National Institute for Public Health
and the Environment
Ministry of Health, Welfare and Sport

Overview of methodologies for the derivation of Occupational Exposure Limits for non-threshold carcinogens in the EU

RIVM Letter report 2014-0153
M.E.J. Pronk

National Institute for Public Health
and the Environment
Ministry of Health, Welfare and Sport

Overview of methodologies for the derivation of Occupational Exposure Limits for non-threshold carcinogens in the EU

RIVM Letter report 2014-0153
M.E.J. Pronk

Colophon

Marja Pronk (Centre for Safety of Substances and Products)

Contact:
Peter Bos
Centre for Safety of Substances and Products
SZWhelpdesk@RIVM.nl

This investigation has been performed by order and for the account of Ministry of Social Affairs and Employment (SZW), within the framework of SZW helpdesk.

This is a publication of:

National Institute for Public Health and the Environment
P.O. Box 1 | 3720 BA Bilthoven
The Netherlands
www.rivm.nl/en

Publiekssamenvatting

Overzicht van Europese methodieken voor grenswaarden voor de werkplek voor niet-drempelwaarde kankerverwekkende stoffen

Werknemers kunnen op hun werkplek blootgesteld worden aan chemische stoffen. Om ervoor te zorgen dat deze blootstelling niet schadelijk is voor de gezondheid, worden zogeheten grenswaarden bepaald. Dit betekent een veilig blootstellingsniveau voor stoffen die mensen op de werkplek kunnen inademen, zodanig dat deze blootstelling, zelfs als deze herhaaldelijk voorkomt gedurende het gehele beroepsleven, niet schadelijke is voor de blootgestelde personen én hun nageslacht.

Voor de groep kankerverwekkende stoffen die directe schade aan het DNA veroorzaakt is echter een andere methodiek nodig dan voor stoffen die een drempel kennen voor het schadelijke effect. Elke blootstelling aan deze zogeheten niet-drempelwaarde kankerverwekkende stoffen, hoe laag ook, brengt namelijk een mogelijk risico met zich mee. Voor deze groep stoffen worden grenswaarden bepaald op basis van een 'risiconiveau': het aantal extra kankergevallen als gevolg van een blootstelling aan een dergelijke stof. Het RIVM heeft geïnventariseerd welke methodieken in de Europese Unie voor dit type stoffen gebruikt worden. De inventarisatie is in opdracht van het ministerie van Sociale Zaken en Werkgelegenheid (SZW) gemaakt vanwege diens wens om de methodieken Europees te harmoniseren.

Er blijken veel overeenkomsten maar ook enkele verschillen te zijn. Een van de overeenkomsten is dat de methodieken op dezelfde uitgangspunten zijn gebaseerd. Zo worden vergelijkbare criteria gebruikt voor de kwaliteit en geschiktheid van de geselecteerde data waarmee de grenswaarden worden bepaald. Ook wordt bij alle methodieken de voorkeur gegeven aan data verkregen uit mensen na blootstelling op de werkplek, boven het gebruik van data uit dierproeven. Hierbij wordt erkend dat deze 'humane data' in veel gevallen niet beschikbaar of ontoereikend zijn.

De voornaamste oorzaak van verschillen in grenswaarden voor deze categorie kankerverwekkende stoffen zijn beleidsmatige keuzes over de hoogte van het risiconiveau. Andere oorzaken zijn de keuze bij dierstudies voor het blootstellingsniveau dat het schadelijk effect veroorzaakt, en factoren zoals de onzekerheidsmarge die wordt gehanteerd bij de vertaalslag van dierproefresultaten naar de mens. Ten slotte zijn overwegingen als sociaal-economische of technisch haalbare van invloed op de uiteindelijke grenswaarden.

Trefwoorden: grenswaarde voor de werkplek, OEL, niet-drempelwaarde kankerverwekkende stoffen

Abstract

Overview of methodologies for the derivation of Occupational Exposure Limits for non-threshold carcinogens in the EU

Workers can be exposed to chemical agents. In order to assure that this exposure will not result in adverse effects on health, occupational exposure limits (OELs) are established. In general this means that a safe level of exposure via the airborne route is set such that this exposure, even when repeated on a regular basis throughout a working life, will not lead to adverse effects on the health of exposed persons and/or their progeny at any time.

For the group of carcinogens which directly damages DNA, a different approach is needed. For these so-called non-threshold carcinogens it is not possible to derive a level of exposure at which no adverse health effects may occur; it must be assumed that any level of exposure, however small, might carry some finite risk. Occupational exposure limits for this type of substances are derived using a 'risk level': the number of additional cases of cancer due to exposure to such substances. The Ministry of Social Affairs and Employment requested the RIVM to make an inventory of the methodologies which are applied in the EU to derive OELs for non-threshold carcinogens.

It was found that there are many similarities, but also some differences. One of the similarities is that the methodologies are based on similar principles. All apply similar general criteria for quality and adequacy of the data selected to derive the limits. All also prefer the use of human data above the use of animal data, but recognize that in most cases these will not be available or will not form a sufficient basis on their own.

Differences observed in occupational exposure limits for non-threshold carcinogens are largely due to differences in cancer risk levels used. Other sources for the differences are the choice for the animal exposure levels which causes the adverse effect, and uncertainty factors applied in the extrapolation from animals to humans. When at a later stage other considerations such as socio-economic or technical feasibility are also taken into account, these may additionally lead to differences in the final occupational exposure limits.

Key words: occupational exposure limit, OEL, non-threshold carcinogen, quantitative risk assessment

Contents

Summary

In order to protect workers against adverse effects on health arising from exposure to chemical agents, occupational exposure limits (OELs) are established. In general this means that a safe level of exposure via the airborne route is set such that this exposure, even when repeated on a regular basis throughout a working life, will not lead to adverse effects on the health of exposed persons and/or their progeny at any time. In establishing OELs, a distinction is made between substances working via a threshold mechanism and via a non-threshold mechanism (e.g. genotoxic carcinogens). For the latter group of substances it is not possible to derive a level of exposure at which no adverse health effects may occur; it must be assumed that any level of exposure, however small, might carry some finite risk.

There is no uniform approach in the EU for the risk assessment of non-threshold carcinogens, nor is there EU legislation setting the 'tolerable' risk level for carcinogens in society. Some organisations/countries apply quantitative, risk-based approaches, whereas others use qualitative approaches. Quantitative approaches generally make use of an extrapolation of cancer risks from high-dose animal studies to the low-dose human situation, whereas qualitative approaches avoid high-to-low dose extrapolation.

The objective of this report is to gain insight in the various methodologies for the derivation of OELs for non-threshold carcinogens in the EU, and to identify similarities and differences. Methods applied or recommended by the EU Scientific Committee on Occupational Exposure Limits (SCOEL) and by the European Chemicals Agency (ECHA) were looked into, as well as methods used in various EU countries.

When looking at the various methods used in the EU for deriving OELs for non-threshold carcinogens at the workplace, all are based on similar toxicological principles and all apply similar general criteria for quality and adequacy of the epidemiological and experimental data. All also prefer the use of human data for risk assessment, but recognize that in most cases these will not be available or will not form a sufficient basis on their own.
When good quality human data are available allowing a quantitative risk assessment, it seems that the choice of point of departure (PoD), dose-response modelling and the low-dose extrapolation (linearly, by default) applied in the various methodologies are quite comparable. When it comes to the use of animal data, all methodologies use linear extrapolation as the default method to estimate the risk at low doses. Differences are however noted in the starting point used (T25 or BMD10 vs. BMDL10) and in the additional factors applied to correct for interspecies differences in toxicokinetics and exposure conditions, although the guidance provided is not always transparent on these latter issues.

In conclusion, the occupational limits proposed by the various organisations and EU countries for non-threshold carcinogens are based on scientific evidence only. Given this and the similarities/differences noted, it seems that when human data are the basis, any differences observed in occupational limits proposed for a certain non-threshold carcinogen would be largely due to differences in the accepted cancer risk levels used in the derivation. When animal data are the basis, differences in starting point and additional factors applied would further contribute to potential differences in proposed limits. When at a later stage other considerations (socio-economic, technical feasibility etc.) are also taken into

account, these may additionally lead to differences in the final occupational limits set for a non-threshold carcinogen at the (inter)national level.

1 Introduction

In order to protect workers against adverse health effects arising from exposure to chemical agents, occupational exposure limits (OELs) are established. In general this means that a safe level of exposure via the airborne route is set in such a way that this exposure, even when repeated on a regular basis throughout a working life, will not lead to adverse effects on the health of exposed persons and/or their progeny at any time. Exposure levels in workplaces must not systematically exceed the OEL, in order to ensure that health is adequately protected.

In establishing OELs, a distinction is made between substances working via a threshold mechanism and via a non-threshold mechanism (e.g. genotoxic carcinogens). For the latter group of substances it is not possible to derive a level of exposure at which no adverse health effects may occur; it must be assumed that any level of exposure, however small, might carry some finite risk. As a consequence, the risk assessment is different for non-threshold substances.

There is no uniform approach in the EU for the risk assessment of non-threshold carcinogens, nor is there EU legislation setting the 'tolerable' risk level for carcinogens in society. Some organisations/countries apply quantitative, risk-based approaches, whereas others use qualitative approaches. Quantitative approaches generally make use of an extrapolation of cancer risks from high-dose animal studies to the low-dose human situation. Qualitative approaches avoid high-to-low dose extrapolation; it is considered to be associated with too many uncertainties, given that the shape of the dose-response relationship at human relevant doses is simply not known. The Margin of Exposure (MoE) approach as applied by for instance the European Food Safety Authority (EFSA) is an example of a qualitative approach. It is based on the application of a wide margin between the lowest carcinogenic effect level in animals and the estimated human exposure level (*i.e.*, the Margin of Exposure (MoE)). Another example is the ALARA (or ALARP) principle (as low as reasonably achievable or practicable) as applied by for instance the UK, although this principle is rather a risk management than a risk assessment tool.

The objective of this report is to gain insight in the various methodologies for the derivation of OELs for non-threshold carcinogens in the EU, and to identify similarities and differences. Methods applied or recommended by the EU Scientific Committee on Occupational Exposure Limits (SCOEL) and by the European Chemicals Agency (ECHA) were looked into, as well as methods used in EU countries. The latter information was derived from a questionnaire sent to experts from institutions across the EU that deal with worker safety, as part of an investigation into the existence of databases containing exposure information on genotoxic carcinogens present at the workplace. In one question the experts were asked if in their country OELs for non-threshold carcinogens were derived. From the responses it appears that Germany, the Netherlands, France and Poland have a methodology in place to set risk-based OELs. Most other countries (among which Austria, Belgium, Denmark, Finland, Norway, Slovakia and Spain) do not set OELs for non-threshold carcinogens themselves, but adopt OELs for these substances as derived by other agencies/committees (like SCOEL, the American Conference of Governmental Industrial Hygienists (ACGIH), etc.). Thus, implicitly, the approach followed by the latter group of countries follows

the assumptions and philosophies from the other agencies/committees where OELs for non-threshold carcinogens are derived. For Austria it is indicated though that there is an intention to establish OELs themselves, using the methodology used in Germany.

In the next section the various methodologies identified are shortly described, with the main characteristics summarized in a table at the end (Table 1).

2 Overview of methodologies for the derivation of Occupational Exposure Limits for non-threshold carcinogens in the EU

2.1 SCOEL

Within the legal framework of Directive 98/24/EC (Chemical Agents Directive, CAD) and Directive 2004/37/EC (on the protection of workers from the risks related to the exposure to carcinogens or mutagens at work, CMD), the Scientific Committee on Occupational Exposure Limits (SCOEL) makes substance-specific Recommendations to be used as the scientific basis for policy discussion at EU level for the development of OELs under CAD/CMD. In doing so, SCOEL distinguishes between substances acting via a threshold and a non-threshold mechanism. Non-threshold genotoxic carcinogens and genotoxic carcinogens for which the existence of a threshold cannot be sufficiently supported at present, belong to the latter category. For these substances, OELs are established following a risk-based approach, if the dataset allows. A series of exposure levels associated with estimated risks (so-called risk-based OELs) are calculated by SCOEL, but SCOEL doesn't give a view on the acceptability of such risks, as that is not within its remit. It is the Commission that, following consultation with pertinent groups (organisations/bodies), sets Binding OELs (BOELs) at levels considered to carry a sufficiently low level of risk. These BOELs are not purely health-based, but also reflect socio-economic and technical feasibility factors.

In establishing OELs, SCOEL follows the work procedure as described in *Methodology for the derivation of occupational exposure limits* (European Commission, 2013). This document, however, does not provide details on how, and using which risk levels, the cancer risk values are calculated. It can only be inferred that all relevant data of good quality (in particular in relation to dose-response information) is taken into account, whether it is from human or animal studies. Human data are preferred over animal data, as are studies conducted by the inhalation route over other routes of exposure. Linear extrapolation is the default method for low-dose risk assessment.

2.2 ECHA

Within the legal framework of Regulation (EC) 1907/2006 on the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), registrants are obliged to demonstrate that the risk arising from the manufacture, import or use of their chemical substance is adequately controlled. The European Chemicals Agency (ECHA) is the agency responsible for the implementation of REACH, and they have published guidance documents explaining the REACH obligations and how to fulfil them. For non-threshold carcinogens it is recommended to derive a so-called Derived Minimal Effect Level (DMEL), if the available data allow. A DMEL is a cancer risk value considered to be of very low concern. The DMEL thus expresses an exposure level corresponding to a low, possibly theoretical, risk. Exposures at the workplace should be controlled to at least this level. The establishment of a reference cancer risk level for the DMEL is not within the remit of ECHA, as this is of societal concern and needs policy guidance. So, in the guidance ECHA only presents examples of cancer risk levels that have been

set and used in different contexts (it is for instance mentioned that 1 x 10^{-5} could be seen as indicative tolerable risk level when setting a DMEL for workers).

The procedure for deriving DMELs is described in the *Guidance on Information requirements and chemical safety assessment – Chapter R.8: Characterisation of dose [concentration]-response for human health* (ECHA, 2012). A DMEL can be derived via two approaches, the 'Linearised' approach and the 'Large Assessment Factor' approach. As the latter approach is not risk-based (it is qualitative, based on the MoE principle as applied by EFSA) it is not further dealt with here.
Using the 'Linearised' approach, different DMEL values can be calculated, representing different lifetime cancer risks, e.g. a risk for cancer in 1 per 100,000 (10^{-5}) or 1 per 1,000,000 (10^{-6}) exposed individuals. DMELs derived via this approach can thus be considered risk-based exposure levels. Both epidemiological and experimental animal data can serve as basis for the calculation of these cancer risk values. Provided of sufficient quality and including adequate exposure data, the use of epidemiological data is preferred (and within that for a meta-analysis or pooled analysis), as this type of data does not involve interspecies extrapolation and has mostly been obtained from relevant (occupational) exposure conditions.
When using human data as basis, the starting point is the quantitative relationship between the exposure to a chemical substance and the relative risk (RR) of cancer (or comparable measure like odds ratio (OR), Standardised Incidence Ratio (SIR), or Standardised Mortality Ratio (SMR)) as obtained by linear modelling (default). The resulting relative risk per unit of exposure (i.e. slope factor) may need to be modified to the correct relative risk, where necessary (e.g. in case data are not from occupational setting, or not from inhalation exposure). Subsequently the (corrected) relative risk of developing cancer is converted to an Excess Lifetime Risk (ELR), either via a 'simple direct method' (ELR = Lifetime Risk * (RR-1)) or (preferably) via a life table approach (no further details provided). Finally, the ELR estimate linked to a known level of exposure is then (linearly) extrapolated to the exposure level corresponding to a risk level societally considered of very low concern, i.e. the DMEL. Where necessary, the DMEL needs to be corrected for quality of database (by application of assessment factors).
With animal data as basis (preferably from studies with the relevant exposure route) the default starting point for calculating the carcinogenic activity of a chemical substance is the T25 (defined as the chronic dose rate that will give rise to tumours in 25% of the animals at a specific tissue site after correction for spontaneous incidence, within the standard life time of that species). Alternatively, the BMD10 (the benchmark-dose representing a 10% tumour response over the background upon lifetime exposure) can be used, when data are adequate for modelling. When exposure duration and/or observation period in the study deviate from the standard lifespan of the tested animal species, the starting point needs to be corrected. Subsequently, the starting point has to be converted into a human equivalent lifetime daily dose ('humanT25' or 'humanBMD10') by correcting it for potential differences between experimental animals and the target population in route, absorption, exposure conditions and respiratory volume, and by application of an assessment factor for allometric scaling. Standard values used for exposure at the workplace are 40 years exposure, 8 hours/day, 5 days/week, 48 weeks/year at an inhalation rate of 10 m^3 per 8-hour working day, as opposed to lifetime exposure for 75 years, 24 hours/day, 7 days/week, 52 weeks/year at an inhalation rate of 20 m^3 per 24 hours. In a final step, the human equivalent lifetime daily dose is to be extrapolated to an exposure level corresponding to a risk level societally

considered of very low concern. The default method is linear extrapolation (unless the data suggest that to be inappropriate), and the high-to-low-dose factor is 25,000 (with T25 as starting point, or 10,000 in case of BMD10) when for instance a DMEL representing a 10^{-5} risk is calculated.

2.3 Germany

Within the framework of the German Hazardous Substances Ordinance, the Committee on Hazardous Substances (AGS) advises the Federal Ministry of Labour and Social Affairs on limit values at the workplace. For carcinogenic hazardous substances, a risk-related concept is in place that is laid down in Technical Rule 910 (AGS, 2014). In this risk-related concept (also known as the traffic light model), three risk areas are defined based on two, socio-politically established risk levels (referring to a working lifetime of 40 years). The first risk level is the acceptable risk, i.e. a risk level that is generally accepted. The acceptable risk ('Akzeptanzrisiko') is 4:10,000, but is intended to be reduced to 4:100,000 in 2018 at the latest. The second risk level is the tolerable risk ('Toleranzrisiko'), which is 4:1,000.
For workplace exposures in the green/low risk area (area below the acceptable risk), the risk is considered acceptable and the need to carry out additional measures is low, but General Protective Measures like Basic Hygiene Measures have to be in fulfilled in any way. For exposures in the yellow/medium risk area (area in between the acceptable and tolerable risk), the risk involved is assessed as undesirable, and only tolerable if accompanied by further measures for risk reduction and control. The need for additional measures increases considerably as the exposure approaches the tolerable risk level. For exposures in the red/high risk area (area above the tolerable risk), the risk is not acceptable (intolerable) and there is a direct necessity for additional measures in order to return at least to the medium risk area.
The methodology for deriving substance-specific exposure-risk relationships and risk concentrations is described in the comprehensive *Guide for the quantification of substance-specific exposure-risk relationships and risk concentrations after exposure to carcinogenic hazardous substances at the workplace* (Annex 3 to TRGS 910; AGS, 2014) and is briefly described below. A comparison between the exposure level at the workplace and the derived substance-specific cancer risk values determines the necessity and urgency of protective measures according to a graduated concept, with the measures to be taken divided into five groups (substitution, technical measures, organizational measures, respiratory protection and administrative measures).

The methodology starts with the derivation of an exposure-risk relationship (ERR) for a carcinogenic substance, i.e. the relation between the substance concentration (inhalation) and the statistical probability of developing cancer. This ERR can be derived from experimental or epidemiological studies and forms the basis for the extrapolation in the area of low risks, which generally cannot be proven in practice by animal experiments or observed epidemiologically. Because of their direct relationship to humans, data from epidemiological studies or human studies are considered of special relevance, but minimum quality criteria are in place before they can be used in the risk derivation. When satisfying, relative measures such as SMR, SIR, RR or OR will generally be used as point of departure (POD), with preference for measures relating to cancer incidence over those to cancer mortality. Following regression analysis, correlating the relative measure with the cumulative exposure value, the risk per unit increase of exposure can be calculated. Subsequently the excess risk can be obtained by the life table method (no further details given) or by multiplying the

relative risk increase to an estimated value for the lifetime risk of the reference group, after subtraction of the risk of the non-exposed persons (e.g. general population).
The POD for animal data is the BMD10 (if the data are of sufficient quality for modelling), otherwise the T25. Use of the BMDL10 (the lower 95% confidence dose of a benchmark-dose representing a 10% tumour response over the background upon lifetime exposure) is not advocated. The POD is to be corrected in case of shorter exposure period as compared to the experimental period, and in case of shorter experimental period as compared to the standard lifespan of the tested animal species. Subsequently, the POD is to be converted into a human equivalent lifetime daily dose (e.g. hT25) by correcting it for potential differences between experimental animals and the target population in route, absorption, exposure conditions and respiratory volume, and by application of an assessment factor for allometric scaling (not in case of inhalation study). Standard assumptions for occupational exposure are 40 years exposure, 8 hours/day, 5 days/week, 48 weeks/year at an inhalation rate of 10 m^3/8 hours for a 70 kg person, as opposed to lifetime exposure for 75 years, 24 hours/day, 7 days/week, 52 weeks/year at an inhalation rate of 20 m^3/24 hours for a 70 kg person.
The final step in the methodology is extrapolation to lower risk levels (intraspecies extrapolation is not carried out). For direct genotoxic carcinogens and for carcinogens with unknown mode of action, the default method is linear extrapolation, unless there is evidence supporting non-linearity. In this way a tolerable and an acceptable concentration for the inhalation route are calculated (expressed as ppm or mg/m^3), the first in accordance with a risk of 4 extra cancer cases per 1,000 over the entire work life, the second in accordance with a risk of 4 extra cancer cases per 10,000 (or 100,000) over the entire work life.

2.4 The Netherlands

In the Netherlands, OELs for non-threshold carcinogens are set using a three-step procedure. At the request of the Minister of Social Affairs and Employment, the Dutch Expert Committee on Occupational Safety (DECOS), a committee of the Health Council of the Netherlands, derives in the first step so-called health-based calculated occupational cancer risk values (HBC-OCRVs). HBC-OCRVs are exposure levels corresponding to an extra risk of cancer that is predefined by the government. Two general reference risk levels have been defined in the Netherlands: a target risk level of 4 x 10^{-5} (4 additional cases per 100,000) for 40 years of occupational exposure, and a prohibitive risk level of 4 x 10^{-3} (4 additional cases per 1,000) for 40 years of occupational exposure. The procedure for deriving HBC-OCRVs, which constitute the scientific basis for determining OELs, is laid down in the *Guideline for the calculation of occupational cancer risk values* (Health Council, 2012) and shortly described below. In the second step, the OEL Subcommittee of the Social and Economic Council (SER) considers the technical feasibility of using the HBC-OCRVs as regulatory occupational exposure limits, involving branch organisations and the major employer and employee organisations in their advice to the Minister of Social Affairs and Employment. In the final step of the procedure, the Minister sets a new legally binding OEL. In practice, the established OELs vary between exposure levels corresponding to the target risk level and the prohibitive risk level. In terms of risk management, the prohibitive risk level implies that this level may not be exceeded whereas below the level of exposure corresponding to the target risk level, no additional protective measures need to be taken.

HBC-OCRVs are derived for non-threshold carcinogens, i.e. for stochastic genotoxic carcinogens (compounds directly interacting with DNA, causing damage) and for genotoxic carcinogens for which the mechanism of action is unknown, but for which a stochastic mechanism is not unlikely. Both epidemiological and experimental animal data can serve as basis for the calculation of these cancer risk values, depending on their suitability and quality, and provided the dose-response has been quantified. The use of epidemiological data is preferred (and within that a combined analysis of various studies over a single study, and the use of incidence statistics over mortality statistics), as this type of data does not involve the uncertainties associated with biological differences between animals and humans, and the exposure conditions in epidemiological studies, in contrast to those in animal studies, are generally representative for the exposures in current occupational settings.
Starting point for the derivation of an excess lifetime risk based on epidemiological data is the quantitative relationship (in the form of a linear regression model or a more complex parametric function) between the exposure to a compound and the RR (or other metric like OR, SIR or SMR). This relative risk is subsequently converted to an extra lifetime risk of cancer by the use of life tables (thereby adhering to an extended age of 100 years). Ultimately, this results in a cumulative exposure level corresponding to a specific extra risk, based on a working period of 40 years. The cancer risk values (HBC-OCRVs) are calculated at the level of cumulative, inhalatory exposure (expressed as mg/m^3) for which the risk of extra cancer cases is 4×10^{-3} (prohibitive risk level) and 4×10^{-5} (target risk level).
When using animal data as basis (preferably from studies with exposure via inhalation), the starting point for calculating the carcinogenic activity of a compound is (by preference) the BMD belonging to a 10% increased incidence over the background for a certain (malignant) tumour (= BMR10). Alternatively, a representative point estimate can be used (generally the lowest level of exposure for which a statistically significant and/or biologically relevant tumour incidence is observed). Where necessary, the starting point is converted to continuous exposure and corrected for differences in exposure time and duration of the experiment versus the standard life expectancy for the animal species in question. The resulting carcinogenic activity in animals is subsequently converted into an additional life-time cancer risk per mg/m^3 under human, occupational exposure conditions, and cancer risk values (HBC-OCRVs) are calculated at risk levels of 4×10^{-3} and 4×10^{-5} using linear extrapolation as a default method (unless scientific data would indicate that using this model is not appropriate). Standard values used for exposure at the workplace are 40 years exposure, 8 hours/day, 5 days/week, 48 weeks/year at an inhalation rate of 10 m^3 per 8-hour working day, as opposed to lifetime exposure for 75 years, 24 hours/day, 7 days/week, 52 weeks/year at an inhalation rate of 18 m^3 per 24 hours.

2.5 France

Mandated by the Ministry of Labour, the French OEL Committee (CES VLEP) of the Agency for Food, Environmental and Occupational Health & Safety (ANSES) develops OELs on the basis of scientific data from human studies (epidemiological and clinical studies) or experimental animal studies (toxicological studies). The procedure for deriving OELs is described in the *Expert appraisal on recommending occupational exposure limits for chemical agents - Reference Document for the derivation and the measurement of exposure limit values for chemical agents in the workplace (OELs)* (ANSES,

2014), in which reference is made to a methodological report (in French) describing the derivation of toxicity reference values for carcinogenic substances (AFSSET, 2010).

For non-threshold substances, the OEL Committee does not consider the method of applying adjustment factors to a reference dose (as is used for threshold substances) to be suitable for establishing an OEL. For each substance considered to act through a non-threshold mechanism, the OEL Committee studies the different quantifications of risk published in scientific literature. The different extrapolation models used are discussed and the Committee decides on the most coherent and reliable model to adopt for quantitative risk assessment. Data permitting, and when no published risk assessment is deemed satisfactory for defining the OEL of a substance, the OEL Committee can decide to carry out its own risk assessment following its methodology. In this methodology, good quality human data with well-characterised exposures is given preference over good quality animal data. Excess lifetime risks based on epidemiological data are calculated using the quantitative relationship between the RR (or other metric like OR, SIR or SMR) and the exposure (average or cumulated over the exposure period). The resulting relative risk per unit of exposure is converted to an ELR, either via a simplified, linear approach (ELR = RR*P-P, where P is the probability of a disease during lifetime in the non-exposed target population) or via a life table approach (no further details given).
For animal data the preferred starting point for the calculation of excess lifetime risk is the BMDL10, where necessary corrected for non-continuous exposure and allometric scaling. The use of the T25 is discouraged. Extrapolating the BMDL10 to the origin and accounting for differences in the experimental and human exposure situation (often 40 years, 8 hours/day, 5 days/week, 48 weeks/year), a slope factor is derived, i.e. the excess lifetime cancer risk per unit of exposure ($\mu g/m^3$ or mg/m^3).
Based on the ELR derived (either from human or from animal data), cancer risk values are calculated for three different risk levels, i.e. 10^{-4}, 10^{-5} and 10^{-6} (presumably for 40 years of exposure, but not clearly stated), using linear extrapolation as a default method. Getting these three so-called individual excess risk (IER) values presented by the OEL Committee, it is then the responsibility of risk managers to establish an acceptable risk level.

2.6 Poland

In Poland, it is the Interdepartmental Commission for Maximum Allowable Concentrations and Intensities for Harmful to Health Agents in the Working Environment that proposes MACs (Maximum Admissible Concentrations) for occupational exposure to chemical compounds to the Minister of Labour and Social Policy. For carcinogenic agents, the Commission has adopted the socially accepted risk at the level of 10^{-3} to 10^{-4}. Risk connected with the presence of a carcinogenic agent in workplace air is assessed as high, even if the exposure is lower than the MAC.

The principles of determining OELs for carcinogens in Poland are presented in a paper by Skowrón and Czerczak (2013). This paper is in Polish, with only a short abstract in English. Some further clarification was provided by one of the authors (personal communication S. Czerczak). It is indicated that in order to assess the health risk for carcinogens, it is necessary to determine the probability of developing a disease or death from cancer as a result of occupational exposure to the carcinogenic substance. It can be inferred from the

paper that both experimental human and animals studies can serve as basis for the MAC determination, with a preference for human data when of good quality and providing dose-response information. Quantitative dose-response information is necessary to derive the relative risk per unit of exposure (the slope factor, or unit risk), generally from animal data and as published by US EPA. In calculating the extra cancer risk per unit of air concentration, standard values used for exposure at the workplace are 40 years exposure, 8 hours/day, 240 days/year, at an inhalation rate of 20 m^3 for a 70 kg person doing heavy duty labor. Linear extrapolation is the standard method used for extrapolation to low doses. MAC-values are calculated, corresponding to socially accepted risk levels of 10^{-3} (one additional cancer case per 1,000) to 10^{-4} (one additional cancer case per 10,000). These risk levels relate to a working life of 40 years.

Table 1 Summary of methodologies for the derivation of Occupational Exposure Limits (OELs) for non-threshold carcinogens in the EU

Country/ Organisation	Limit (i.e. cancer risk value) proposed	Basis	Preferred starting point for exposure-risk relationship	Correction for interspecies differences	Correction for exposure-related issues	Default extrapolation method to lifetime/lower exposures	Cancer risk level specified
EU – SCOEL	Risk-based Occupational Exposure Level (risk-based OEL)	Epidemiological or Experimental animal data	Not stated	Not stated	Not stated	Linear extrapolation	No
EU – ECHA	Derived Minimal Effect Level (DMEL)	Epidemiological or Experimental animal data	RR (or OR, SIR, SMR) T25, or BMD10	No Allometric scaling (only for non-inhalation study)	Where necessary accounted for r-t-r extrapolation and for differences in: - absorption - experimental exposure conditions vs lifetime occupational conditions - rest vs light activity	Linear extrapolation	No (but examples presented)
DE – BAuA (AGS)	Acceptable concentration and Tolerable concentration	Epidemiological or Experimental animal data	RR (or OR, SIR, SMR) BMD10, or T25	No Allometric scaling (only for non-inhalation study)	Where necessary accounted for r-t-r extrapolation and for differences in: - absorption - experimental exposure conditions vs lifetime occupational conditions - rest vs light activity	Linear extrapolation	Acceptable risk: 4×10^{-4} (interim level) 4×10^{-5} (at the latest from 2018) Tolerable risk: 4×10^{-3} Both levels of risk refer to a working lifetime of 40 years

Country/ Organisation	Limit (i.e. cancer risk value) proposed	Basis	Preferred starting point for exposure-risk relationship	Correction for interspecies differences	Correction for exposure-related issues	Default extrapolation method to lifetime/lower exposures	Cancer risk level specified
NL – Health Council of the Netherlands (DECOS)	Health-based calculated occupational reference values (HBC-OCRV)	Epidemiological or Experimental animal data	RR (or OR, SIR, SMR) BMD10	Not stated	Where necessary accounted for differences in experimental exposure conditions vs lifetime occupational conditions	Linear extrapolation	Target risk: 4×10^{-5} for 40 years of occupational exposure Prohibitive risk: 4×10^{-3} for 40 years of occupational exposure
FR – ANSES (CES VLEP)	Individual excess risk (IER)	Epidemiological or Experimental animal data	RR (or OR, SIR, SMR) BMDL10	No Allometric scaling (only for non-inhalation study)	Where necessary accounted for differences in experimental exposure conditions vs lifetime occupational conditions	Linear extrapolation	No (IERs calculated relate to 10^{-4}, 10^{-5} and 10^{-6} risk, presumably per working life but not clearly stated)
PL – Interdepartm. MAC Commission	Maximum admissible concentration (MAC)	Epidemiological or Experimental animal data	Not stated	Not stated	Where necessary accounted for differences in experimental exposure conditions vs lifetime occupational conditions	Linear extrapolation	10^{-3} to 10^{-4} for 40 years of occupational exposure

3 Comparison

When looking at the various methods used in the EU for derivation of risk-based values or OELs for non-threshold carcinogens at the workplace, all are based on similar toxicological principles and all apply similar general criteria for quality and adequacy of the epidemiological and experimental data. All also prefer the use of human data for risk assessment, but recognize that in most cases these will not be available or will not form a sufficient basis on their own. For most methods described, the guidance provided for the use of animal data is therefore more extensive than for the use of human data. The key documentation of SCOEL does not provide details at all on how cancer risk values are calculated, complicating the comparison between the SCOEL methodology and those of others.

When good quality human data are available allowing a quantitative risk assessment, it seems that the starting point, dose-response modelling and the low-dose extrapolation (linearly, by default) applied in the various methodologies is quite comparable. When it comes to the use of animal data, all methodologies use linear extrapolation as the default method to estimate the risk at low doses. Differences are however noted in the starting point used and in the corrections applied for interspecies differences in toxicokinetics and exposure conditions, although the guidance provided is not always transparent on these latter issues. With respect to the starting point, ECHA and Germany for instance recommend the use of the T25 or BMD10 (with a preference for the latter if the data allow modelling), but not the BMDL10 (as is used by France). They consider it appropriate to use these central tendency estimates rather than the more conservative lower bound level, because there is already conservatism built in the assumption of linearity below the BMD10/T25 dose range. France on the other hand advises against the use of T25, as it is considered a rather rough estimate, at a level where linearity of dose-response is considered doubtful. In view of better taking into account uncertainties in the experimental protocol, France prefers the use of the lower bound over the central tendency of the BMD.

4 Conclusions

The health-based occupational limits proposed by the various organisations/countries for non-threshold substances are based on scientific evidence only. Given this and the similarities/differences noted above, it seems that when human data are the basis, any differences observed in occupational limits proposed for a certain non-threshold carcinogen would be largely due to different cancer risk levels used in the derivation. When animal data are the basis, differences in starting point and corrections applied would further contribute to potential differences in proposed limits, to a more or less degree.

However, occupational limits are not only based on scientific considerations. When at a later stage other considerations (socio-economic, technical feasibility etc.) are also taken into account, this may additionally lead to differences in the final occupational limits set for a non-threshold carcinogen at the (inter)national level. Information on how the respective member states deal with these factors and how these considerations finally may affect an OEL is not available. This information is important for an adequate comparison of published occupational exposure limits for non-threshold carcinogens.

Finally, an issue that was beyond the scope of the present report but that should be mentioned here is the choice of the critical study (either human or animal). Different committees may choose for different studies to deliver the starting point for the calculations, which may also contribute to differences in the final occupational limits.

References

AFSSET (2010). Méthode de construction de Valeurs toxicologiques de référence (VTR) pour les substances chimiques cancérogènes. Rapport d'expertise collective. Saisine n°2004/AS16. Mars 2010. Agence française de sécurité sanitaire de l'environnement et du travail, Maisons-Alfort Cedex.

AGS (2014). Technical Rules for Hazardous Substances (TRGS) 910 – Risk-related concept of measures for activities involving carcinogenic hazardous substances. February 2014. Ausschuss für Gefahrstoffe, Bundesanstalt für Arbeitsschutz und Arbeitsmedizin (BAuA), Dortmund, GMBl 2014 p. 258-270 [No. 12].

ANSES (2014). Expert appraisal on recommending occupational exposure limits for chemical agents – Reference Document for the derivation and the measurement of exposure limit values for chemical agents in the workplace (OELs). Collective expert appraisal. Request n°2009-SA-0339. Report of October 10, 2013, as modified on January 8, 2014. Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail, Maisons-Alfort Cedex.

ECHA (2012). Guidance on information requirements and chemical safety assessment. Chapter R.8: Characterisation of dose [concentration]-response for human health. Version 2.1, November 2012. European Chemicals Agency, Helsinki.

European Commission (2013). Methodology for the Derivation of Occupational Exposure Limits. Scientific Committee on Occupational Exposure Limits (SCOEL). Key Documentation (version 7), June 2013. European Commission – Employment, Social Affairs and Inclusion, Brussels.

Health Council (2012). Guideline for the calculation of risk values for carcinogenic compounds. Publication no. 2012/16E, October 2012. Health Council of the Netherlands, The Hague.

Personal Communication S. Czerczak, September 2, 2014.

Skowrón, J. and Czerczak, S. (2013). Zasady ustalania dopuszczalnych poziomów narażenia dla czynników rakotwórczych w środowisku pracy w Polsce i w krajach Unii Europejskiej [Principles for establishing occupational exposure limits for carcinogens in Poland and other EU countries]. Medycyna Pracy 64(4):541–563.

RIVM
Committed to *health and sustainability*