calculation of risk values for carcinogenic substances in 2008.[28]

Human data

For a risk assessment based on human data, the AGS has a preference for the use of incidence statistics. The starting point for a risk assessment may be either an absolute or a relative risk. In the latter case, the additional cancer risk (namely the additional cases of cancer due to exposure) can be calculated directly using the direct method as described by the ECHA. The AGS also considers the use of life tables, taking into account a lifetime of at least 80 years.

Animal data

The AGS has a preference for a BMD10 as a starting point. The AGS notes that the primary use of the BMD10 is to compare the carcinogenic potency of different substances. A lower BMD, down to a BMD0.1, may be used as a starting point for linear extrapolation, but only if information about the mechanism of action supports a non-linear course in the low dose range. If no reliable BMD analysis is possible, the AGS uses the T25 as a starting point.

The AGS does not apply default uncertainty factors to compensate for interspecies and intraspecies differences, as these uncertainty factors are not evidence-based:

Uncertainty factor	Standard value
Interspecies variation	Allometric scaling[a]
Intraspecies differences	Not applied
Nature of carcinogenicity[b]	Not applied
Use of a LOAEL instead of a NOAEL	Not applied

[a] If applicable. The standard uncertainty factor of 2.5 for other interspecies differences is not applied

[b] Factor for uncertainties relating to inter-individual differences in processes involved in the genotoxic mechanism of action

If animals are not exposed for life, this is corrected for. A correction is subsequently made for factors that negatively impact the comparability of exposure between humans and animals (such as differences in exposure duration and route, bioavailability and respiratory volume).

Finally, the corrected starting point is extrapolated, by default linearly, to lower exposure levels.

E.6 HSE

The British government and its advisory bodies (including the HSE; Health and Safety Executive) base the risk assessment of exposure to genotoxic carcinogens on a guideline that is published by the Committee on *Carcinogenicity of chemicals in food, consumer products and the environment.*[29] This Committee has indicated that calculation of low exposure risks from animal studies in which high doses are used, is associated with too much uncertainty. Therefore, the Committee proposes the ALARA principle,* rather than a quantitative approach, for carcinogens with a mechanism of action for which no threshold value can be derived. The ALARA principle however, is not a risk assessment method but a risk management tool.

In some cases, such as unavoidable exposure to genotoxic substances (e.g. contaminants or impurities), the ALARA principle can be supplemented by a quantitative approach. The Committee proposes a margin of exposure approach for this.

* The COC Guidelines describes the ALARA principle as *As Low As Reasonably Practicable* (ALARP).

E.7 In summary

Internationally, two different risk assessment approaches are being used for genotoxic carcinogens with a stochastic mechanism of action. Specific cancer risk values (exposure levels associated with a specific risk) can be calculated, alternatively, the margin of exposure concept can be used. The advantage of the latter approach is that the discussion regarding the extremely uncertain extrapolation to the low dose range is avoided.

The methods described by international agencies differ in terms of implementation, but they are based on the same toxicological principles and apply the same general (quality) criteria. Usually, similar choices are made. For example, human data is preferred for risk assessment. Further, when possible a model is used for describing a dose-response relationship. If reliable data on the dose-response relationship are lacking (particularly in the low dose range), linear extrapolation is the default method used to estimate the risk.

The described frameworks though, currently provide limited guidance, in particular for the use of human data. In Table 4, the Committee summarises the different methodologies for risk assessment of genotoxic carcinogens with a stochastic mechanism of action.

Table 4 Summary of (internationally) used methodologies for risk assessment of genotoxic carcinogens.

Organisation	Risk assessment	Preferred starting point for risk assessment	Correction for species differences	Standard extrapolation method to lower exposure	Comment
ECHA	Quantitative (*linearised approach*)	BMD10	Interspecies extrapolation based on caloric requirement	Linear extrapolation	ECHA does not specify a tolerable risk
	Qualitative (*large assessment factor approach*)	BMDL10	Not explicit, taken into account in determination of the margin between exposure and starting point	Not applicable	Qualitative method in which the margin between the BMDL10 and the exposure must be >10,000 (general population) or >5,000 (employees)
EFSA	Qualitative	BMDL10	Not explicit, taken into account in determination of the margin between exposure and starting point	Not applicable	Qualitative method in which the margin between the BMDL10 and the exposure must be >10,000
SCOEL	Quantitative	Unknown	Unknown	Linear extrapolation	
US EPA	Quantitative	BMDL1, BMDL5 or BMDL10	Interspecies correction based on caloric requirement	Preferably based on a dose-response relationship. Otherwise via linear extrapolation	EPA does not identify a tolerable risk
AGS	Quantitative	BMD10, lower BMD where possible	Interspecies correction only if supported by data. No correction for intraspecies differences	Preferably based on a dose-response relationship. Otherwise via linear extrapolation	
HSE	None	Not applicable	Not applicable	Not applicable	Risk management according to ALARA principle

Annex **F**

Terminology

BMD analysis

In the BMD method using carcinogenicity data, a dose-response model is applied to fit the tumour incidence observed. The BMD(x) is the dose relating to a predefined increase (x) in tumour incidence. The BMDL corresponds to the 5% lower limit of the BMD confidence interval.

Cancer risk value

A cancer risk value is an exposure level (concentration in the air) consistent with a predefined (by the government) additional risk of developing cancer due to this exposure. The scientific term used by the Health Council of the Netherlands is ‘Health Based Calculated Occupational Cancer Risk Value’ (HBC-OCRV).

Case-control studies

In a case-control study, exposure is estimated for a group of patients (cases) with a certain form of cancer, and compared to a control group without the disease. As no underlying risks are known in patient-control studies, a relative risk cannot simply be calculated. Instead, the ratio is calculated of the odds of cancer occuring in an exposed group to the odds of cancer occuring in a non-exposed group.

Cohort studies

In a cohort study, a group of people (a ‘cohort) exposed to a (potentially) carcinogenic substance, is followed for a long period of

time. The risk of cancer due to exposure can be derived by comparing the occurrence of cancer in this cohort, to the occurrence of cancer in a reference cohort or the general population.

Health-based recommended occupational exposure limit

An health-based recommended occupational exposure limit is a scientifically derived exposure level. For (occupational) exposure equal to or below the health-based recommended occupational exposure limit, no harmful health effects are to be expected.[2]

Individual and aggregate data

Data at the individual level are data that are registered for each individual in the study, and therefore provide the opportunity to correct for confounding variables. For aggregate (combined) data (such as an average or a category), certain characteristics have been lost, which can limit the comparability of different studies.

Individual risk level

The individual risk level is the extra likelyhood during life, that a person will develop cancer due to exposure to a substance. The individual risk level (per year) used in policy is calculated by dividing lifetime risk by human lifespan (in years).

Life table analysis

In life table analysis, an extra risk of developing cancer is calculated based on a relationship between a relative risk or odds ratio and corresponding exposure. Mortality due to other causes, and the age-depedendency of cancer development can be taken into account.

Meta-analysis

Meta-analysis is a quantitative summary of the results of separate studies.

Meta-regression

Meta-regression is a method used in meta-analysis to map the effects of confounding variables on the studied effect.

Occupational exposure limits

Occupational exposure limits are legally defined, maximum permissible (time-weighted average) concentrations of substances in the air at the workplace.

Regression analysis

In regression analysis, the correlation that exists between two variables is used to predict the value of one variable on basis of the other. Linear regression describes the relationship between two

continuous variables as a straight line. Logistic regression analysis is used to study the effects of various factors on a dichotomous outcome.

Starting point

The starting point for a risk estimation is a representative measure for the carcinogenic activity of a substance. If epidemiological data are used, the starting point is an estimate of the relative risk at a specific level of exposure, while for animal studies, the starting point is a dose consistent with a pre-determined increased tumour incidence.

T25

The T25 is the dose associated with a tumour incidence of 25%, corrected for spontaneous tumours and, if necessary, intercurrent mortality.

Health Council of the Netherlands

Advisory Reports

The Health Council's task is to advise ministers and parliament on issues in the field of public health. Most of the advisory opinions that the Council produces every year are prepared at the request of one of the ministers.

In addition, the Health Council issues unsolicited advice that has an 'alerting' function. In some cases, such an alerting report leads to a minister requesting further advice on the subject.

Areas of activity

Optimum healthcare
What is the optimum result of cure and care in view of the risks and opportunities?

Prevention
Which forms of prevention can help realise significant health benefits?

Healthy nutrition
Which foods promote good health and which carry certain health risks?

Environmental health
Which environmental influences could have a positive or negative effect on health?

Healthy working conditions
How can employees be protected against working conditions that could harm their health?

Innovation and the knowledge infrastructure
Before we can harvest knowledge in the field of healthcare, we first need to ensure that the right seeds are sown.

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