SETTING OCCUPATIONAL EXPOSURE LIMITS

Practices and outcomes of toxicological risk assessment

Linda Schenk
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This compilation thesis consists of an introduction and the following papers:

I Schenk L., Hansson S.O., Rudén C., Gilek M. (2008) Occupational exposure limits: A comparative study. *Regul Toxicol Pharmacol* 50:261-270
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II Schenk L., Hansson S.O., Rudén C., Gilek M. (2008) Are occupational exposure limits becoming more alike within the European Union? *J Appl Toxicol* 28:858-866
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III Schenk L. (2010) Comparison of data used for setting occupational exposure limits. *Int J Occup Environ Health* 16:249-262
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IV Schenk L. and Johanson G. (2010) Use of uncertainty factors by the SCOEL in their derivation of health-based occupational exposure limits. *Crit Rev Toxicol* 40:791-798
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V Schenk L. and Johanson G. (2010) A quantitative comparison of the safety margins in the European indicative occupational exposure limits and the derived no-effect levels under REACH. *Submitted manuscript*

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ABSTRACT

Occupational Exposure Limits (OELs) are used as an important regulatory instrument to protect workers' health from adverse effects of chemical exposures. The main objective of this thesis is to study risk assessment practices in the setting of OEL in order to produce knowledge that will help improve the consistency and transparency of OELs.

For the purpose of **paper I** a database of OELs for a total of 1341 substances was compiled. Of these, only 25 substances have OELs from all 18 included organisations while more than one third of the substances are only regulated by one organisation alone. The average level of OELs differs substantially between organisations; the US OSHA exposure limits are (on average) nearly 40 % higher than those of Poland.

In **paper II** six EU member states' OELs are compared to the European Commission's OELs. Also within Europe there is a large difference concerning the average level of OELs (35%). The average level of lists tends to decrease over time, although there are exceptions to this. There are also indications that the exposure limits of EU member states are converging towards the European Commission's OELs.

The work presented in **paper III** identifies steps in the risk assessment that could account for the large differences in OELs for 14 different substances. Differences in the identification of the critical effect could explain the different level of the OELs for half of the substances. But the age of the data review could not account for all the differences in data selection, only one fifth of the documents referred to all available key studies. Also the evaluation of the key studies varied significantly.

The aim of **paper IV** was to investigate how the Scientific Committee on Occupational Exposure Limits (SCOEL) of the European Commission uses assessment factors when proposing health-based indicative OELs. For only one third of the investigated OELs were explicit assessment factors given. On average the safety margin of the recommendations was 2.1 higher when an explicit assessment factor had been used. It is recommended that the SCOEL develop and adhere to a more articulate framework on the use of assessment factors.

Paper V focuses on the Derived No-Effect Levels (DNELs) which are to be calculated under the new European Union REACH legislation. It is a comparison of the safety margins of 88 SCOEL recommendations with those of the corresponding worker-DNELs, derived according to the default approach as described in the REACH guidance document. Overall, the REACH safety margins were approximately six times higher than those derived from the SCOEL documentations but varied widely with REACH/SCOEL safety margin ratios ranging by two orders of magnitude, from 0.3 to 58.

Keywords: Assessment Factor, DNEL, European Union, Occupational Exposure Limit, REACH, Risk Assessment, Regulatory Toxicology, SCOEL, Uncertainty Factor

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ABBREVIATIONS

ACGIH	American Conference of Governmental Industrial Hygienists
ADME	Absorption, Distribution, Metabolism and Excretion
AEGL	Acute Exposure Guidance Level
ANOVA	Analysis of Variance
BMD	Benchmark Dose
CAS	Chemical Abstracts Service
DECOS	Dutch Expert Committee on Occupational Safety
DFG	Deutsche Forschungsgemeinschaft (German Research Foundation)
DMEL	Derived Minimal Effect Level
DNEL	Derived No-Effect Level
EC	European Commission
ECETOC	European Centre for Ecotoxicology and Toxicology of Chemicals
ERPG	Emergency Response Planning Guidelines
EU	European Union
EUF	Explicit Uncertainty Factor
ISM	Implicit Safety Margin
JSOH	Japan Society of Occupational Health
LOAEL	Lowest Observed (Observable) Adverse Effect Level
MAK	Maximale Arbeitsplatz-Konzentration (Maximum workplace concentration)
NIOSH	National Institute of Occupational Safety and Health
NOAEL	No Observed (Observable) Adverse Effect Level
OEL	Occupational Exposure Limit
RA	Risk Assessment
REACH	Registration, Evaluation and Authorisation of Chemicals
SCOEL	Scientific Committee on OELs
STEL	Short Term Exposure Limit
TLV	Threshold Limit Value
TWA	Time Weighted Average
US OSHA	Occupational Health and Safety Administration of the United States

CONTENTS

1 BACKGROUND

Exposure to chemicals is often associated with probabilities of causing negative health effects. The nature and severity of these effects depend on the inherent properties of the substances and the exposure situation. Solvents, like for instance toluene, might cause damage to the nervous system (Win-Shwe and Fujimaki, 2010), carbon tetrachloride is known to be hepatotoxic and carcinogenic (Manibusan et al., 2007) and occupational exposure to benzene has been linked to leukaemia (Khalade et al., 2010). Hämäläinen et al., (2009) present an analysis of the global trend of occupational accidents and fatal work-related diseases. Between 1998 and 2003 the number of fatal diseases and accidents were increasing although the fatality rates per 100 000 workers have decreased during the same period. In 2002 the global number of fatal work-related diseases was close to two million, this number however also includes diseases caused by other factors than air pollutants at the workplace. Driscoll et al. (2005) estimated the global burden of lung cancer, leukaemia and malignant mesothelioma caused by occupational carcinogens for the year 2000. They found that some 152 000 fatalities and nearly 1.6 million Disability Adjusted Life Years (a measure of premature deaths and years with disease) weighted according to severity of the disease were due to exposure to occupational carcinogens world-wide. Perhaps as expected only a small proportion of the global burden of disease is found in Europe, the European Agency for Safety and Health at Work (2009) estimated that about 74 000 work-related deaths may be linked to hazardous substances at work each year in the EU. This in turn is approximately a factor of 10 higher than the number of deaths caused by workplace accidents. Several of these diseases mentioned above are caused by exposures in the past, for instance mesothelioma usually develops some 20 to 40 years after the exposure to asbestos. However, this illustrates the effects of lack of knowledge and underlines the importance of proactive regulations.

The Swedish Work Environment Authority and Statistics Sweden yearly publish reports on occupational exposure to chemicals and work-related disorders. In 2009 28% (±2%) of men and 16% (±1%), of women (average 22%) stated that they were exposed to air pollutants, defined as palpable dusts or chemicals, at work (AV, 2010a). As there are approximately 4.5 million workers in Sweden, this can be expressed as close to one million Swedes are exposed to air pollutants at work. The Swedish proportions are somewhat higher than the average for the EU where 19% report breathing in dust, fumes and smoke in their workplaces (European Agency for Safety and Health at Work, 2009). Within the building sector 60% (±5%) of the men in Sweden state that they are exposed to air pollutants (AV, 2010a). Between January and March 2010 0.5% of the employed women and 0.4% of the employed men stated that they had experienced work-related disorders due to chemical exposures during the last twelve months (AV, 2010b)

Thus workplace exposure to airborne pollutants calls for regulatory action from the authorities to protect workers against negative health effects. There are many different ways to regulate the exposure to chemicals in the workplace. The use of certain substances can be prohibited or restricted, and for instance imposed with certain requirements such as use of personal protective

equipment. The exposure can also be restricted in such sense as to regulate the maximum allowable concentrations of a certain substance in the work-place air, i.e. occupational exposure limits (OELs).

1.1 AIMS OF THIS THESIS

This thesis focuses on one area of regulation and one tool of risk management: OELs. In this thesis I study how OELs are set, in order to increase the understanding of the process towards an OEL. The overall aim of this work has been to find out what kind of factors within the risk assessment and risk management paradigm that influence the setting of OELs. The European Union is also a comparably new actor regarding OELs with a potential to substantially influence the actual levels OELs take on, as well as risk assessment methodologies through its Scientific Committee on OELs (SCOEL) and the new chemicals regulation REACH. Thus, special attention has been given to European aspects in this thesis. Specific questions have been: (1) How do different standard-setters' lists of OELs differ, in respect to which substances that are included and average level, between different standard-setters? (2) Do the European Commission (EC) OELs affect which substances are selected for regulation by the member states? (3) Do the EC OELs influence the level of member states' OELs, i.e. the numeric values for specific substances' OELs? (4) Why do some standard-setters set such different levels of OELs for the same substance? (5) How is uncertainty handled in the setting of EC OELs? (6) What are the similarities and differences between REACH Derived No Effect Levels (DNELs) for workers and OELs? (7) How will the numerical values of REACH worker-DNELs compare to OELs?

By addressing these issues the main objective is to produce knowledge that can help improve the process towards OELs and increase the consistency and transparency of them.

1.2 OUTLINE OF THESIS

Section 2 introduces the key concepts of this thesis: including OEL risk assessment, risk management and previous research on the issue of OELs. The methods that have been used are briefly described in section 3. In section 4 the results of each paper are summarised, which is followed by a discussion of the joint results of the five papers in section 5. Finally, an outlook is presented in section 6.

2 INTRODUCTION

To justify regulatory action for a substance there must be a known, estimated or suspected risk associated to it, this means identifying its harmful potential and possible exposures. Regulatory toxicology is a collective term for the branches of toxicology that work with supplying the regulators with data for toxicological risk decisions. Regulatory toxicology encompasses not only

the production of scientific data but also the gathering and evaluation of data in risk assessments. In the following sections branches of regulatory toxicology of importance for OEL setting are described.

2.1 TOXICOLOGICAL KNOWLEDGE

There are several kinds of methods to generate toxicological knowledge, ranging from structure-activity relationships to investigations that involve human subjects. Of course the applicability of the knowledge to human risk assessment varies between these sources. This could also be expressed as the degree of uncertainty increases the further away the method is from the human conditions of interest (Eaton and Klaassen, 2001).

Data derived from computer modelling, often referred to as *in silico methods,* draw information from the structure of the chemicals, and known effects of other chemicals or functional groups. Structure-activity relationships can be used to show that a part of a molecule is related to a certain effect. When using statistical methods to show the strength of these relationships the method is called quantitative structure-activity relationships. In *read across*, substances are grouped into chemical categories of similar molecules. When data are missing for substances within such a category, data from other substances in the same category can be used to predict toxicity. This kind of information might be used for screening or priority setting, but presently there are limitations to the extent to which these kinds of data can be used in risk assessment (Cronin and Madden, 2010)

Using cell cultures instead of entire organisms is called *in vitro methods*, there are many different kinds of cells or tissues that might be used for in vitro testing, giving knowledge about specific responses or mechanisms on the cellular level. The major weaknesses are that one cannot gain information on if or how the substance would reach this tissue, identify the critical organ or get reliable dose-response data. There are in vitro assays for many different endpoints; the most common use in risk assessment is however for the evaluation of mutagenicity of a substance (Klaassen, 2001).

Performing experiments on living and intact organisms, *in vivo*, gives a more realistic picture of the toxicity of a substance as this includes the whole process of absorption, distribution, metabolism and excretion (ADME). Of course depending on the organism the relevance for human risk assessment varies, but a general assumption in regulatory toxicology is that data from vertebrates give a good indication of what might happen in the human body (Eaton and Klaassen, 2001; Faustman and Omenn, 2001). A major advantage of experimental studies, regardless of species, is that they allow manipulation and exact control of the exposures. Measuring exposures can be difficult, depending on substance and exposure level, and the variability of the result is often large (Nieuwenhuijsen, 1997). The uncertainties of a dose-response relationship established

in an observational study are thus expected to be larger than those of an experimental study. Also other factors that might confound the results are possible to control in an experiment, especially in animal experiments. An important issue to consider is the ethical implications of an experiment. Obviously experiments on humans give the most relevant data, but the kind of substances and exposure levels that are allowed to investigate are strictly regulated (e.g. in Sweden by SFS, 2003). Experiments on humans are done for instance for substances known to have reversible effects and the duration as well as the level of exposure is much more limited than in experiments on animals. Of course animal experiments are also subject to ethical rules, but generally higher exposures, longer duration and more severe effects are accepted. Also animals used for these kinds of studies, most often rodents, have a shorter life span than humans. Thus it is possible to cover a life-time's exposure in two years using a rat. The statistical power of an experiment depends on the criterion used to decide statistical significance (usually 0.05), the magnitude of the effect and the sample size, i.e. the number of test subjects. Increasing the exposure levels or the number of test subjects are thus the more readily available means to increase the power of an experiment, and for the reason outlined above these measures are more likely to be acceptable in animal experiments. However, all experiments whether on humans or on animals are very expensive, which of course affects the amount of available data on substances' toxicity.

Epidemiological data, i.e. data from experiences of human exposures, are of course the most relevant for the human condition. This is however not a proactive method, as the existence of epidemiological data implies that people have been exposed to hazardous substances and experienced adverse effects due to this exposure. An epidemiological study is of an observational rather than experimental nature. As mentioned, this also means that exposures are measured or estimated rather than controlled, increasing the uncertainties of the results. There are also other major statistical constraints to epidemiological evidence; to prove causality the effects need to be specific to the exposure in question and/or be present in many persons. In epidemiological studies there are also many confounding factors further diminishing the statistical power, because people differ in many respects, such as age, weight, activity level and smoking habits (Faustman and Omenn, 2001). In an animal experiment most of these factors are possible to control, by using animals of the same genetic strain, of the same age, give them the same food and the same environment. It is therefore important to keep in mind that an epidemiological study that cannot statistically prove the existence of a causal relationship between exposure and the examined effect does not constitute solid evidence that the effect is not related to said exposure. There are however methods to calculate the statistical power of detecting a certain effect, which might help in determining importance of a negative result (Faustman and Omenn, 2001).

Epidemiological studies are often time consuming, especially if the study is started before the effect has manifested, as for instance in *prospective* studies. If the study uses persons with the effect as a starting point, as in *retrospective* studies, also the exposure assessments have to be

performed in retrospect, usually resulting in even larger uncertainties (Faustman and Omenn, 2001). The exposure assessments in retrospective studies are often based on a questionnaire addressed to the participants. It is then possible that participants suffering from the investigated effect to a greater extent than other participants (controls) reflect on the causes of the effect and therefore to a larger extent remember a suspected exposure. This phenomenon is called recall bias.

There are many different types of epidemiological study designs, for instance case control, cohort and cross sectional studies. Case control studies are usually retrospective, starting after the effect has manifested. In this design, study subjects with the disease of interest (cases) are matched with subjects without it (controls), followed by a comparison of previous exposures with the aim to identify a potential cause(s) of the investigated disease. In cohort studies the subjects are divided into categories (cohorts) depending on certain characteristics, for instance exposure levels. The incidence of disease is then compared between the different cohorts. Cohort studies can be both prospective and retrospective. Both cohort studies and case-control studies can give estimates of relative risk (Ulm, 2008). Cross sectional studies aim at investigating the entire population rather than a limited subset defined by either exposure or disease. With this study design data on exposures and disease are collected in parallel from the studied population. It is thus not possible to decide whether effect or exposure occurred first (Faustman and Omenn, 2001).

Case-reports are another source of data on human exposures that might be found in the scientific literature. These describe single, or a series of, cases of a specific disease or health effect. The described effects can usually also be linked to a specific environmental exposure or suspected cause or contribute to the activity. Case reports can help us to discover and describe new, unexpected or rare health effects, but will usually not provide quantifications of dose-response relationships (Vandenbroucke, 2001).

2.2 RISK ASSESSMENT AND RISK MANAGEMENT

Toxicological risk assessments are performed in many different regulatory areas and by different actors of course resulting in differences in aims and methodologies. What is a general characteristic is that they aim to use the toxicological knowledge in order to find out what might happen to humans that are exposed to the investigated agent. Risk assessment has been structurally defined by several agencies (NRC, 1983; 1488/1994/EC; ECHA, 2008a). Usually risk assessment is described as consisting of three main steps: **Assessment of effects,** which is a toxicological evaluation of a substance, comprising *hazard identification* and *dose-response assessment*. This step identifies the inherent capacity of the substance to cause adverse effects and the relationship between dose and these effects. In dose-response assessment the aim is often to identify the lowest observed (or observable) adverse effect level (LOAEL) and no observed (or observable) adverse effect levels (NOAEL). This is followed by an **exposure assessment**, which

estimates what doses the subjects are exposed to and identifies the part of the population that is exposed. **Risk characterisation** is the final step, estimating the incidence and severity of the adverse effects likely to occur.

Risk management should be based on the results from the risk assessment, but also considers aspects other than the toxicological effects, e.g. economic and technological feasibility. Stakeholders may be invited to give their opinion on the conclusion or proposed measure. Risk management measures may take many shapes, from the ban of certain substances to limiting harmful exposures by setting OELs, or by provision of information like a classification and labelling system. A consequence analysis is sometimes performed, comparing the effects of implementing different risk management strategies.

2.3 HISTORY OF OCCUPATIONAL HYGIENE AND TOXICOLOGY

A number of diseases have been related to the occurrence of harmful substances in the occupational setting, for instance asthma, allergies and several forms of cancer. In his essay on the history of occupational medicine, Gochfeld (2005) describes how diseases connected to working conditions are mentioned in several early works on natural philosophy or medicine, some of which are probably written more than 4000 years ago. More detailed accounts specifically concerned with occupational hygiene seem however not to have been produced until the late 1400s (Gochfeld, 2005). Ellenbog's writing from 1473 might be the first work on occupational hygiene, concerning the occupational hazards of goldsmiths and metalworkers and giving advice on how to avoid lead and mercury poisoning (Gochfeld, 2005). In the first half of the 16th century Agricola and Paracelcus described adverse health effects caused by mining, smelting and metallurgy (Thorne, 2001; Gochfeld, 2005). In 1700 the famous book *De Morbis Artificum Diatriba,* or as is its English title *A Treatise on the Diseases of Workers*, was published. Its author was Bernardino Ramazzini, an Italian physician also known as the father of occupational medicine. The second edition of this book contains 54 chapters, of which 12 were not included in the first edition, each treating a certain occupation or group of occupations (Ramazzini, 1713). Ramazzini realised that there was a connection between people's diseases and their occupation, and in the foreword to the second edition he points out that a doctor should add the question about occupation to the standard register of questions to make a diagnosis. Ramazzini identified two major causes of workers' diseases: air borne pollution and ergonomics. The risk management measures he prescribed are in many respects similar to those prescribed and used today. For instance he recommended that mines need to be ventilated and that miners need face masks to lower exposure to dusts. Although Ramazzini recognised the need for ventilation in several kinds of workplaces, also other than mines, this need was not generally recognised until approximately a century later. One early example of regulatory recognition is the British factories Act of 1864 which identified six different "dangerous trades" and required that the factories in these trades should be ventilated to as far as possible reduce the amount of

harmful air pollutants (Lee, 1973). The most substantial progress in the area of occupational hygiene and toxicology waited even longer and was made during the 20th century (Nielsen and Øvrebø, 2008). It was first in this period that the effects of asbestos, quarts and other dusts and fibres were identified. Also metal toxicity and the carcinogenicity of numerous substances were established in this century (Gochfeld, 2005). In the time period between World War I and II, developments regarding air measurement methods were providing the possibility of establishing quantitative exposure-disease relationships (Gochfeld, 2005; Nielsen and Øvrebø, 2008).

2.4 ORIGIN OF OCCUPATIONAL EXPOSURE LIMITS

Max Gruber's identification of a probable NOAEL in the range of 200-500 ppm for carbon monoxide in 1883 has been referred to as the first known OEL. This NOAEL was based on experiments on hens, rabbits and also himself (Paustenbach, 2000). In 1886 Karl Bernhard Lehman published a list of "maximum tolerable concentrations in the workplace" covering both short term and long term exposures (Henschler 1991). Another early description of the concept of regulatory OELs was given by Duckering (1910, qtd. in Piney 1998):

> The most scientific way of regulating a dusty trade would be to impose a limit on the amount of dust which may be allowed to contaminate the air breathed by the workpeople and to leave the manufacturer a completely free choice of methods by which this result may be attained.

In 1912 Kobert published acute exposure limits for twenty substances, listing four limits per substance corresponding to (1) rapidly fatal, (2) dangerous in 0.5 to one hour, (3) 0.5 to one hour without serious disturbances, and (4) only minimal symptoms observed (qtd. in Paustenbach, 2000). His example was followed by others, and several multi-value lists were published in the 1920's and 1930's (Piney, 1998). For instances the US bureau of mines published a list of 33 values in 1921. One of the last multi-value lists published was that of Sayers and Dallavalle from 1935. It listed five categories, of which the fifth was a long-term exposure limit (Piney, 1998). Lehman and Flury (1938) and Bowditch (1940) were the first to publish papers with single value lists (qtd. in Piney, 1998).

In 1938 an organisation called the National Conference of Governmental Industrial Hygienists was formed, which in 1946 changed its name to American Conference of Governmental Industrial Hygienists (ACGIH). This organisation soon became one of the most influential organisations world-wide when it comes to occupational health regulations (Piney, 1998; Hansson, 1998a). According to the ACGIH webpage (www.acgih.org) the original goal of the organisation was: "to encourage the interchange of experience among industrial hygiene workers and to collect and make accessible such information and data as might be of aid to them in the proper fulfilment of their duties". The ACGIH has standing committees on many areas of interest within occupational hygiene, of which the most well known is that on Threshold Limit Values

(TLVs) for chemical substances formed in 1941 (www.acgih.org). The ACGIH published their first limit values in 1941, followed by a list of 63 substances in 1942 (Paustenbach, 2000). In 1946 a list of 148 substances was published (www.acgih.org) The fact that the limit values then were referred to as "maximum allowable concentrations" without further definition led to criticism for conveying an impression of truly safe-level thresholds. The term TLV was introduced in 1956, and since 1962 also the documentation of the TLVs is published.

During the 1950's and 1960's many national agencies adopted the ACGIH TLVs as national OELs (Piney, 1998) and the concept of exposure limits has become the most extensively used management tool of chemicals in the occupational setting. The ACGIH process to determine their TLVs has been criticised for lack of transparency and industrial bias (Castleman and Ziem, 1988; Roach and Rappaport, 1990; Rappaport, 1993; Hansson, 1998a; Rudén, 2003). Nevertheless, the TLVs and their documentations are still used world-wide (paper I), although an increasing number of countries produce own lists of OELs and corresponding substantiating documentation.

2.5 OCCUPATIONAL EXPOSURE LIMITS TODAY

The rationale behind OELs is that if the exposure to a chemical is sufficiently low no, or acceptably small, negative health effects will arise. The dose-response relationship differs of course with the different inherent traits of each chemical.

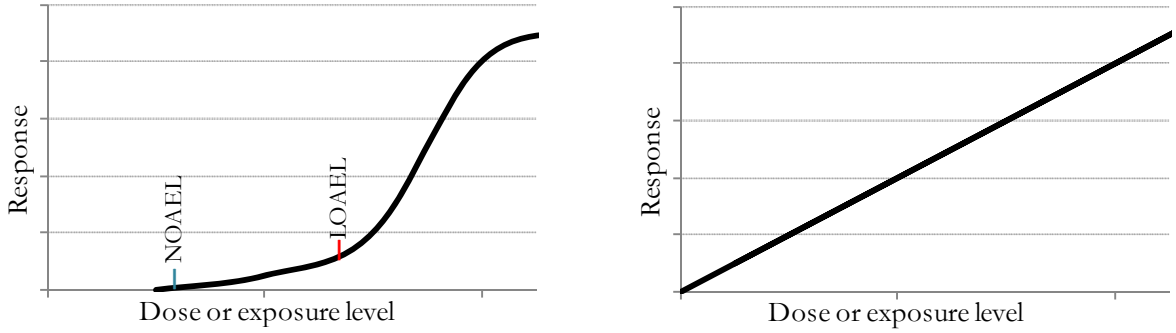

Figure 1 Dose-response relationships with (to the left) and without (to the right) thresholds. Potential locations of NOAEL (No observed adverse effect level) and LOAEL (lowest observed adverse effect level) are marked out in the dose-response curve to the left. The identification of these does not only depend on the true dose-response relationship but also the tested doses and the statistical power of the experiment.

For some chemicals evidence suggests that a negative health effect only occurs above a certain level of exposure, which means that a safe level of exposure is possible to achieve (figure 1 to the left). For other chemicals this is not the case though, either there is not enough knowledge to derive a no effect level, if such a safe level does exist, or if there is in fact a linear dose-response relationship without any threshold (figure 1 to the right). In the latter case low-level exposure might only lead to very low individual risks but if many persons are exposed the collective exposure can result in substantial population effects.

An OEL restricts the allowed concentrations of a harmful substance in the work-place air, averaged over a period of time. The OEL thus does not take other routes of exposure into consideration, for instance dermal uptake. The level of the OEL depends on the outcome of the risk assessment and risk management processes for the corresponding substance. Time weighted averages (TWAs) are usually set for an eight hour day during a 40 hour week. They are intended to ensure that no unacceptable adverse effects occur during the entire working life. To protect against acute effects, usually irritation, the limit is set for a shorter period of time. Short term exposure limits (STELs) usually limit a concentration for a 15 minute period. There are also so called ceiling limits, concerning an even shorter period of time than STELs.

Biological limit values are related to OELs, and limits the biological burden of an exposure by indicating a highest acceptable concentration in a biological matrix. The biological matrix can be e.g. blood, urine or saliva. This also means the exposure is controlled in retrospect, while air monitoring could be, but not necessarily is, performed before or during work. For instance lead is regulated by a biological limit value in the EU, allowing no more than 70 µg lead/100 ml blood (98/24/EC). Biological exposure limits might give a more accurate view of the biological load, but also do not separate between occupational and non-occupational exposure sources. Biological monitoring might become more important in medical surveillance of exposed workers (Bolt and Thier, 2006), especially since it can cover dermal exposure as well as inhalation exposure. However, biological limit values are outside the scope of this thesis.

2.6 THE PROCESS OF SETTING OCCUPATIONAL EXPOSURE LIMITS

The risk decision process differs somewhat between agencies as well as between regulatory areas. Figure 2 is a schematic depiction of a probable procedure of setting and enforcing OELs, although there obviously are differences to this procedure between different standard-setters. In this context it is important to recognise that OELs are only one of several means for the control of potentially hazardous substances in workplaces. Other means include the application of specific work procedures and safety measures for certain substances and the replacement of hazardous substances by less hazardous ones.

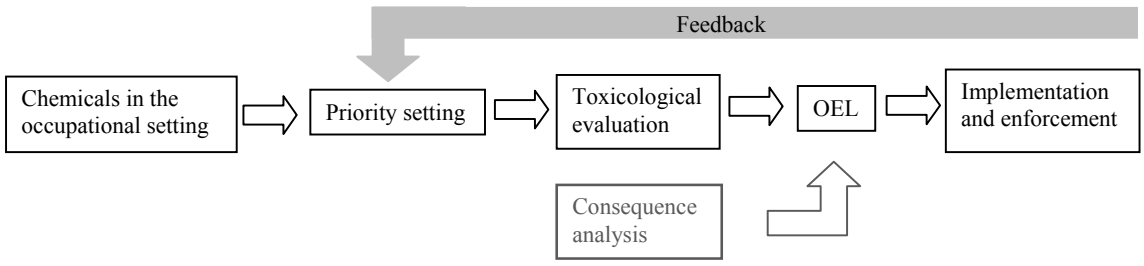

Figure 2 Schematic representation of the process concerning the setting and enforcement of OELs.

For a substance to be regulated by an OEL it has to be proved harmful. This means that the lists of OELs are so called negative lists; what is not regulated, either by exposure limits or otherwise, is generally allowed or perceived as allowed. In other areas of regulation the approach is the other way around, e.g. biocides. To be able to put a biocide on the European market its producer needs to get it authorised according to the directive concerning the placing of biocidal products on the market (98/8/EC). Also food additives need to be authorised at EU level before use in manufacture or preparation of foodstuffs (89/107/EEC as amended by 94/34/EC). What is not regulated in these instances is not allowed at all, which can be referred to as positive lists. Many occupational health and safety regulations do have demands on the employers to ensure the health and safety of its employees, which of course complements the lists of OELs, banned and other-wise restricted substances. It can however be expected that these unspecific requirements are more difficult to enforce, emphasising the differences between a negative and a positive list.

The supervision of workplace health and chemicals exposure is very important since it has the potential to detect both the need to regulate a substance as well as the need to apply stricter limits to already regulated substances. Also, much of the epidemiological evidence on harmful effects of chemicals on human health originates from scientific research on occupational exposure.

Most regulatory agencies take both human health, i.e. data from the risk assessment, and feasibility into account when determining an OEL. Often some sort of consequence analysis is performed assessing feasibility in terms of economical and technical restrictions.

The implementation and enforcement of the OELs is a step separate from setting them, and the methods of this also vary between countries. The prevalence of chemical health risks in workplaces depends not only on the chosen levels of OELs but also on other factors, including how stringently these OELs are implemented and enforced. The most basic use of an OEL as a risk reduction measure is to compare it to actual exposures at the work-place. This implies that workplace exposures have to be actually measured (or modelled), to give the opportunity for this use of OELs. It should also be noted that exposure measurements are not unproblematic in their nature, as exposures vary considerably over time and between individuals (Rappaport et al., 1993). Therefore, no conclusions should be drawn about the quality of actual working conditions from the material presented in this thesis.

2.7 SUBSTANTIATION OF AN OCCUPATIONAL EXPOSURE LIMIT

Once it is concluded that there is a need for an OEL, the level of it has to be decided and substantiated. The process of setting an exposure limit does not conform fully to the classical risk assessment scheme presented in section 2.1. Rather the focus is on the first part, the assessment of effects, which is performed through a toxicological evaluation. In the process towards an OEL the risk characterisation in some sense comes before the exposure assessment, because the OEL

should correspond to the acceptable risk, i.e. that level of exposure which will lead to no, or acceptably low, adverse health effects. Hence, the substantiation of an OEL will be referred to as a toxicological evaluation rather than a full risk assessment. Figure 3 schematically depicts the steps of the toxicological evaluation that through literature review aims at determining the adverse health effects of a substance. The toxicological evaluation is performed in order to determine a critical effect and a quantitative point of departure for that critical effect from which an OEL can be extrapolated.

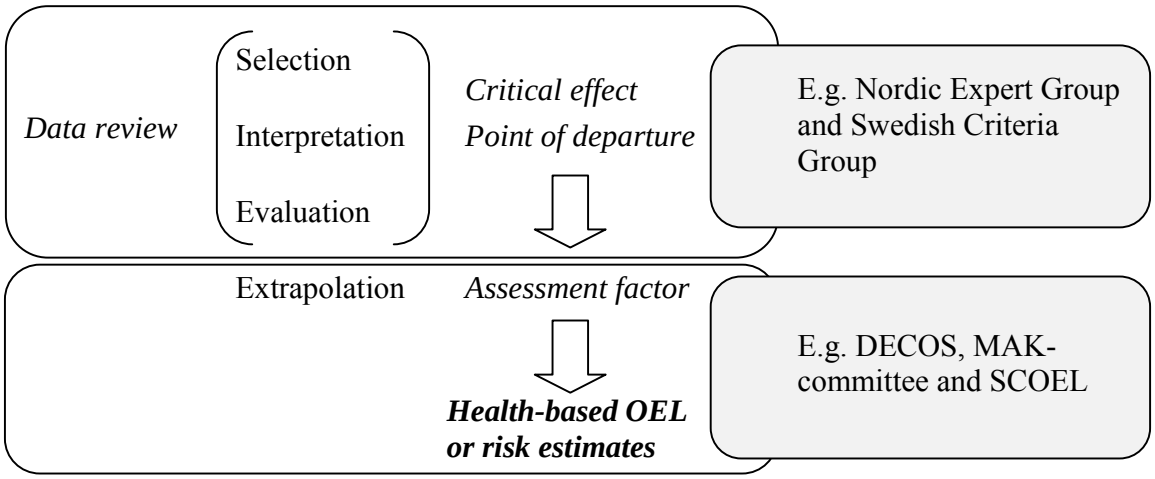

Figure 3 Steps in the toxicological evaluation expected to potentially affect the level of the health-based OEL recommendation. Not all expert groups proceed beyond the identification of critical effect and point of departure. Some expert groups present risk estimates for non-threshold substances. DECOS - Dutch Expert Committee on Occupational Safety, MAK - Maximale Arbeitsplatzkonzentrationen [maximum workplace concentrations], SCOEL – Scientific Committee on Occupational Exposure Limits

2.7.1 Identifying the critical effect and point of departure

The critical effect is the adverse effect which is considered to be the most important to protect humans from (e.g. Nordberg et al., 1988; Hansson, 1997; Faustman and Omenn, 2001). When reading the documentation of an OEL the critical effect is the effect that the OEL is stated to foremost protect against. The point of departure is the dose-level from which the OEL is extrapolated. The point of departure can take many forms, it might originate from animal or human data and the dose-level can correspond to different effect-levels. It commonly is a NOAEL, i.e. a tested level of exposure that does not cause a statistically significant effect. However, sometimes all the tested doses cause an (adverse) effect, and in those cases the point of departure might be a LOAEL as a NOAEL cannot be derived. Also if the critical effect is judged to be very mild the LOAEL can be considered more appropriate as a point of departure than the NOAEL. Since conclusive epidemiological data are sparse, these values are as a rule based on animal data. Another method to derive a point of departure for an exposure limit is to use the benchmark dose (BMD) approach (Crump, 1984). The BMD approach applies a curve fitting model to the entire data set, thus using all tested doses (not only NOAEL and LOAEL) to predict

the shape of the dose-response curve. As is shown in paper III this approach has not been commonly used for OELs.

2.7.2 Extrapolation to the occupational exposure limit

The OEL is derived from the point of departure, usually by performing an extrapolation to cover the variation within and between species, differences in exposure duration and uncertainties due to lack of data. This extrapolation might be performed by assigning numerical values to the different sources of uncertainty, multiplying these values, and finally dividing the point of departure by the product. The values are multiplied rather than added since the usual assumption is that each source of variability or uncertainty acts independently. This method of extrapolation is referred to as the assessment factor method, and is commonly used in for instance food safety. Assessment factors might also be called safety factors, uncertainty factors or modifying factors. However, for simplicity will only the term assessment factor be used in the following sections. When setting OELs explicit assessment factors are not used in the same extent as in other regulatory areas (Hansson 1997; paper III), and if used they generally are comparatively lower than recommended assessment factors for the general population (Nielsen and Øvrebø 2008; paper IV; paper V).

For instance the Swedish Criteria Group and the Nordic Expert Group do not apply assessment factors nor do they give a recommendation for a health-based OEL. Nevertheless, there are some indications that the explicit use of assessment factors might be increasing in the context of OELs. The DECOS decided in the 1990's to use explicit assessment factors in their update of existing OELs (Stouten et al., 2008). In the SCOEL guidance note (SCOEL, 1999; 2009a) assessment factors are mentioned as the means used for extrapolation but no numerical recommendations are given. The following aspects that these assessment factors should cover are mentioned: nature and severity of the critical effect (e.g. local or systemic effect), nature of the point of departure, (e.g. animal or human data, NOAEL or LOAEL), known species differences, consistency (i.e. agreement between different toxicity data sets), slope of the dose response curve and information on ADME. The SCOEL states that their assessment factors are to be decided on a case-by-case basis, rather than using the assessment factors of 10, 100 or 1000 (where 100 is the default) commonly used to derive limit or guidance values for the general public. The SCOEL also argues that assessment factors used to derive OELs should be lower than the ones applied when setting guidance values or exposure limits for the general population. The arguments are that (1) workers are less heterogeneous than the general population and do not include the very old and young, implying less variability, (2) workers are not exposed for a full life time, but for 8h/day, 5 days /week 204 days/year up to 45 years, and (3) workers' health may be controlled by occupational health surveillance and monitoring programs (SCOEL, 1999; 2009a). The guidance note further gives advice on how to define an adverse effect, how to identify the critical effect and which kind of information that is relevant for the derivation of an OEL. The most clear-cut example is however that of the new European chemicals legislation (1907/2006/EC), commonly called

REACH. The REACH guidance document (ECHA, 2008b) has introduced a systematic use of assessment factors for deriving safe levels of chemicals for workers as well as the general population. In the guidance document (ECHA, 2008b) a potential need for assessment factors is defined for five different aspects. These are interspecies differences, intraspecies differences, issues related to the dose-response relationship, differences in duration of exposure and quality of database. Also some factors that might be reasons to modify the point of departure are given, for instance differences in exposure conditions and route.

The extrapolation from the point of departure to the OEL might be performed with or without the consideration of technical and socio-economic feasibility, as is indicated in figure 1 a consequence analysis might affect the level of the OEL. The consequence analysis is however not part of the toxicological evaluation (figure 2).

2.8 THE EUROPEAN UNION'S OCCUPATIONAL EXPOSURE LIMITS

The European Community announced its first Action Programme on health and safety at work in 1978, which was aimed at harmonising provisions and measures regarding the protection of workers' health within Europe. Previous to this, Community involvement in occupational health and safety had been scarce and with limited influence (Walters, 2002). One of the most important outcomes of the 1978 Action Programme was the framework directive 80/1107/EEC; it was the first directive to define a European legal framework for chemicals at the workplace and set out a number of preventive measures (Walters and Grodzki, 2006). In article 4 of the framework directive the setting of OELs was prescribed. This directive has since been replaced by the 89/391/EEC which is the framework now in effect. The first indicative OELs were laid down in directive 91/322/EEC. These indicative OELs were proposed by the EC which by the time had an informal group of scientific experts to its help. In 1995 this group of experts received a formal status (95/320/EC) as the Scientific Committee on Occupational Exposure Limits (SCOEL). Substances are selected for evaluation by the SCOEL by the Directorate-General for Employment, Social Affairs and Equal Opportunities. The SCOEL recommends health-based OELs for these substances to the EC. When the SCOEL finds it impossible on the basis of current knowledge to identify a threshold dose below which no harm to human health can be anticipated, the SCOEL recommends a pragmatic OEL that is deemed to carry a "sufficiently low" risk. Up to 2009 the SCOEL has adopted 124 summary documents, of which 20 currently are under review and another 40 under preparation. The OELs recommended by the SCOEL are evaluated with respect to feasibility by a separate committee, the Advisory Committee for Safety, Hygiene, and Health at Work. It is an assembly of representatives from governments, employers' organisations and trade unions. Indicative OELs are established by the EC when it is concluded that there is a clear threshold dose below which there are no adverse effects on human health. The indicative exposure limits are to be taken into consideration by each member state, but the national OEL is allowed to be higher or lower than the EC indicative OEL (e.g. 06/15/EC). Binding OELs are

mandatory and each member state must either implement the limit set by the EC or a lower limit (Feron, 2003). Up to date decisions have been made on 115 substances resulting in 105 indicative OELs and 10 binding OELs (Table 1). The EU does not seem to be a pioneering agency neither concerning coverage of substances nor the level of the OELs. Rather it seems as if the Commission chooses to set exposure limits for substances already regulated by several European countries (paper II).

Table 1 EU directives containing indicative and binding OELs.

Directive	**Type of OEL**
91/322/EEC	Indicative
96/94/EC	Indicative *(later repealed by 00/39/EC)*
98/24/EC	Binding for Lead
00/39/EC	Indicative
03/18/EC	Binding for Asbestos
04/37/EC	Binding for Wood dusts, Vinyl Chloride and Benzene
06/15/EC	Indicative
09/161/EU	Indicative

2.9 REACH

In December 2006 the proposition for the new chemicals legislation within the European Community was passed by the European Parliament and the Council of the European Union. It entered into force on the first of July 2007. REACH, which is the common name of this new legislation, stands for regulation, evaluation and authorisation of chemicals and is a framework on how to produce basic information about the chemicals that are on the market today. One important aspect is that greater responsibility for data-generation and risk assessment is laid on the manufacturers and importers of chemicals. The test strategies suggested for the substances produced or imported in volumes of 1- 10 tonnes per year will not produce enough data to determine an OEL (Regulation 1907/2006/EC; Walters and Grodzki, 2006). However, REACH will help to produce initial information on a large number of substances and might according to Nielsen and Øvrebø (2008) help to keep up the pace of setting and revising OELs. It might also be expected that the labelling and classification of hazardous chemicals might be improved by the information requirements of REACH. The requirements on the producers to provide safety data sheets has been transferred from the Safety sheets directive (91/155/EEC) and the requirements on the safety data sheets have been extended, which might improve the flow of information on potential hazards. Especially the exposure scenarios that are to be attached as annexes to the safety data sheets are of importance to this. Exposure scenarios must be prepared for industrial substances within the scope of REACH that are produced or imported in quantities above 10 tonnes per year and if the substance is classified as dangerous, a persistent, bioaccumulative, toxic substance or very persistent or a very bioaccumulative substance. An exposure scenario

should include the allowed uses and appropriate risk management measures that properly implemented, ensure that the potential risks from the substance are adequately controlled.

In order to identify what exposure levels might correspond to, an adequate control of the risks so called DNELs are to be calculated for substances that have identifiable threshold effects. For substances without identifiable thresholds Derived Minimal-Effect Levels are to be calculated, that should correspond to a risk level "which is considered to be of very low concern". Within the guidance for the implementation of REACH, workers are mentioned as one subpopulation requiring a specific DNEL, and an overview of how to derive such worker-DNELs is also given in ECHA (2008b). Discussions on how national regulations should relate to the DNELs have already started; the Polish case is treated by Gromiec (2008). One of the issues pointed out in this paper is that the DNELs are derived by manufacturers and importers while national OELs are developed by governmental agencies.

2.10 PREVIOUS RESEARCH

Previous studies of OELs show that there are national differences in risk assessment and management of occupational chemical exposure. Henschler (1992) investigated the definition of adverse effect in relation to OEL setting and found a wide range of interpretations. Hansson (1998a) investigates the ACGIH, the German and Swedish systems for OELs, performing detailed studies of the relationship between OELs and underlying toxicity. Hansson (1998a) found inconsistencies in all three countries, even though the standard of scientific documentation was found to be much higher for the German and the Swedish lists than for the ACGIH. Also the Swedish system was found to be more transparent than the other two due to its organisational separation of risk assessments from risk management decisions. Hansson (1998a) emphasises the need for transparent and consistent principles for the setting of OELs. Haber and Maier (2002) showed that differences in methodology and scientific policy lead to large variations in the OELs set for chromium, even if similar toxicological data was reviewed. The International Council on Mining and Metals reviewed the OELs for nine substances from five different standard-setters (34 documentations in total) and found that the use of key studies, identification of critical effects and use of assessment factors was very variable (ICMM, 2007).

Taylor et al. (2007) reviewed the implementation of the regulations for lead issued by the EU in directive 98/24/EC. They concluded that the biological limit value, defined as the concentration in blood, for lead varied considerably between countries, as it ranged from 20 to 80 μg/100 ml blood. The OELs did not vary as much between the studied countries; the authors found the EU binding OEL for lead to be a plausible explanation for this. But still 5 out of 15 countries had set a lower limit than the EU. Some countries defined special arrangements to account for differences in sensitivity due to gender or age.

Differences in risk assessment practices and outcomes are also reported in other regulatory fields (e.g. Hansson and Rudén, 2006). In a study of the substantiation of acute guideline levels for emergency response discrepancies in level between the Acute Exposure Guidance Levels (AEGL) and Emergency Response Planning Guidelines (ERPG) were found (Öberg et al., 2010). Of the 59 substances that had both an AEGL and an ERPG 34 had levels differing by more than a factor of 3. Choice of critical effect, selection and interpretation of key study and use of different assessment factors were found to be causes for these discrepancies. In a series of case studies Rudén scrutinised the scientific basis behind 30 risk assessments for trichloroethylene authored by expert groups on OELs as well as other areas (e.g. Rudén 2001a; b; 2003). The data sets used by the different risk assessors were found to be surprisingly diverse, and the differences were not possible to explain by data availability alone. The interpretation and evaluation of the different studies also varied between the risk assessors.

Nielsen and Øvrebø (2008) in their review of processes for derivation of health-based OELs concluded that assessment factors used for OEL setting are relatively low compared to other regulatory areas. Fairhurst (1995) presented an analysis of health-based OELs for 24 substances set in the UK between 1990 and 1993. For these OELs the severity of the critical effect seems to have had some influence on the magnitude of the assessment factor. Hansson (1997) calculated the ratio between the OEL and the point of departure for Swedish OELs based on human data, which is analogue to the inverse of an assessment factor had it been explicitly stated. He found the correlation between these ratios and the severity of the critical effect to be surprisingly low and that the magnitude of these ratios did not satisfactorily reflect the distinction between LOAELs and NOAELs. In the review of 34 OEL documentations by the International Council on Mining and Metals a discussion on assessment factors was only found in three, two of these also explicitly stated assessment factors. Stouten et al. (2008) found that the safety margins of the Dutch OELs increased significantly after the introduction of a framework of assessment factors. In paper IV it was shown that the ratios between the point of departure and the OEL were larger in those instances where assessment factors had been explicitly stated by the SCOEL.

It has been shown that when OELs are revised they tend to be gradually decreased (Hansson 1998a; paper I; paper II), this is also illustrated for the OELs of the ACGIH, the EC and Sweden in figure 4. From the OELs with CAS-designations included in paper I it is also possible to identify the changes made to individual OELs. In the period between 1995 and 2005 Sweden has lowered the OELs for 13 substances while the EC has lowered for three OELs since 1991; no OELs were increased by these two standard-setters in this period. The ACGIH lowered its TLVs for 63 substances and increased the TLV for one substance. The one increase was for butane, in 2003 it was proposed to withdraw the 800 ppm OEL for butane and instead assign a new OEL of 100 ppm for aliphatic hydrocarbon gases: alkanes [C_1-C_4]. Greenberg (2004) made a review of the published material concerning the derivation of British asbestos exposure limits from 1898 to 2000 and Markowitz and Rosner (1995) reviewed the TLV for silica from 1935 to 1990. Both

these studies show that the OEL are lowered as more, and better information on adverse effects becomes available and the protection of workers' health has been given higher priority.

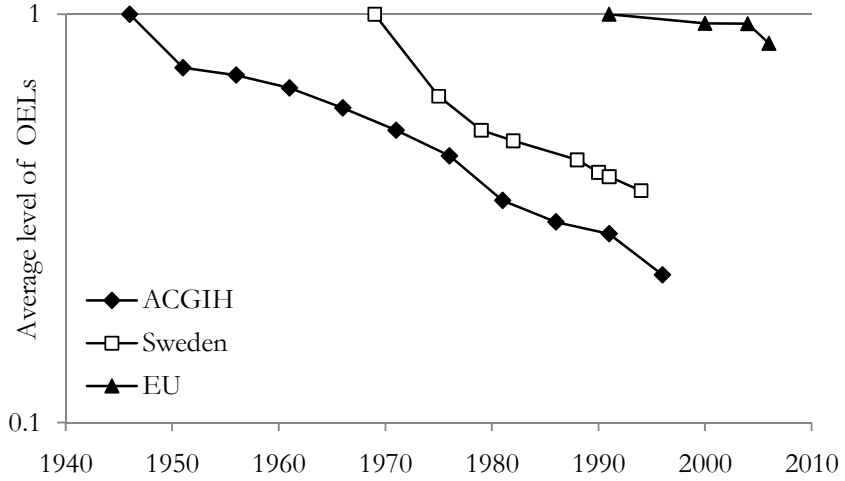

Figure 4 Average level of OELs from ACGIH, European Commission and Sweden calculated using the geometric means method. Each list is standardised against its own first version. Data for ACGIH 1946-1996 and Sweden 1969-1994 are from Hansson (1998a).

The ACGIH TLVs have been under scrutiny and severe criticism especially during the 1980's and 1990s. Castleman and Ziem (1988) found that for more than one sixth of the approximately 600 TLVs of 1986 the TLV Documentation placed important or total reliance on unpublished corporate communications. Roach and Rappaport (1990) analysed the references of the 1976 TLV Documentation and concluded that the TLVs had a stronger correlation to the measured exposure in industry than to the levels associated with negative health effects. The scientific basis of the ACGIH TLVs was again subject of scrutiny in Rappaport (1993) where ACGIH and the Occupational Health and Safety Administration (OSHA) of the United States (US) were compared, resulting in the conclusion that the TLV setting procedure of ACGIH depends heavily on the assessment of achievability of the TLVs. Hansson (1998b) investigated some practices in the ACGIH's TLV committee that were found to not comply with standard scientific procedures, for instance insufficient documentation and lack of references to major peer-reviewed publications. Cunningham et al. (1998) discussed the justification of the 10-fold increase of the TLV in 1992 for amorphous silica fume. Their conclusion was that the health evidence supports an OEL of 0.3 mg/m^3 instead of the then adopted 2 mg/m^3. Bigelow et al. (2004) reviewed the ACGIH TLVs and the British Columbia OELs for a number of substances in an effort to evaluate the differences and what implications a change from the British Columbia OELs to the ACGIH TLVs would have for healthcare workers in British Columbia. A number of discordances between the British Columbia 8 hour TWA OELs and the ACGIH TLVs were revealed. For 49 substances the British Columbia OELs were lower, while in 8 instances the ACGIH TLVs would

be lower. A review of six of these chemicals indicated that there was a potential for increased health-risks if the ACGIH limits were to supersede British Columbia's own OELs.

3 METHOD

The five studies constituting this thesis are comparative in their nature. Paper I presents a comparison of the selection of which substances are regulated and at what level. In paper II, in addition the similarity to the EC OELs was compared between the studied countries. In paper III the scientific substantiation of a selection of OELs was compared in respect to what primary literature is reviewed in the documentation and whether any explicit policy statements were included. Paper IV is focused on the quantitative handling of uncertainty by one expert group and how it was distributed over a number of categories theoretically predicted to be of importance. Paper V also concerns the quantitative handling of uncertainty, comparing worker-DNELs derived according to the REACH guidance document with SCOEL's recommended OELs. Table 2 presents an overview of the methods used in the different papers.

Table 2 Overview of methods used for the different papers.

	Paper I	Paper II	Paper III	Paper IV	Paper V
nm-MDS	✓				
Geometric means method	✓	✓			
Geometric similarity		✓			
Regression analysis				✓	
ANOVA				✓	
Document studies	(✓)	(✓)	✓	✓	✓

ANOVA- Analysis of variance; nm-MDS- Non-metric multidimensional scaling

3.1 QUANTITATIVE COMPARISONS AND ANALYSES

The first step was to compile a database of OELs. Only OELs with a CAS-number were included in this database, because a CAS-number is a more specific identifier of a substance than chemical nomenclature or trade names which are used somewhat differently between the different OEL-setting agencies. Using the CAS-numbers as identifiers had the additional benefit of being useable as labels when consolidating several lists. The software used for this was Microsoft Excel and its consolidation function only accepts numerical row-labels. The final database of paper I comprises of OELs from 18 organisations for 1341 substances. For use in paper II this database was scaled down to the 7 European countries and the European Commission OELs.

3.1.1 Non-metric multidimensional scaling

In paper I a non-metric multidimensional scaling was performed to get a visual representation of the similarity of selection of substances between the included agencies. The full database was transformed to a binary response describing whether a substance was regulated or not and a

distance-matrix was calculated using Euclidean distances. A non-metric multidimensional scaling is a suitable tool for data exploration, in this case visualising an approximation of how similar the selection of regulated substances is between the included agencies. The stress value of the plot indicates a "badness of fit"; the higher the stress value, the more distorted is the two-dimensional representation. Thus the stress value is important for the reliability of the plot, and a rule of thumb is that a stress value below 5% indicates a good fit, although a value up to 10% still is satisfactory (Kruskal, 1964). It should also be noted that the selection of distance matrix is important for the outcome of the plot

3.1.2 The geometric means method

In both paper I and II the average level of lists of OELs were compared by using the geometric means method, first used by Hansson (1998a). This means that the OELs of the different standard-setters were divided by the corresponding OELs of a comparison list resulting in a new list of ratios. The geometric mean was then calculated from these ratios.

Table 3 Comparison of arithmetic mean to geometric mean. Using the arithmetic mean gives the impression that the list of OELs is on average 3.7 times higher than the comparison list.

Substance	**Comparison list**	**OEL list**	**Ratio** (OEL/Comparison list)
A	10	1	0.1
B	1	1	1
C	0.1	1	10
Arithmetic mean			**3.7**
Geometric mean			**1**

The geometric mean differs from the arithmetic mean in that sense that the geometric mean is a measure of the central tendency in a logarithmic scale, while the arithmetic mean measures on a linear scale. The geometric mean is preferred over the arithmetic mean because the logarithmic scale is considered to be the proper scale for these kinds of data. On a logarithmic scale the same weight is given to a difference of 10 ten times higher as to a difference of 10 times lower. Table 3 shows an example calculation comparing the arithmetic mean to the geometric mean.

A comparison list is used to standardise all the list of OELs, so that OELs only on one list should not affect the resulting average level. For this reason it is also important to use a comparison list that includes many substances that are commonly regulated. The less representative the comparison list is for the investigated lists, the less validity has the geometric mean as a measure of the average level of these lists. The level of the values on the comparison list does however not matter for the outcome, as they only are a means of standardisation.

3.1.3 The geometric similarity measure

In paper II the similarity of the national OELs to the EC OELs was calculated, using a modification of the geometric means method which has been named the geometric similarity measure. The geometric similarity measure is similar to the geometric means method in that it starts with the calculation of ratios between investigated OELs and a comparison list. For the purpose of investigating similarity to a certain list of OELs, that list should be used as the comparison list. In addition, before extracting the geometric mean, the ratios above one should be inverted. By this inversion deviations from the comparison list are given the same weight regardless of direction, i.e. regardless of whether the specific OEL is higher or lower than the OEL of the comparison list. As a result, a geometric mean of one indicates complete similarity to the comparison list while a lower geometric mean indicates lower similarity. The same constraints regarding the representativeness of the comparison list apply to the geometric similarity measure as to the geometric means method. Table 4 shows an example of how the geometric similarity is calculated.

Table 4 Example showing the calculation of the geometric similarity.

Substance	**Comparison list**	**OEL list**	**Ratio** (OEL/Comparison list)	**Similarity ratio**
A	10	1	0.1	0.1
B	1	1	1	1
C	0.1	1	10	0.1
Geometric mean				0.22

3.1.4 Univariate statistics

In paper IV trends were analysed using linear regression models. A simple linear regression fits a straight line through a set of points in such a way that makes the sum of squared residuals of the model as small as possible. The r^2 is an estimate of how much of the variance in the data set that can be explained by the predictor variable. An r^2 of 1 means that the data points perfectly fit the linear model. The p-value gives the probability of the data points fitting this well or better to the linear model even if there really is no such relationship. A linear regression analysis assumes that the errors are normally distributed.

Also in paper IV, differences between categories were analysed using analysis of variance (ANOVA) or Welch's t-test. A one-way ANOVA was used, i.e. only one explanatory factor was included in each performed test. Each factor might have several levels and a one-way ANOVA tests whether there is a significant difference in the average of the samples within each level and the average of all samples. The p-value gives the probability of finding an effect that large by chance, even if there is no actual difference between levels or groups. Errors are assumed to be normally and randomly distributed. Welch's t-test is in many ways similar to a one-way ANOVA, using only two levels of the explanatory factor, and the interpretation of the p-value is

the same. Welch's t-test is an adaptation of Student's t-test that does not assume equal variances within the two levels.

3.2 DOCUMENT STUDIES

A document study is close reading of one or several texts, or parts thereof, in order to identify the essential content. A document study can constitute of both qualitative and quantitative elements. The document studies performed for the purpose of this thesis have mainly been aimed at identifying and/or quantifying content in terms of predetermined categories. Document studies have been used to some degree in all papers of this thesis. In papers I and II document studies were used to identify qualitative aspect of the OELs, e.g. legal status and whether they are health-based or pragmatic, as well as the numerical values of these. In paper III the scientific substantiation of a number of OELs from the original database was under scrutiny. The selection of documents for scrutiny was based on (1) that the OELs varied by at least a factor of 100 between different standard-setters and (2) that the documentation was published in English, French or any of the Nordic languages. The included documentations were searched for statements of critical effect and the adhering point of departure. After the point of departure was identified the primary studies cited as source of it or as giving strong support to it were identified. These primary studies were called key studies and when they were cited by several risk assessors the interpretation and evaluation of them were compared. This method very much relies on the identification of critical effect, point of departure and key studies, and thus on a coherent application of the criteria for the identification of these parameters.

Document studies also constituted a significant part of paper IV and V. In paper IV the SCOEL documents substantiating indicative OELs from the EC were studied in order to extract information on aspects which theoretically should affect the size of the safety margin of the indicative OEL. In order to calculate the safety margin the point of departure was also identified. For paper V the data-set used in paper IV was extended to cover all adopted SCOEL documents. The point of departures were in this study used not only to calculate the implicit safety margins of the SCOEL recommendations but also to derive a worker-DNEL according to the REACH guidance document (ECHA, 2008b).

4 PREVIEW OF PAPERS

4.1 PAPER I

In paper I the lists of OELs of 18 different organisations were compared quantitatively, using a list of 191 well known substances as a base for comparison. Fifteen regulatory agencies of different countries or territories and three organisations were included: the American Conference

of Governmental Industrial hygienists (ACGIH), the Japan Society for Occupational Health (JSOH), both non-governmental, and the European Union, issuing both mandatory and indicative exposure limits. The fifteen countries or territories were: Alberta (Canada), Australia, British Columbia (Canada), California (USA), Estonia, Finland, France, Germany, New Zealand, Ontario (Canada), the US OSHA, Poland, Quebec (Canada), Sweden and United Kingdom. The OELs were compared with respect to: (1) what chemicals have been selected and (2) the average level of exposure limits for all chemicals. The database contained OELs for a total of 1341 substances; of these 25 substances have OELs from all 18 organisations while more than one third of the substances are only regulated by one organisation. A non-metric multidimensional scaling also showed that the selection of substances was more similar between non-European countries including the ACGIH, than between European countries including the EU. Finland was the country that differed most from the others; this can be explained by the large number, nearly 200, of substances that were only on the Finnish list.

The average level of OELs was shown to differ substantially between organisations; the US OSHA OELs were in 2005 (on average) nearly 40% higher than those of Poland. Surprisingly also the EC OELs were on average high compared to the other organisations, exceeded only by the US OSHA OELs. No evidence was found to indicate that this variation was explainable by differences in legal status of the OELs (i.e. mandatory or recommended) or by deviations in the principles for risk assessment and risk management explicitly stated, such as the intended level of health protection. In fact the OELs of Finland are said to list concentrations "known to be hazardous". The values on this list are not mandatory but intended to be used for the assessment of air quality and work exposure. Considering that, it was somewhat surprising that the Finnish OELs were among the lowest. The other lists define airborne concentrations that are said to be safe or acceptable, considering an eight hour exposure a day and a forty hour working week. Three organisations besides Finland have clearly stated a purely health-based approach: ACGIH, JSOH and the EC. The comparatively low levels of the ACGIH and JSOH OELs are in line with the rationale that lower exposure limits are generally more protective of human health, even though it should be noted that their overall level is by no means the lowest. A comparison between the indicative OELs of the EC that are claimed to be health-based and the Finnish OELs shows that there are contradictory assessments of substances' toxicity within the range of this survey.

For eight standard-setters the study also encompassed lists of OELs published in preceding regulations. These were used for further analyses of the development during the ten past years. The average level of the exposure limits was shown to have declined during the past ten years for six of the eight organisations in the study for which historical data were available; it has increased for Poland and remained nearly unchanged for Sweden.

4.2 PAPER II

In paper II the focus was on the European Union and its influence on the member states concerning occupational health and safety. There are reasons to expect an effect of the EU regulations on the coverage of substances on national lists, considering that a national risk assessment and management process is mandatory for the substances that are assigned an indicative OEL. Exposure limits established by seven different national regulatory agencies of EU member states were compared to those of the EC. The included countries were: Estonia, Finland, France, Germany, Poland, Sweden and the United Kingdom. The comparison concerned: (1) what chemicals have been assigned an OEL, (2) the average level of OELs for all chemicals, and (3) the similarity between the OELs of different EU member states and the OELs set by the EC.

Using 102 substances with EC OELs as a standardisation list resulted in the EU having the level of 1, Estonia and the United Kingdom was the only countries having an average level higher than this. Poland had the lowest exposure limits, nearly 35% lower than Estonia. Not all 102 substances were regulated by all agencies, but all countries except Germany had more than 80 substances in common with the EU, Germany had 70. Most substances given indicative OELs did have national exposure limits already before the directive in question. The actual effect of the EU on the coverage is thus not clear, but it is possible that countries that develop new occupational health and safety regulations are more influenced by the EU standards than countries with already institutionalised practices.

Historical data were available for Finland, Germany, Poland, Sweden and the United Kingdom. The average level of the exposure limits had declined during the past ten years in four of these five countries, although Poland has not changed its level noticeably. Germany was the notable exception since its average level had increased. A few of the exposure limits have been lowered since the first list of indicative OELs was established by the EC.

For the study a similarity index was developed. None of the countries included were completely similar to the EU; Estonia was the country most similar. Using historical OELs the similarity index indicates that the exposure limits of EU member states are converging towards the EC OELs.

4.3 PAPER III

In paper III causes for the variations seen in papers I and II were sought. Substances for which the limits values vary by a factor of 100 or more were identified by cross-referencing 18 different lists, using the CAS-number as identification. The final selection was restricted by language of OEL documentations and included 14 of these substances and 8 organisations. A selection of these documents was sought for further scrutiny. The selection included the documentation for

the highest and lowest limit in the range, and in addition, the available documentation for OELs from the ACGIH, Germany and Sweden, since these OELs are acknowledged as very influential on the international arena (Walters and Grodzki, 2006). Forty-five documents were scrutinised in this study, and the year of publication for these documents ranges from 1971 to 2003. What study or studies that have been used to derive the point of departure (referred to as key studies) was compared between the risk assessors. The evaluation and interpretation of these key references have been compared when cited in more than one document.

The results show that for these 14 substances, older OELs are generally higher. Several OELs were more than 30 years old and were based on out-dated knowledge. Difference in the identification of the critical effect could explain the different levels of the OELs for half of the substances. What is determined to be the critical effect is expected to be influenced by the selection of primary data that is reviewed in the toxicological evaluation. Time for the data review is also expected to be an important factor due to data availability. But time was not found to be the only explanation for the differences in data review. Only eight of the documents (18%) referred to all available key studies. The interpretation of the key studies did not differ between the risk assessors. However, relevance or quality evaluation of the key studies did vary. Only nine (11%) of the 85 identified key studies were used to derive the point of departure in more than one toxicological evaluation. Three studies that were considered key studies in at least one document were significantly criticised in another document.

The point of departure used for the OEL was in most instances an effect level, and only in a few cases it was a NOAEL. Not one risk assessment used a benchmark dose as the point of departure. Four of the documentations stated an explicit use of an assessment factor.

The conclusion from this study was that documentation of the OELs is crucial in the comprehension of what effects the substances can give rise to and what the limits actually aim at protecting. Hence it is important that these documents are readily available to users of harmful substances and that the deduction of an acceptable effect level is transparent to the users.

4.4 PAPER IV

The aim of paper IV was to investigate how the SCOEL uses assessment factors (called uncertainty factors by the SCOEL) when proposing health-based indicative occupational exposure limit values. In total, 75 indicative OELs in 62 summary documents published from 1991 to 2003 were analysed. For 31 of the indicative OELs, no explicit uncertainty factor (EUF) was stated. For these, an implicit safety margin (ISM) was calculated as the ratio between the point of departure and the proposed indicative OELs. The EUFs and ISMs were analysed in order to determine whether date of recommendation, type of critical effect, nature of point of departure or amount of available data influenced the magnitude of them. The ISMs varied little (range 1-5),

while the EUFs showed more variability (range 1-50). The EUFs remained unaffected over time and the ISMs decreased slightly. When comparing over critical effects no differences were found between the safety margins for irritation and those for more severe systemic effects. The nature of the point of departure, i.e. whether it was a NOAEL or a LOAEL and whether it was human or animal data, affected the ISMs and EUFs only slightly and less than expected. Both EUFs and ISMs showed a weak but significant negative correlation with the amount of available toxicological data, measured as the number of relevant publications in PubMed, whereas SCOEL's own statements on data sufficiency in the summary documents had no influence. Nor were the EUFs or ISMs affected by the presence or absence of data on absorption, distribution, metabolism and excretion in the summary documents. Overall, the most striking difference was that between EUFs and ISMs, the former being on average 2.1 times higher.

Thus, the analyses suggest that the safety margins become higher when UFs are explicitly used to derive the OELs. In contrast, the EUFs and ISMs used by the SCOEL in the years 1991-2003 do not seem to be systematically predictable by any of the factors expected on a theoretical basis to cause differences in the magnitude of the ISMs. Based on the results of this study, it is recommended that the SCOEL should develop and adhere to a more articulate framework for their use of uncertainty factors. The first step would be to define default numerical values for sub-factors that account for typical situations such as extrapolations from animal to human, from oral to inhalation and from sub-chronic to chronic exposures. Secondly, the choice of uncertainty factors and their rationales should always be clearly described in the Recommendation sections of the SCOEL summary documents. These efforts will likely enhance the consistency and transparency of the SCOEL recommendations.

4.5 PAPER V

Within the new chemicals legislation REACH, DNELs will be calculated for substances within the scope of REACH and produced in quantities above 10 tonnes per annum. There will be several different kinds of DNELs of which worker-DNELs is one. As worker-DNELs probably will be calculated for many more substances than there currently are OELs, they are expected to play an important role in occupational hygiene. Paper V presents a quantitative comparison of the safety margins of health-based occupational exposure limits recommended by the SCOEL and a set of REACH worker-DNELs calculated according to the REACH guidance document (ECHA, 2008b). As the SCOEL's OEL recommendations might be used instead of a worker-DNEL, differences in safety margins are an important aspect to investigate. The comparison concerns 88 substances already given a recommendation by the SCOEL, and the worker-DNELs have been derived from the same point of departure as the respective SCOEL recommendation.

The results show that the safety margins become approximately six times higher when applying the REACH framework for modification of the point of departure and default assessment factors

for derivation of DNELs compared to the safety margins of the SCOEL recommendations. However, it should be noted that the REACH guidance document does not use the concept critical effect, instead registrants are meant to calculate DNELs for all known effects and determine a leading effect by identifying which effect that gives rise to the lowest DNEL, then called the critical DNEL. Thus, the final worker-DNELs for these substances in some instances should be lower than those calculated for the purpose of this study.

The guidance document on derivation of DNELs encompasses close to 150 pages (ECHA, 2008b), but despite this massive amount of information the selection of the assessment factors was in some instances quite ambiguous. The guidance document would generally benefit from more examples, including numerical advice, of when and how to deviate from default assessment factors. The following aspects are identified as missing:

- Guidance on how to calculate a DNEL when only acute data are available.
- Guidance on how to account for registrants' lack of experience.
- Numerical suggestions of assessment factors to cover for issues concerning severity of the critical effect and quality of database.

In addition, we suggest that the manner in which the assessment factors presented in the guidance document should be changed. Currently the guidance document presents default assessment factors of 1 for issues related to dose-response and quality of database. We suggest that instead of presenting the lowest assessment factors of a range in the tables use the highest assessment factors of the ranges as defaults. This would be more in line with a precautionary approach and also promote a closer reading of the guidance document.

4.6 SUMMARY OF RESULTS

As presented in section 1.2, the studies of this thesis have been mainly driven by seven different questions. In this section the main results will be shortly summarised following the structure of these questions, offering some tentative answers or potential explanations.

How do lists of OELs differ, in respect to which substances that are included and average level, between different standard-setters? In paper I it was shown that there are substantial differences in what substances are selected for regulation. Only 25 substances were given OELs by all 18 studied standard-setters, and one third of the 1341 included substances had OELs from only one standard-setter. The average level, for a selected number of commonly regulated substances, also varied. The highest OELs were from the US OSHA and were 40% higher than those from Poland, which were the lowest OELs.

Do the European Commission OELs affect which substances are selected for regulation by the member states? The EC had no uniquely regulated substances in paper I. The results from paper

II also suggest that the EC selects substances already regulated by several member states. A comparison of when the substances given EC OELs were introduced in five member states' lists shows that at most 27 substances (Poland) were given national OELs a year or more after they had been given EC OELs.

Do the European Commission OELs influence the level of member states' OELs, i.e. the numeric values for specific substances' OELs? For four out of five investigated member states OELs substances introduced on the national list after being given an EC OEL were more similar to the EC OELs than the entire list. Also shown in paper II is that since the first list of EC OELs was published, these five member state lists have all become more similar to the EU list. It is however unclear whether it is the EC OELs that has driven this trend towards increased similarity or other factors.

Why do some standard-setters set such different levels of OELs for the same substance? A very important factor seems to be the age of the OEL, for the 14 substances studied in paper III the older limits were generally higher. Also, what is determined to be the critical effect seems to affect the level of the OEL; differences in the identification of critical effect coincided with differences in the level of the OELs for 50% of the studied substances. Substantial differences in data selection were identified and time-related availability of data was not the main factor explaining these as only 18% of the documents referred to all studies deemed as key studies in at least one documentation available at the time for evaluation. In addition, the evaluation of the quality and relevance of studies varied considerably among organisations; only 11% of the key studies were given the highest weight in more than one documentation.

Two other factors that might influence the level of the OEL were the use of explicit assessment factors and the identification and protection of sensitive subgroups. Among the documentations studied in paper III only 9% explicitly stated a use of assessment factors. For one substance different OELs were determined with different accounts regarding the protection of sensitive groups.

How is uncertainty handled in the setting of European Commission OELs? According to the SCOEL key document assessment factors should be used, but the scrutiny in paper IV shows that only 44 of the 75 included OELs are derived using an explicit assessment factor. Although the safety margin is on average twice as high when explicit assessment factors have been used also the explicit assessment factors seem to be low compared to what is recommended in other regulatory areas. Also contrary to expected, the average safety margins for irritation were similar to those for more severe systemic effects. The kind of information that was used as the point of departure (NOAEL or LOAEL and animal or human data) affected the safety margins only slightly and less than expected. The safety margins showed a weak but significant negative correlation with the amount of available toxicological data, whereas SCOEL statements on data

sufficiency had no influence. It is recommended that SCOEL should develop and adhere to a more articulate framework for their use of assessment factors.

What are the similarities and differences between REACH Derived No Effect Levels (DNELs)for workers and OELs? Worker-DNELs are meant to be a tool to evaluate what can be considered a safe use of a substance before allowing that use, while OELs can be considered to be a tool to evaluate if a certain use already in practice is safe. The overall purpose for both is to protect workers' health. One major difference is that the scientific basis and the final level of the worker-DNELs is derived by industry (producers and importers) while the substantiation of an OEL usually is developed by an independent group of experts and the decision of a regulatory OEL is taken by the authority in question. The derivation of worker-DNELs also follows a relatively detailed framework (ECHA, 2008b) with predefined default assessment factors. Expert groups might have a framework such as SCOEL's, however the importance of a case-by-case basis and expert judgment is emphasised and explicit assessment factors are often not used. As worker-DNELs are to be derived for all substances produced or imported in quantities above 10 tonnes per year, and that workers are exposed to, the number of worker-DNELs is expected to highly exceed the number of OELs.

How will the numerical values of REACH worker-DNELs compare to OELs?
According to the interpretation of the REACH guidance presented in paper V, the worker-DNELs will be significantly lower than current OELs. In a comparison of the SCOEL recommendations and the calculated worker-DNELs, the worker-DNELs were on average six times lower than the SCOEL recommendations.

5 DISCUSSION

The studies presented in this thesis all concern OELs as a tool for risk management of chemical exposure in the occupational setting. I have presented a brief overview of general risk assessment as well as some detail on the process that precedes the setting of an OEL. While paper I and II concern comparisons of average levels between different actors, paper III investigates the regulation of a number of individual substances. These studies have shown that the assessments of existing risks and what is found acceptable differs. There were large differences, up to 40%, in average level of OELs between standard-setters (paper I). No evidence has been found that this variation can be explained by differences in legal status or by deviations in the explicitly stated principles for risk assessment and risk management, such as the intended level of health protection. Many significant differences were however found in how the levels of OELs were decided. For instance what is considered a high quality study or relevant data for human risk assessment differs between standard-setters (paper III). Also how uncertainty is handled varies between standard-setters, and might not be predictable even within one expert-group (paper IV). Paper V considered one framework for the handling of uncertainty presented by the European

Chemicals Agency. In the discussion I will focus on two themes of this thesis: trends within the EU and use of assessment factors. Finally, I will give some thoughts on the future of OEL setting.

5.1 TRENDS WITHIN THE EUROPEAN UNION

It seems reasonable to expect EU regulations to have a significant effect on the coverage of substances on national lists, considering that the indicative OELs have to be taken into consideration by the member states in their occupational health and safety regulations. Still, up to now most substances given indicative OELs have had national exposure limits already before the directive in question. The actual effect of the EU on the coverage is thus not clear, but it has been shown that the member states' OELs have become more similar to EC OELs and that the average level of OELs varies less today than in 1995 (paper II).

Another EU level regulation expected to influence risk management of chemical exposure at the workplace is the chemicals legislation REACH (1907/2006/EC). This legislation encompasses many aspects of the handling of chemicals and puts many requirements on registrants. Accordingly a set of guidance documents have been produced by the European Chemicals Agency to help industry to comply with REACH. This framework will potentially harmonise the risk assessment procedure within the EU, since it applies equally to those actors in Europe that fall under the requirements of REACH.

In another sense the worker-DNELs are expected to increase the diversity because they are expected to be considerably lower than previously set OELs (figure 5); mainly due to the different default assessment factors given in the guidance documents. Even larger differences between worker-DNELs and OELs than those found in paper IV might be expected. Kreider and Spencer (2010) derived a long-term worker-DNEL for styrene which was 50 times lower than the corresponding OELs for styrene from the German MAK-commission and the ACGIH. As REACH will employ a large number of actors for a large number of substances it can also be expected to increase the number of exposure limits for the workplace. REACH DNELs are not equivalent to regulatory OELs, and it should not be expected that the DNELs will be enforced in the same manner as one can expect national or EU level OELs to be. However, there are parallels and connections between worker-DNELs and OELs. The most notable is that the EU indicative OELs under some circumstances are allowed to be used as a replacement for worker-DNELs. The main function of the DNEL is to evaluate different exposure scenarios and to approve certain uses. This is in essence not so far from measuring the levels at a work-place to see if the current practices are in compliance with an OEL. The relationship between OELs and worker-DNELs needs to be clarified, as has also been pointed out by Gromiec (2008) and in paper V.

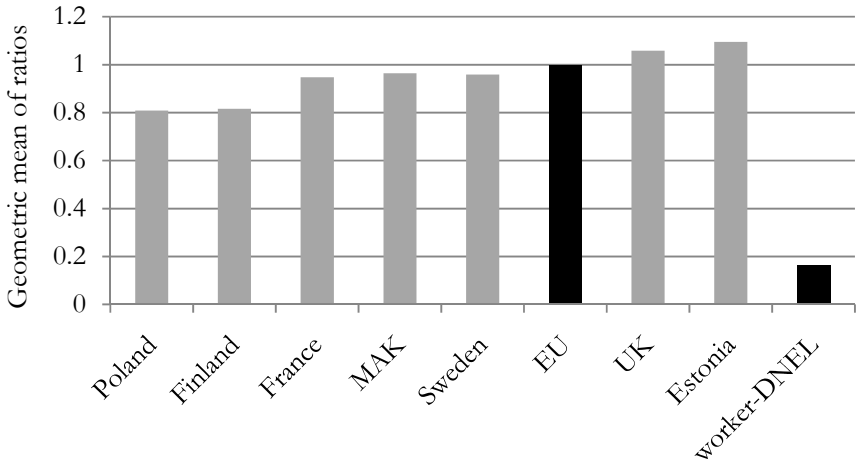

Figure 5 Showing a combination of selected results from paper II and paper V, comparing the worker-Derived No-Effect Levels (DNELs) calculated in paper V with corresponding OELs of other European countries. The lists of OELs and the worker-DNELs have been standardised against the European Commission OELs (EU), thus the EU has the average level of 1 in the figure. Lower geometric mean indicates lower average level of OELs. MAK- German MAK-kommission, UK- United Kingdom.

5.2 USE OF ASSESSMENT FACTORS

A common theme in paper IV and V was the handling of uncertainty in the derivation of health-based OELs using assessment factors. As shown in the section on previous research (2.10) the use of explicit assessment factors has been scarce when setting OELs, and when applied, low in comparison to other regulatory areas. Also the implied analogues of explicit assessment factors, called implied safety margins in paper IV and V, are low. I would describe them as too low, since the OELs generally tend to be lowered when revised. To illustrate this, the proportions of lowered and increased OELs for ACGIH, Sweden and the EU have been plotted in figure 6.

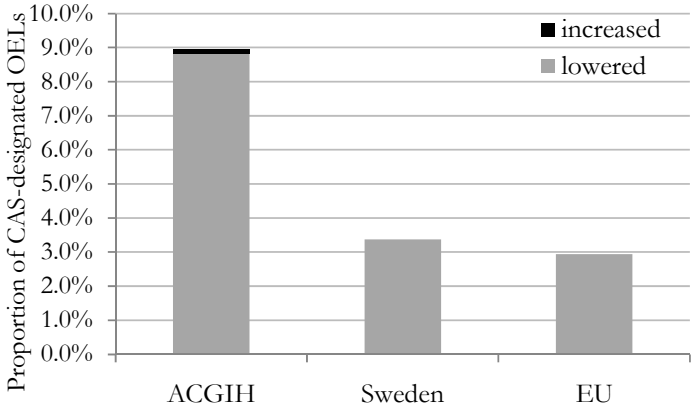

Figure 6 The proportion of OELs, with a Chemical Abstract Services (CAS) number, lowered or increased during 1995 and 2005 (ACGIH), 1996 and 2005 (Sweden), 1991 and 2006 (EU). The proportion has been calculated by divinding the number of CAS-designated OELs that have been changed by the number of CAS-designated OELs at the later of the two dates.

Had the assessment factors or implied safety margins been too high one would expect that as more knowledge is revealed OELs would be revised to higher levels more often than to lower levels. One main reason for using assessment factors is to cover uncertainties, including epistemic uncertainties; increase in knowledge about a substance's toxicology should thus reasonably in some instances lead to increases of OELs. One could argue that if the magnitude of assessment factors is well balanced future revisions of OELs would lead to decreases and increases in equal proportions, presumably the largest proportion will be of retained levels. However, there are numerous other factors that also might affect the way OELs are revised, such as policies on what kind of effects are acceptable or technical development allowing identification of more sensitive endpoints. It is thus expected that the revision of OELs will more often lead to lower levels than higher. Nevertheless, the historic trend of decreasing OELs could be used as an argument to increase the magnitude of assessment factors applied in the setting of future OELs.

A first step towards using higher assessment factors when setting exposure limits for the occupational setting is the REACH worker-DNELs. The accuracy of the REACH guidance default assessment factors have already been subject to some discussion. Malkiewicz et al. (2009) argued that the assessment factors for extrapolation of duration of exposure should be higher for a conservative approach. On the other hand, the European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC, 2010) argues that several of the assessment factors given by (ECHA, 2008b) are too high for setting OELs and "unjustified by the current state of scientific knowledge". It should be noted that the REACH guidance document (ECHA, 2008b) does not exclude the use of chemical specific assessment factors when sufficient knowledge is available. Thus, the default assessment factors of the REACH guidance should not be considered too high without further research and experience of the derivation of worker-DNELs for data-poor substances. Of course further research effort should also be directed at developing methods to decrease the uncertainties, such as physiologically based pharmacokinetic modelling or probabilistic approaches of quantifying variability and uncertainties.

5.3 TOWARDS FUTURE OCCUPATIONAL EXPOSURE LIMITS

The setting of OELs is a constant work in progress; a limit once set still needs continuous revision as new knowledge is produced. In paper III the documentation for the studied OELs were published in the rather large time span (1971 to 2003). The fact that several OELs were based on more than 30 year old documentations indicates that these OELs might be lowered if revised. The toxicological evaluation of a substance for the setting of OELs is a time-consuming process. The Nordic Expert Group has published 154 toxicological evaluations (www.nordicexpertgroup.org) since 1978. If possible, the Swedish Criteria Group base their toxicological evaluation on an evaluation performed by the Nordic Expert Group, and they have produced approximately 250 toxicological evaluations during the same time interval (www.av.se

/teman\hygieniska/kriteriegruppen/). Although also the SCOEL often bases its summary documents on a toxicological evaluation from a member-state expert group, it has only produced about 125 summary documents in 20 years (SCOEL, 2009b). The ACGIH have produced approximately 700 TLVs and 50 biological exposure indices since the mid 1940s. The average production of toxicological evaluations from these groups thus ranges from six to twelve per year. Cooperation between agencies on evaluation of both new and old chemicals in the workplace could help shorten the time for the up-date procedures. It might also result in reduced costs for involved parties if duplication of work can be avoided. This would be beneficial to workers as well as the agencies; keeping the OELs up to date, minimising the risk according to current knowledge and saving resources by reducing the duplication of work.

The use of OELs is an important tool for the efficient management of risks at individual workplaces. However, use of OELs is not sufficient without further consultation on what effects are expected and whether more sensitive subgroups have been identified. The OEL documentations are an important source for this kind of information, and thus needs to be publicly and easily available to users of OELs. The preferable way should be to publish the documentations in a down-loadable format on the Internet, which today is done by for instance the Nordic Expert Group, the Swedish Criteria Group and the SCOEL. More publishing on the scientific arena would also be beneficial for the development of methodology. Not only occupational health and safety practitioners are involved in the management of chemical hazards in the workplace, also several other professional groups possess relevant knowledge. Web-publishing or scientific publishing should be used as an arena for discussion.

Working on a, possibly international, framework on toxicological evaluations for OELs will help increase the transparency of OELs. Such a framework should strive for giving guidance on the evaluation of data on how to define an adverse health effect. This should be performed in a transparent and clearly defined manner in order for users such as occupational hygienists to evaluate the potential health effects at any particular workplace. As also noted in the conclusion of paper IV, such a framework should encompass a list of aspects of uncertainty that need to be discussed, possibly defining default assessment factors for all (known) aspects (as e.g. ECHA, 2008b).

6 OUTLOOK

My impression is that the assessment of chemical risk has very much been an area-to-area practice; risk assessors of chemical risk in the work-place have not to a sufficient extent shared experiences with risk assessors from other regulatory areas. Also, learning how to be a risk assessor has very much been the business of learning by doing. Regardless of how skilled these assessors are, one of the limitations of the system is that the borders between different regulatory areas are maintained. It is my belief that risk assessment of chemicals in one regulatory area can

learn from other areas. Thus, I not only wish to propose that the cooperation within the regulatory area should be increased; I also wish to encourage further interdisciplinary research. During these years that I have been a PhD student I have encountered several educational programmes within the areas of risk assessment, most of which have been imitated during these last five years. The CASCADE network of excellence (www.cascadenet.org) organised a training programme on health risk assessment, continued by the RA-courses project of which I have had the benefit of participating in several modules. Other examples of efforts within the advanced training of toxicologists and future risk assessors are the Dutch Post graduate Education of Toxicologists (www.toxcourses.nl), the Risk Assessment Summer School (http://www.iutox.org/rass.asp), the EUROTOX education and training programme (www.eurotox.org) and the TRISK programme (www.trisk-project.eu). I think these efforts are valuable because they constitute an arena where practitioners and advanced students can meet, and reach across the borders between scientific and regulatory areas.

In this thesis my focus has been on air-borne exposures and primarily the inhalation route. Measures to control chemical risks could be crudely divided into two major groups. One group is constituted by general measures that are aimed at exposure to chemicals in general, not to any specific chemical. This may include ventilation, personal protective equipment, automation of work processes, education aiming at better work procedures, etc. The other major group of measures is the substance-specific measures that aim at controlling the use of substances that are considered to require specific measures in addition to the general ones, usually because of the potential risks they pose under the exposure conditions at hand. An efficient control of chemical hazards at workplaces should reasonably employ a combination of both general and substance-specific measures. The use of measurements to control exposures against OELs is one of several types of substance-specific measures. Concerning occupational hygiene also the dermal exposure route is of considerable importance and might be more complicated to regulate than air-borne contaminants. Exposure limits might be a suitable risk management tool for some kinds of products, for instance limiting the amount of certain substances in professionally used mixtures or using biological limit values. Besides from the practical difficulties of biological limit values, for instance finding useable biomarkers and separating between multiple exposure sources, using biological limit values also conveys many ethical complications. Depending on the biological matrix used the methods might be too invasive or potentially violate the integrity of monitored persons. Hence, in my opinion, it will be more relevant to build technical solutions to avoid exposures, and if this proves insufficient, require use of personal protective equipment. For instance, to use gloves of suitable material for the exposure at hand at repairs of equipment not possible to fully clean. The use of personal protective equipment not only sets demands on the company organisation but also on the exposed individuals, who need to actually put on these gloves for certain tasks. This is of course not an issue limited to dermal exposures and the use of gloves, but rather related to the use of personal protective equipment in general. I would like to move towards studying risk management and risk communication at workplaces in the future.

After spending this time studying the substantiation of OELs, I am curious about their implementation and how they are perceived among the population that they are intended to protect. Some of the more specific questions I aim to work with in my future research are: How do workers and workplace safety managers perceive the workplace risks in chemical industry? How are OELs interpreted? Are they found useful by persons working with health and safety issues at workplaces? The purpose of investigating the current role of OELs as a tool for chemical risk reduction is to identify potential obstacles in the implementation and use of OELs as a risk management tool, and possibly be able to propose recommendations for improvements of this regulatory process.

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