General remarks

Health-based Reassessment of Administrative Occupational Exposure Limits

Committee on Updating of Occupational Exposure Limits,
a committee of the Health Council of the Netherlands

No. 2000/15OSH/000, The Hague, 14 December 2000

Chapter 1

General introduction

1.1 Background of the project

In September 1995, TNO Nutrition and Food Research Institute (Zeist, the Netherlands) reported the Minister of Social Affairs and Employment about the degree of health protection of the administrative occupational exposure limits (OELs) in the list of Maximal Accepted Concentrations (MAC) of 1994. The major part of these OELs were adopted from the American Conference of Governmental Industrial Hygienists' list of Threshold Limit Values in the 1970s. For the purpose of the evaluation concise toxicity profiles were prepared based on the documentation of the ACGIH and European criteria documents on almost 300 substances. TNO concluded that for 109 substances the current OEL was suspected to be too high from a health protection point of view, with deviations ranging from a factor of 2 to 250. For another 106 substances the toxicological data base was judged to be too poor to recommend a health-based OEL.

On September 24, 1996 the State Secretary of Social Affairs and Employment presented a plan to re-evaluate the administrative OELs to the Social and Economic Council. After the Social and Economic Council had given a positive reaction the State Secretary requested the Health Council on April 16, 1997, to re-evaluate these substances in a condensed procedure and to recommend health-based OELs. Given the international character of the request and in view

of the European harmonization, the State Secretary requested the Health Council to invite scientists from outside the Netherlands to participate in the project.

1.2 Setting OELs in the Netherlands

In the Netherlands the legally-binding occupational exposure limits for chemical substances are set using a three-step procedure. In the first step a scientific evaluation of the data on the toxicity of the substance is made by the Dutch Expert Committee on Occupational Standards (DECOS), a committee of the Health Council, on request of the State Secretary of Social Affairs and Employment. This evaluation should lead to a health-based recommended occupational exposure limit for the concentration of the substance in workroom air.*

In the next phase of the three-step procedure the Social and Economic Council advises the State Secretary on the feasibility of using the health-based value as a legally-binding OEL, or recommends a different OEL. In the final step of the procedure the State Secretary sets the regulatory OEL.

The three-step procedure will also be followed for health-based OELs derived in the present re-evaluation project.

1.3 Committee

As a first step the Health Council requested several regulatory authorities of European countries to nominate internationally acknowledged experts in toxicology, epidemiology or occupational medicine with experience in setting OELs. All nominees were requested to send a brief curriculum vitae and a list of publications. The committee was selected from the list of nominees using the following criteria: one member from each foreign country, the expertise within the committee should cover all aspects of hazard assessment of chemical substances, and good spread in (former) affiliation of the members (academia, national institutes and industry). All members were invited on a personal title, except for the corresponding member representing ACGIH. The members of the Committee on Updating of occupational exposure limits are listed in Chapter 2.

* For genotoxic carcinogens DECOS does not derive an OEL but presents an exposure-response relationship.

1.4 Procedure

Under the authority of the Ministry of Social Affairs and Employment, for each substance a short document is prepared by a toxicologist at a research institute in the Netherlands. The requirements for the contents of these short documents were established by the committee during a trial phase*. The documents should be based on a full literature search including at least the data bases Medline, Toxline and Chemical Abstracts. From the published literature a key study is identified serving as the basis for deriving a health-based OEL. For extrapolation of the data (from the key study) to the occupational exposure situation an overall assessment factor is applied covering the aspects inter- and intraspecies variation, differences in duration and pattern of exposure between the key study and the situation of the worker, type of the critical effect, dose-effect relationship and quality of the total data base. In deriving the overall assessment factor the committee uses a check list of the different aspects, adopted from a TNO-report, to discuss and thoroughly weigh all available data. In each case the committee considers the appropriateness of applying default values, see Chapter 3. In case the key study refers to an oral animal experiment, scaling to humans is based on caloric demand (body weight to the power 0.75) rather than on body weight. For the recommendation of a health-based OEL the committee decided to make use of the preferred value system** given the inherent uncertainty of any OEL.

To derive a health-based OEL for a substance at least data on acute toxicity, including irritation (and sensitization), and on repeated-dose toxicity are required. The committee considers as a minimum the availability of a multi-dose study in which a relevant animal species was exposed via a relevant exposure route for a relevant exposure time and in which relevant toxicological endpoints were studied (preferably including body weight gain, haematology, clinical biochemistry, gross and microscopic pathology). Preferably the study provides information about the target organ and critical effect, and produces a no observed adverse effect level.

---

* The aims of this phase were to determine the requirements for the documents, to develop and test the procedure, and to judge the feasibility of the project. The fourteen substances under consideration during this phase were selected by the Ministry of Social Affairs and Employment in consultation with regulatory authorities in the participating countries.

** The preferred value system implies that OELs are rounded up or down to ‘preferred values’, e.g. 0.1, 0.2, 0.5, 1, 2, 5, 10 mg/m^3 etc.

In case the data base is insufficient to recommend a health-based OEL the committee will strive to judge in a semi-quantitative way whether or not the current administrative limit is health-protective.

Carcinogenic substances are not taken into consideration by the committee. When the data base of a substance indicates carcinogenic and/or genotoxic potential, the committee recommends an evaluation and classification of the substance by DECOS. For substances tested for and proven to be toxic to fertility or development, the committee ascertains that the recommended health-based OEL protects against these effects as well. For quite a number of substances, however, these data were not available.

A draft of each document was released for public review during a period of six weeks and comments received were taken into account in the final version of the document.

The Hague, 14 December 2000,
for the committee

dr CA Bouwman, scientific secretary	prof. dr J Noordhoek chairman

Chapter 2

The committee

- J Noordhoek, *chairman* †
  professor of toxicology; University of Nijmegen, Nijmegen, The Netherlands
- A Aitio
  senior scientist; International Programme on Chemical Safety, World Health Organization, Switzerland
- PL Chambers †
  co-ordinator toxicology studies; University of Dublin, Ireland
- VJ Feron
  professor of toxicology; TNO Nutrition and Food Research Institute, Zeist, The Netherlands
- H Greim
  professor of toxicology; GSF National Research Center for Environment and Health, Oberschleissheim, Germany
- U Hass
  senior researcher in toxicology; Institute of Food Safety and Toxicology; Søborg, Denmark
- CJ Högberg
  professor of toxicology; National Institute for Working Life and Karolinska Institutet, Stockholm, Sweden

- G De Mik
  toxicologist; National Institute of Public Health and the Environment, Bilthoven, The Netherlands
- A Moses
  consultant toxicologist; Cheshire, United Kingdom
- W Seinen
  professor of toxicology; Utrecht University, Utrecht, The Netherlands
- GMH Swaen
  epidemiologist; University of Maastricht, Maastricht, The Netherlands
- WMD Wagner, *corresponding member*
  American Conference of Governmental Industrial Hygienists, Cincinnati, Ohio, USA
- RD Zumwalde
  senior scientist; National Institute for Occupational Safety and Health, Cincinnati, Ohio, USA
- LCMP Hontelez, *advisor*
  Ministry of Social Affairs and Employment, The Hague, The Netherlands
- WF Passchier, *observer*
  Health Council of the Netherlands, The Hague, The Netherlands
- CA Bouwman, *scientific secretary*
  Health Council of the Netherlands, The Hague, The Netherlands

Chapter 3

Default values

Adopted from the report ‘Methods for establishment of Health-based Recommended Occupational Exposure Limits for existing substances’, V96.463, 4 July 1996, by TNO Nutrition and Food Research Institute, Zeist, the Netherlands (see also De Raat *et al*, Reg. Toxiol. Pharmacol. 25, 1997: 204-210).

aspects	default value
interspecies differences	3
intraspecies differences	3
differences between experimental conditions and exposure pattern of the worker	1-10
type of critical effect	1
dose-response curve	1
confidence of the data base	1

Chapter **4**

Abbreviations

Organisations and occupational exposure limits

ACGIH	American Conference of Governmental Industrial Hygienists
DECOS	Dutch Expert Committee on Occupational Standards
DFG	Deutsche Forschungsgemeinschaft
EPA	Environmental Protection Agency (USA)
FDA	Food and Drug Administration (USA)
HBR-OEL	health based recommended occupational exposure limit
HSE	Health and Safety Executive (UK)
IARC	International Agency for Research on Cancer (WHO)
IPCS	International Programme for Chemical Safety
MAC	maximaal aanvaarde concentratie (maximal accepted concentration)
MAK	Maximale Arbeitsplatz Konzentration
MEL	maximum exposure limit
NIOSH	National Institute for Occupational Safety and Health (USA)
NTP	National Toxicology Programme (USA)
OECD	Organisation for Economic Cooperation and Development
OEL	occupational exposure limit
OES	occupational exposure standard
OSHA	Occupational Safety and Health Association (USA)
PEL	permissible exposure limit
REL	recommended exposure limit
RTECS	Registry of Toxic Effects of Chemical Substances
SCOEL	Scientific Committee for Occupational Exposure Limits
SER	Social and Economic Council (Sociaal-Economische Raad NL)
STEL	short term exposure limit
TLV	threshold limit value
TWA	time weighted average
WHO	World Health Organisation

Toxicological terms

BALF	bronchio-alveolar lavage fluid
bw	body weight
CNS	central nervous system
EC_{50}	concentration at which a described effect is found in 50% of the exposed animals or at which the effect is decreased up to 50% of the control value
FCA	Freunds Complete Adjuvans
FEV	forced expiratory volume
FVC	forced vital capacity
GD	gestation day(s)
GPMT	guinea pig maximisation test
GSH	glutathione
h	hour
IC_{50}	concentration at which inhibition of a certain function is found up to 50% of the control value
im	intramuscular
ip	intraperitoneal
it	intratracheal
iv	intravenous
LC_{50}	lethal concentration for 50% of the exposed animals
LC_{lo}	lowest lethal concentration
LD_{50}	lethal dose for 50% of the exposed animals
LD_{lo}	lowest lethal dose
LDH	lactate dehydrogenase
LOAEL	lowest observed adverse effect level
MAlvC	minimal alveolar concentration
MFO	mixed function oxidase
MMAD	mass median aerodynamic diameter
MOAEL	minimal observed adverse effect level
NOAEL	no observed adverse effect level
n	number
ppb	parts per billion (v/v)10^{-9}
ppm	parts per million (v/v)10^{-6}
PNS	peripheral nervous system
po	*per os* (= oral)
RBC	red blood cells
RD_{50}	concentration at which a 50% decrease of respiratory rate is observed
SCE	sister chromatid exchange
sc	subcutaneous
UDS	unscheduled DNA-synthesis
V_{max}	maximal reaction velocity of an enzyme
w	week

Statistical terms

CL	confidence limits
GM	geometric mean
OR	odds ratio
RR	relative risk
SD	standard deviation
SEM	standard error of mean
SMR	standard mortality ratio

Analytical methods

BEI	biological exposure index
GC	gas chromatography
HPLC	high performance liquid chromatography
MS	mass spectrometry
NMR	nuclear magnetic resonance
PAS	personal air sampling
TLC	thin layer chromatography