Managing chemical risk through occupational exposure limits

Linda Schenk
STOCKHOLM 2009

This licentiate thesis consists of an introduction and the following papers:

Schenk L., Hansson S.O., Rudén C., Gilek M. (2008) Occupational exposure limits: A comparative study. *Regul Toxicol Pharmacol* 50:261-270
(Reprinted with kind permission of Elsevier.)

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
(Reprinted with kind permission of John Wiley & Sons.)

Schenk L. The use of primary data in risk assessment for occupational exposure limits. Manuscript.

Linda Schenk, Division of Philosophy, Department of Philosophy and the History of Technology, Royal Institute of Technology (KTH), SE-100 44 Stockholm, Sweden

Abstract
Occupational Exposure Limits (OELs) are used as an important regulatory instrument to protect workers' health from adverse effects of chemical exposures. The OELs mirror the outcome of the risk assessment and risk management performed by the standard setting actor. In paper I the OELs established by 18 different organisations or national regulatory agencies from the industrialised world were compared. The comparison concerned: (1) what chemicals have been selected and (2) the average level of exposure limits for each organisation. In paper II the OELs established by 7 different national regulatory agencies of EU member states are compared to those of the European Commission (EC). In addition to the same comparisons as performed in the first study a comparison level was introduced (3) the similarity between the OELs of these EU member states and the OELs recommended by the EC.

List of OELs were collected through the web-pages of, and e-mail communication with the standard-setting agencies. The selection of agencies was determined by availability and language of the lists. The database compiled for the purpose of paper I contains 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 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 this database was narrowed down to the European perspective. Also within Europe there was a nearly as large difference concerning the average level of OELs. The average level of lists tends to decrease over time, although there are exceptions to this. The similarity index in paper II indicates that the exposure limits of EU member states are converging towards the European Commission's recommended OELs. These two studies also showed that OELs for the same substance can vary significantly between different standard-setters. The work presented in paper III identifies steps in the risk assessment that could account for these differences. Substances for which the levels of OELs vary by a factor of 100 or more were identified and their documentation sought for further scrutiny. Differences in the identification of the critical effect could explain the different level of the OELs for half of the substances. The results reported in paper III also confirm the tendency of older OELs generally being higher. Furthermore, several OELs were more than 30 years old and were based on out-dated knowledge. 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.

Keywords: occupational exposure limit, risk assessment, risk management, chemicals regulation, regulatory toxicology, European Union

ISSN 1654-627X
ISBN 978-91-7415-206-7

Acknowledgements

I have written this thesis while being employed by the School of Life Sciences at Södertörn University and accepted as a PhD student at the Department of Philosophy and the History of Technology at the Royal Institute of Technology. First and foremost I thank my supervisors Christina Rudén and Michael Gilek, for giving me this opportunity and for the help and support they have offered me. Thanks for support and co-authoring are also due to Sven Ove Hansson. I am hugely indebted to Anna-Karin Lindberg and Kerstin Gustafsson for teaching me all the very crucial facts about being a PhD student.

Thanks to my wonderful co-workers at Södertörn University, and to the enthusiasts of pubs and films at Life Sciences: you rule! Thanks also to my colleagues at the Division of Philosophy and the "risk seminars", an extra one to Marlene Ågerstrand. I am ever so indebted to all my friends for their support and encouragement. Thanks especially to Johan Olin; you got me, and my furniture, to Stockholm.

My work has been funded by the Baltic Sea Foundation. Financial support has also been granted by Helge Ax:son Johnssons stiftelse, Kungliga Vetenskapsakademien, Längmanska Kulturfonden and Stiftelsen A&M Erikssons minnesfond. Their support is gratefully acknowledged.

Abbreviations used:

ACGIH	American Conference of Governmental Industrial Hygienists
CAS	Chemical Abstracts Service
DFG	Deutsche Forschungsgemeinschaft (German Research Foundation)
DMEL	Derived Minimal Effect Level
DNEL	Derived No-Effect Level
EC	European Commission
EU	European Union
JSOH	Japan Society of Occupational Health
LOAEL	Lowest Observable Adverse Effect Level
MAK	Maximale Arbeitsplatz-Konzentration (Maximum Allowable Concentration)
NEG	Nordic Expert Group
NIOSH	National Institute of Occupational Safety and Health
NOAEL	No Observable Adverse Effect Level
OEL	Occupational Exposure Limit
RA	Risk Assessment
REACH	Registration, Evaluation and Authorisation of CHemicals
SEG	Scientific Expert Group
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

Paper I
Schenk L., Hansson S.O., Rudén C., Gilek M. (2008) Occupational exposure limits: A comparative study. *Regul Toxicol Pharmacol* 50:261-270

Paper 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

Paper III
Schenk L. The use of primary data in risk assessment for occupational exposure limits. Manuscript.

1. Introduction

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 extent of exposures. People are exposed to a variety of chemicals during their life which calls for regulatory action from the authorities to protect against negative health effects. This thesis concerns the issue of chemical exposure at the work place, and more specifically a risk management tool that is widely used, namely Occupational Exposure Limits (OELs), and the risk assessments performed to derive these. Lists of OELs are presented as numerical values, allowing quantitative comparisons. Paper I and II present and compare average values of national exposure limits. A difference in these average values can have many explanations; differences in risk acceptance or a time lag in the up-date procedure are two possible alternatives. By scrutinising the primary data used and the health criteria specified, scientific reasons for differences, like the emergence of new knowledge, can be separated from non-scientifically justified reasons. Examples of policy issues are the definition of what effects present a significant risk to human health and the magnitude of risk that is accepted.

1.1 Aims of this thesis

This thesis focuses on one area of regulation and one tool of risk management: OELs. Describing similarities between countries in selection of what substances to regulate and comparing the average level of OELs was the first aim. This was followed by a focus on the European Union and questions about whether the EU OELs have had any influence on the national states concerning which substances to regulate and the levels of the OELs. The final aim of this thesis is also to describe how some of the currently enforced OELs are substantiated. By such a study of OELs and substantiating documents the main objective is to uncover possible discrepancies and to produce knowledge that can help improve the risk decision process. I also wish to put the setting of OELs in a context of general risk assessment.

1.2 Outline of thesis

Section 2 introduces the key concepts of this thesis: The risk decision process including risk assessment and risk management are outlined in 2.1, OELs are given an introduction in 2.2, 2.3 presents the risk decision process specifically concerning OELs and 2.4 presents the risk assessment performed to substantiate an OEL. The European Union aspects of these issues are presented briefly in 2.5. Section 2.6 contains a summary of

previous research on the issue of OELs. The methods that have been used are briefly described in section 3. In sections 4.1 to 4.3 the results of each paper are summarised, which is followed by a discussion of the joint results of the three papers, in section 5. Section 5.1 summarises the main conclusions drawn from papers I-III and an outlook is presented in section 5.2. I discuss some different ways in which I might continue my work towards a PhD in section 6.

2. Background

To justify regulatory action for a substance there must be a known risk associated to it, this means identifying its harmful potential and possible exposure to it. Of course risks can exist even if they are not identified, but as a rule they also remain unregulated until identified. 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. Furthermore, developing standardised methodologies for these activities also falls under the umbrella of regulatory toxicology. Hansson and Rudén (2006) suggested the addition of another branch of studies that aim at evaluating the performance of the risk decision process. Schwenk et al. (2002) outlines the diversity of methods and expertises found under the collective name of regulatory toxicology, which corroborates the view of regulatory toxicology having a broader disciplinary scope than toxicology on its own.

2.1 Risk Assessment and Risk Management

Traditionally the risk decision process is perceived as split into two separate steps, risk assessment and risk management. The risk assessment uses primary data to scientifically evaluate the risks of a certain substance. Risk assessment has been structurally defined by several agencies (NRC, 1983; EC, 2003; 1488/94/EC). The EC Technical guidance document (EC, 2003) specifies three main steps: **Assessment of effects** which comprises *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. 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 applies the results from the risk assessment. Policy enters the process at the step of risk management, also considering other aspects e.g. economic and technological feasibility and in this part of the process stakeholders may give their opinion on the conclusion or proposed measure. A consequence analysis is sometimes performed, comparing the effects of implementing different risk management strategies. It is important to note that the risk assessment and risk management are not as separate as is depicted at times. Thus, when studying the regulatory decision process one needs to keep in mind that risk decisions are made before, during and after the risk assessment is performed.

2.2 Occupational Exposure Limits

Working life may be a major contributor to the chemicals exposure that humans experience during their life. 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. One can conclude that the risks associated with chemical exposure and their regulation in the work place is well worth scientific scrutiny. The rationale behind OELs is that if the dosage of 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 the specific chemical. For some chemicals evidence suggests that a negative health effect only occurs above a certain level of exposure, this means that a safe level of exposure is possible to achieve. 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. 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.

OELs restrict the allowed concentrations of harmful substances in the work-place air, averaged over a period of time. The level of the OELs 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 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.

Being the first to frame a risk also means that you have the opportunity to define the problem or risk. This first framing or definition often affects later definitions of the risk as well. One can very well argue that when the American Conference of Governmental Industrial Hygienists (ACGIH) published the first list of the Threshold Limit Values (TLVs) in 1946 it in a sense framed the issue of workplace risks induced by chemicals, and postulated the management tool of limit values. Since then many national agencies have adopted the ACGIH TLVs (Piney, 1998) and the concept of exposure limits has been 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, 1998; Rudén, 2003). Nevertheless, the TLVs and their documentations are still used world-wide (paper I), although more and more countries have occupational health and safety agencies of their own, which produce lists of OELs and corresponding substantiating documentation.

2.3 The risk decision process

The risk decision process differs somewhat between agencies as well as between regulatory areas. Figure 1 is a schematic depiction of the procedure in the case of OELs. For a chemical to be regulated in the occupational setting it has to be proved harmful, this means that the lists of OELs are so called negative lists; what is not regulated (either by

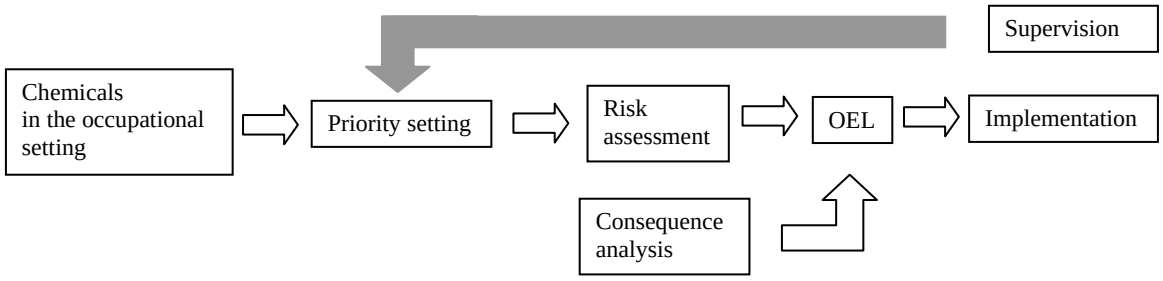

Figure 1 Schematic representation of the risk decisions concerning an OEL.

exposure limits or otherwise) is 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). The US law of Food Additives Amendment also requires that food additives need to be proven not harmful before exposing humans.

What is not regulated in these instances is not allowed at all. The same requirements on food additives apply in the EU.

The supervision of work place 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 enforcement of the OELs is a step separate from the determination of 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. Therefore, no conclusions should be drawn about the quality of actual working conditions from the material presented in this thesis.

2.4 Substantiating an OEL

Once it is concluded that there is a need for an OEL for a substance a risk assessment has to be performed for that substance. Figure 2 schematically depicts the steps of the risk

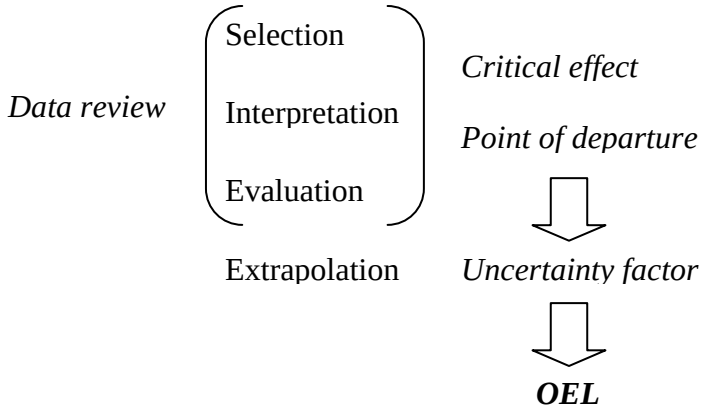

Figure 2 Steps in the risk assessment expected to potentially affect the level of the OEL.

assessment that through literature review aims at determining the adverse health effects of a substance. The risk assessment 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. The process of setting an exposure limit does not confirm fully to the classical risk assessment scheme presented in 2.1. The major focus is on the first part, assessment of effects, while the analogy of exposure assessment and risk characterisation is the determination of an exposure level that will lead to acceptably low adverse health effects.

The critical effect is the adverse effect which is considered to be the most important to protect humans from (paper III). When reading a risk assessment document for an OEL the critical effect is that 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 may be a no observable adverse effect level (NOAEL) which is the level of exposure that does not cause a significant effect. In some instances all doses tested cause an (adverse) effect, meaning that a NOAEL cannot be derived. In instances like these the point of departure might be a lowest observable effect level (LOAEL). Since conclusive epidemiological data are sparse, these values are as a rule based on animal data. Another method to derive a starting point for an exposure limit is to use the benchmark dose (BMD) approach instead of determining LOAELs and corresponding NOAELs (Crump, 1984). The BMD approach applies a model to the entire data set, thus using higher doses to predict the shape of the dose-response curve at the low levels. The methodology includes the testing of several models and the calculation of likelihoods for each of them, thus determining which is the most appropriate. The aim is to find the dose that corresponds to a pre-determined effect level. This method of deriving a point of departure has been used in risk assessments for instance in the derivation of the EU air quality standard for benzo[a]pyrene (WHO, 2002); however, as is shown in paper III this approach is not commonly used for OELs.

From the point of departure the OEL is extrapolated, this extrapolation is made to cover the variation within and between species, differences in exposure duration and uncertainties due to lack of data. In other regulatory areas, for instance food safety, often explicit assessment factors are used. The factor used for extrapolation might also be called safety factor, uncertainty factor or modifying factors (e.g. US EPA). When setting

OELs explicit safety factors are not used in the same extent as in other regulatory areas (Hansson 1997; paper III).

2.5 The European Union's OELs

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 the setting of OELs was prescribed. This directive has since been replaced by the 89/391/EEC which is the framework now in effect. Indicative OELs are established through Commission directives and Binding OELs through Council directives. Adopting a Commission directive does not require a formal consultation with the European Parliament, which a Council directive does. The first indicative OELs were laid down in directive 91/322/EEC. These indicative OELs were proposed by the EC which then to its help had an informal group of scientific experts. In 1995 this group of experts received a formal status (95/320/EC) as the Scientific Committee on Occupational Exposure Limits (SCOEL). The SCOEL recommends health-based OELs to the EC. When they find 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. 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. 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 I). The EU is not 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 I EU directives containing indicative and binding OELs

Directive	**Type of OEL**
91/322/EEC	Indicative
96/94/EC	Indicative
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

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 authorization 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. How this information will affect the regulation of chemicals in the workplace is uncertain. 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. For substances within the scope of REACH, excluding e.g. cosmetics and pharmaceuticals, that are produced in quantities above 10 tonnes a chemical safety report is to be prepared. One of the requirements of this is to identify so called Derived No-Effect Levels (DNELs) for substances that have identifiable threshold effects. Within the guidance for the implementation of REACH (ECHA, 2008) workers are mentioned as one subpopulation requiring a specific DNEL, and an overview of how to derive such worker-DNELs is also given in chapter R.8. For a substance without an identifiable threshold effect a Derived Minimal Effect Level (DMEL) is to be derived. A DMEL should correspond to a risk level “which is considered to be of very low concern”. 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.

2.6 Previous research

Rudén (2001) showed that for trichloroethylene the evaluation and interpretation of primary data differed in several of the studied risk assessment documents. Previous studies of OELs show that there are national differences in risk assessment and management of occupational chemical exposure. Nielsen and Øvrebø (2008) published a review of approaches and trends concerning the setting of health-based 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. Taylor et al. (2007) reviewed the implementation of the regulations for lead issued by the EU. 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. Also some, but not all, countries defined special arrangements to account for differences in sensitivity due to gender or age. 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.

As OELs are revised they tend to be gradually decreased (Hansson 1998; paper I; paper II). Other studies concern limits for specific substances and show that the OELs are lowered as more, and better information on adverse effects becomes available (Markowitz and Rosner, 1995; Greenberg, 2006).

3. Method

The presented studies are comparative in their nature. In paper I the comparison concerned the selection of which substances were regulated and at what level. In paper II in addition the similarity to the EU 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.

3.1 Quantitative methods

The first step was to compile a database of OELs. Only OELs with a CAS-number were included in this database. The number of chosen organisations was limited to the availability of the lists of OELs through web-pages and e-mail correspondence. The final database comprises of OELs from 18 organisations for 1341 substances. For use in paper II this database was scaled down to the 7 European countries for which lists of OELs were available and the EU.

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.

In both paper I and II the average level of lists were compared by using the geometric means method. This means that the OELs of the different agencies were divided by the OELs of a comparison list resulting in a new list of ratios. The geometric mean was then calculated from these ratios. In paper I the comparison list used was a combination of the EU OELs and the original list of the ACGIH TLVs. In paper II the comparison list comprised of only the EU OELs.

In paper II the similarity of the national OELs to the EU OELs was calculated in a similar fashion as the average level by the geometric means method. The ratios were computed using the EU list of OELs as a comparison list but before extracting the geometric mean the ratios above one were inverted. By this inversion the geometric mean of one indicates complete similarity to the EU OELs while the similarity decreases the lower the geometric mean is, giving deviations in both directions (i.e. higher or lower) from the EU OELs the same weight.

3.2 Qualitative methods

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 2) that the documentation was published in English, French or any Nordic language. 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 in a coherent application of the criteria for the identification of these parameters.

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 198 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), Occupational Health and Safety Administration (OSHA) of the United States, 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 non-European countries' selection of what substances to include on the list was more similar to the ACGIH list than the European Countries. 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 exposure limits were in 2005 (on average) nearly 40 % higher than those of Poland. Surprisingly also the EU exposure limits were on average high compared to the other organisations, only the US OSHA exposure limits were higher. No evidence was found to indicate that this variation was explainable by differences in legal status 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 of airborne substances “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 EU. 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 over-all level is by no means the lowest. A comparison between the indicative OELs of the EU that are claimed to be health-based and the Finnish OELs shows that contradictory assessments have been made within in the range of this survey.

For eight lists the database also included 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 6 of the 8 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 7 different national regulatory agencies of EU member states were compared to those of the European Commission (EC). The included countries were: Estonia, Finland, France, Germany, Poland, Sweden and the United Kingdom. The comparison concerned: (1) what chemicals have been selected, (2) the average level of exposure limits for all chemicals, and (3) the similarity between the OELs of different EU member states and the OELs recommended by the European Commission.

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 that this. Poland had the lowest exposure limits, nearly 35 per cent 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 a 100 per cent 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 European Commission's recommended 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 of 18 different lists, using the CAS number as identification. The final selection 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. Nearly 50 documents were scrutinised in this study, 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 generally are 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 level 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 risk assessment. 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 ten of the documents (20%) 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 ten of the 87 identified key studies were used to derive the point of departure in more than one risk assessment. Five 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, 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 uncertainty 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.

5. Discussion

Previous studies of OELs have shown that there are large and unsystematic differences between decisions made for different chemicals with similar adverse health effects (Hansson and Rudén, 2006). Case studies concerning certain areas of occupation (Haber and Maier, 2002; Bigelow et al., 2004) or certain chemicals (Taylor et al., 2007; paper III) also demonstrate that there are national differences in risk assessment and management of occupational chemical exposure. The results presented in paper I and II do not investigate the regulation of individual substances, but the comparison of the average levels of OELs confirm that there are differences between different actors.

The listing of OELs started in a very uniform fashion. The industrialised countries almost without exception started their own work with the lists of OELs by copying the ACGIH TLVs. As time passed and national agencies introduced their own risk assessment procedures there has been an increasing diversity and today both coverage of substances

and level of OELs vary considerably among countries. In paper I it was shown that the US OSHA had almost 40% higher limits than Poland and in paper II the differences within Europe were shown to be nearly as large, almost 35%. 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. The ACGIH still has a noticeable impact on national regulations and new forces for unifying the OELs have arisen due to the EU directives laying down indicative and binding OELs. EU regulations can be expected to have a significant effect 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. But up to now most substances given indicative OELs had national exposure limits already before the directive in question. The actual effect of the EU on the coverage is thus not clear, possibly it is so that countries which develop new occupational health and safety regulations are more influenced by the EU standards than countries with already established practices.

There is no demand on the individual countries to implement the exact value of the EU indicative OELs. A calculation of the similarity to the EU levels for substances added nationally after being assigned an EU OEL showed that Finland and UK have assimilated the exact same levels as the EU OELs while Germany, Poland and Sweden have not (paper II). It has also been showed that the national exposure limits generally have become more similar to the EU OELs since the mid 1990's (paper II). Also, the average level of the OELs varied more among countries ten years ago than it does today. It cannot be determined whether this is an effect of harmonisation without further scrutiny of the each country's motives for the individual OELs.

As is discussed in paper II many benefits come from harmonisation. Among those benefits are reduced costs for involved parties if duplication of work can be avoided. It could also lower the possibility that low demands on occupational health will not become one of the means to create competition in order to attract industries, at least not within the EU. Also, international collaboration would be able to improve the speed at which new substances are added and old limits are revised. But, since most European countries have an average level of exposure limits that is lower than that of the EU, harmonisation could lead to regulations offering less protection for human health. That is, if the indicative OELs of the EU are simply assimilated without adjustment, it would lead to an increase in the average level. This development could be a cause for concern if it leads to a lower

margin of safety being accepted. Harmonisation can also have another negative effect. Important changes in OELs, not necessarily implying only lowering the numerical value of an OEL, are more likely to be introduced by pioneering agencies suggesting advancements of safety demands and methodology. One not very desirable effect of harmonisation could be that these front-runners will become scarce in the future.

In paper III the documentations of 14 substances were scrutinised in order to discover factors in the risk assessment that might cause differences in the conclusions on a substance. To achieve this selection of what substances to study was made by identifying substances for which large differences in the level of OELs prevailed. This makes the selection non-random, which should be kept in mind when applying the conclusions from this study. The definition of what is the critical health effect varies for the same substances between risk assessors (paper III). The definition of what should be aimed at with an OEL also varies, in Sweden it is explicitly stated that the critical effects for a substance in the occupational setting should be the adverse effect occurring at the lowest dose (Nordberg et al., 1988). The study of the OEL documentations in paper III shows that not all agencies follow this definition. The definition of an adverse health effect and the evaluation of them 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. International harmonisation procedures like the development of guidance documents on risk assessment, for instance within the EU, can be one means to achieve this.

The ACGIH documentation has the advantage of being well structured and being available, although against a fee. To be able to apply the OELs in a sensible way in occupational health and safety management one needs to be familiar with the documentation, requiring it to be available. These documents are often published in forums not available to the public since they are, as it is sometimes referred to, grey literature. The preferable way should be to publish them in a down-loadable format on the Internet, which today is not the case for many agencies. 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 work place, several other professional groups possess relevant knowledge. Open access publishing or scientific publishing should be used as an arena for discussion.

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 of 1971 to 2003. The fact that several OELs were based on more than 30 year old risk assessments indicates that these OELs might be lowered if revised. Cooperation between agencies on risk assessment of both new and old chemicals in the workplace could help shorten the time for the up-date procedures. 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.

5.1 Concluding remarks

The studies presented in this thesis all concern OELs as a tool for risk management of chemical exposure in the occupational setting. I have in this introduction presented a brief overview of general risk assessment as well as some detail on the risk decision process that precedes the setting of an OEL. While papers 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 what risks exist and what risks are acceptable differ. For instance, what is found to be the critical effect can, which was shown in paper III, differ for one substance between different risk assessors. Partly, this is related to the fact that there is no single definition of what is to be considered an adverse effect. The identification of critical effect depends to a high extent on the individual experts performing the risk assessment. Also the selection what literature to review in a risk assessment and how the evidence is weighed depends on the individual experts performing the risk assessment.

One of my recommendations from this thesis is that agencies should continue to cooperate to enhance the efficiency of the risk assessment procedure. As was shown in paper III the OELs for several substances probably were not sufficiently stringent to protect from adverse effects detected in more recent time. Aiming at this kind of harmonisation will reduce costs for the agencies as well as be beneficial for exposed workers. The risk assessments, or OEL documentations, need to be presented in an accessible form as well as in an accessible forum. To efficiently manage the risks at individual workplaces the exposure limits are important tools, but they are not sufficient tools without further consultation on what effects are expected and whether more sensitive subgroups have been identified. Working on a, possibly international, frame-work on risk assessment for OELs will help develop the efficiency of the use of OELs.

5.2 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 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. However skilled these assessors are, one of the limitations of this 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.

6. Future work towards a PhD-thesis

The immediate future will involve a study of the application, or rather non-application, of assessment factors when setting OELs. This study will be based on the same OELs that are scrutinised in paper III, possibly with an expansion of the material to further cover more recent practices. The analysis will involve the calculated margin of safety in those instances where no assessment factor has been explicitly given, and the a discussion of the distinction between these calculated, or implicit, margins of safety depending on what is considered to be the critical effect and what is used as a point of departure.

From this point the work could continue in two directions as I currently see it. My interest lies primarily in the handling of uncertainty in risk assessments and specifically how that is expressed by the use of assessment factors. A continuation of my work could be to use the application of assessment factors in risk assessments as a starting point for the comparison between different regulatory areas.

The second direction in which I could work to complete my thesis would be to thematically stay within the area of occupational hygiene. After having studied the OELs for so long, I am curious on the implementation of them and mainly the perception of them among the population that they are intended to protect. How do workers perceive the workplace risks of a chemical industry, how do they interpret the OELs and what is the level of awareness concerning chemical risks?

References

80/1107/EEC: Council Directive 80/1107/EEC of 27 November 1980 on the protection of workers from the risks related to exposure to chemical, physical and biological agents at work.

89/391/EEC: Council Directive 89/391/EEC of 12 June 1989 on the introduction of measures to encourage improvements in the safety and health of workers at work.

91/322/EC: Commission Directive 91/322/EEC of 29 May 1991 on establishing indicative limit values by implementing Council Directive 80/1107/EEC on the protection of workers from the risks related to exposure to chemical, physical and biological agents at work.

93/67/EEC: Commission Directive 93/67/EEC of 20 July 1993 laying down the principles for assessment of risks to man and the environment of substances notified in accordance with Council Directive 67/548/EEC.

95/320/EC: Commission Decision of 12 July 1995 setting up a Scientific Committee for Occupational Exposure Limits to Chemical Agents**.**

96/94/EC: Commission Directive 96/94/EC of 18 December 1996 establishing a second list of indicative limit values in implementation of Council Directive 80/1107/EEC on the protection of workers from the risks related to exposure to chemical, physical and biological agents at work.

98/8/EC: Directive 98/8/EC of the European Parliament and of the Council of 16 February 1998 concerning the placing of biocidal products on the market.

98/24/EC: Council Directive 98/24/EC of 7 April 1998 on the protection of the health and safety of workers from the risks related to chemical agents at work (fourteenth individual Directive within the meaning of Article 16(1) of Directive 89/391/EEC).

00/39/EC: Commission Directive 2000/39/EC of 8 June 2000 establishing a first list of indicative occupational exposure limit values in implementation of Council Directive 98/24/EC on the protection of the health and safety of workers from the risks related to chemical agents at work.

03/18/EC: Directive 2003/18/EC of the European Parliament and of the Council of 27 March 2003 amending Council Directive 83/477/EEC on the protection of workers from the risks related to exposure to asbestos at work (Text with EEA relevance).

04/37/EC: Directive 2004/37/EC of the European Parliament and of the Council of 29 April 2004 on the protection of workers from the risks related to exposure to carcinogens or mutagens at work (Sixth individual Directive within the meaning of Article 16(1) of Council Directive 89/391/EEC).

06/15/EC: Commission Directive 2006/15/EC of 7 February 2006 establishing a second list of indicative occupational exposure limit values in implementation of Council Directive 98/24/EC and amending Directives 91/322/EEC and 2000/39/EC.

1488/1994/EC: Commission Regulation (EC) No 1488/94 of 28 June 1994 laying down the principles for the assessment of risks to man and the environment of existing substances in accordance with Council Regulation (EEC) No 793/93 (Text with EEA relevance).

1907/2006/EC: Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), establishing a European Chemicals Agency, amending Directive 1999/45/EC and repealing Council Regulation (EEC) No 793/93 and Commission Regulation (EC) No 1488/94 as well as Council Directive 76/769/EEC and Commission Directives 91/155/EEC, 93/67/EEC, 93/105/EC and 2000/21/EC.

Bigelow P., Moore D., Yassi A. (2004) Assessing the health implications for healthcare workers of regulatory changes eliminating locally developed occupational exposure limits in favor of TLVs: An evidence-based bipartite approach. *Int J Occup Environ health* 10(4): 433-444

Crump K.S. (1984) An improved procedure for low-dose carcinogenic risk assessment from animal data. *J Environ Pathol Toxicol Oncol* 5:339-348

ECHA- European Chemicals Agency (2008). Guidance on the implementation of REACH. Guidance on information requirements and chemical safety assessment Chapter R.8: Characterisation of dose [concentration]-response for human health.

Feron V.J. (2003) Setting Occupational exposure limits in the European Union. In: Occupational exposure limits – approaches and criteria. Proceedings from a niva course held in Uppsala, Sweden, 24–28 September 2001. Ed. Johanson G. *Arbete och hälsa,* 2003:17, Stockholm, Sweden.

Greenberg M. (2006) Revising the British Occupational Hygiene Society asbestos standard: 1968-1982. *Am J Ind Med* 49(7):577-604

Gromiec J. (2008) [Problems concerning the integration of “derived-no-effect-levels” (DNELS) into occupational safety and health regulations]. Abstract (article available in Polish). *Med Pr* 59(1):65-73

Haber L.T. and Maier A. (2002) Scientific criteria used for the development of occupational exposure limits for metals and other mining related chemicals. *Regul Toxicol Pharmacol* 36:262-279

Hansson S.O. (1997) Critical effects and Exposure Limits. *Risk Analysis* 17(2):227-236

Hansson S.O. (1998) Setting the Limit. Occupational health standards and the limits of science. Oxford University Press, New York, 1998. ISBN: 0-19-512160-0

Hansson S.O. and Rudén C. (2006) Evaluating the risk decision process. *Toxicology* 218:100-111

Markowitz G. and Rosner D. (1995) The Limits of Thresholds – Silica and the Politics of Science, 1935 to 1990. *Am J Public Health* 85(2):253-262

Nielsen G.D. and Øvrebø S. (2008) Background, approaches and recent trends for setting health-based occupational exposure limits: A minireview. *Regul Toxicol Pharmacol* 51(3): 253-269

Nordberg G.F., Frostling H., Lundberg P., Westerholm P. (1988) Swedish occupational exposure limits – developments in scientific evaluation and documentation. Am J Ind Med 14(2):217-221

NRC – National Research Council (1983) Risk Assessment in the Federal Government: Managing the Process. National Academy Press, Washington D.C., USA. 1983. ISBN: 0-309-03349-7

Piney M. (1998). Exposure limits and health risks arguments for a paradigm shift. In: The politics of chemical risk. Scenarios for a regulatory future. Eds. Bal R and Halffman W. Kluwer Academic publishers, Dordrecht, The Netherlands. ISBN: 0792348917

Rappaport S.M. (1993) Threshold Limit Values, Permissible Exposure Limits, and Feasibility . The Bases for Exposure Limits in the United States. *Am J Ind Med* 23(5) 683-694

Roach S.A. and Rappaport S.M. (1990) But they are not thresholds: A critical analysis of the documentation of threshold limit values. *Am J Ind Med* 17(6):727-753

Rudén C. (2001) The use and evaluation of primary data in 29 trichloroethylene carcinogen risk assessments *Regul Toxicol Pharmacol* 34:3-16

Rudén C. (2003) Scrutinizing ACGIH risk assessments – the trichloroethylene case. *Am J Ind Med* 44:207-213

Schwenk M., Werner M., Younes M. (2002) Regulatory toxicology: objectives and tasks defined by the working group of the German society of experimental and clinical pharmacology and toxicology. *Toxicol Letters* 126:145-153

Taylor A., Angerer J., Arnaud J., Claeys F., Kristiansen j., Mazarraza O., Menditto A., Patriarca M., Pineau A., Valkonen S., Weycamp C. (2007) Differences in national legislation for the implementation of lead regulations included in the European directive for the protection of the health and safety of workers with occupational exposure to chemical agents (98/24/EC). *Int Arch Occup Environ Health* 80:254-264

Walters D. (2002) The Framework Directive. In: Regulating Health and Safety Management in the European Union. A study of the dynamics of change. Ed: Walters D. P.I.E. Peter Lang, Brussels, Belgium. ISBN: 90-5201-998-3

Walters D. and Grodzki K. (2006) Beyond Limits? Dealing with chemical risks at work in Europe. Elsevier Ltd., Oxford, UK. ISBN: 0-08-044858-5

WHO - World health organization (2002) Air Quality Guidelines for Europe. 2nd ed. WHO Regional Publications, European Series, No. 91.
Available at: www.euro.who.int/air