National Institute for Public Health
and the Environment
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Human risk assessment of single exposure in chemical incidents

Present situation and emerging scenarios

RIVM report 320300001/2010

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Abstract

Human risk assessment of single exposure in chemical incidents

The release of chemicals from their containment, either accidentally or deliberately, is one of the most relevant risk scenarios in Europe. A human health risk assessment is a prerequisite for chemical incident prevention, preparedness and response. European guidance and harmonized Acute Exposure Reference Values (AERVs) are urgently needed for effective human health risk assessment in the context of chemical incidents.

At present, no broad European consensus is available on guidance for risk assessment, risk management and risk communication purposes in case of chemical incidents. A review of legislation, existing or currently under revision, suggests that harmonized European guidance is not expected to be developed in the short term. An increasing number of European countries are developing their own procedures to assess the human health risk of chemical incident scenarios. The AERVs thus produced serve different purposes and are not interchangeable. Lack of international harmonization seriously obstructs a consistent response in chemical emergencies with transboundary effects within and beyond the EU, will hamper multinational companies attempting to make consistent risk assessments worldwide and will hinder consistent and transparent assessment, and management and communication of risks by different stakeholders.

Emerging chemical incident risk scenarios and risk drivers have been identified. It is recommended to monitor more frequently at an early stage for new trends in chemicals, scenarios and risks from chemical incidents. A need for a specific approach to deal with single exposure to mixtures of chemicals is identified, as well as for specific guidance to adequately protect professional first responders.

Keywords:
Chemical incident, acute exposure, human health risk, risk assessment

Rapport in het kort

Risicobeoordeling van eenmalige blootstelling aan chemische stoffen bij incidenten

Het vrijkomen van chemische stoffen, ten gevolge van een incident of een doelbewuste (terroristische) actie, vormt één van de belangrijkste risicoscenario's binnen Europa. Een nauwkeurige inschatting van de gezondheidseffecten in relatie tot de concentratie en de duur van de blootstelling is hierbij van belang. Europese richtlijnen en geharmoniseerde Acute Exposure Reference Values (AERVs) zijn hiertoe een vereiste.

Op dit moment bestaan er binnen Europa geen geharmoniseerde richtlijnen voor de risicobeoordeling, -beheersing en -communicatie gericht op eenmalige blootstelling bij chemische incidenten noch wordt deze op korte termijn verwacht. Een toenemend aantal Europese lidstaten ontwikkelt op dit moment eigen methodologieën voor het vaststellen van AERVs. Tevens dienen deze AERVs vaak verschillende doelen en zijn daardoor niet uitwisselbaar. In de praktijk worden ze wel als zodanig gebruikt, wat leidt tot inconsistenties en onjuistheden bij het beoordelen van risico's bij chemische incidenten.

Uit een internetenquête blijkt dat binnen Europa grote behoefte bestaat aan overeenstemming en harmonisatie van AERVs. Het ontbreken hiervan staat een consistente en uniforme respons bij (grensoverschrijdende) chemische incidenten in de weg, het belemmert een transparante en eenduidige risicobeoordeling, -beheersing en -communicatie en het bemoeilijkt multinationals bij het opzetten van een consistente risicobeoordelingsmethodiek.

Nieuwe scenario's voor de risicobeoordeling bij chemische incidenten zijn geïdentificeerd. Aanbevolen wordt om actief regelmatig en vroegtijdig nieuwe trends in ontwikkeling van chemische stoffen en risicoscenario's voor chemische incidenten te signaleren. Blootstelling aan mengsels van stoffen alsmede het ontwikkelen van richtlijnen ter bescherming van hulpverleners, verdient hierbij specifieke aandacht.

Trefwoorden:
Chemische incidenten, acute blootstelling, risicobeoordeling, humane gezondheidsrisico's

Contents

Summary

Chemical incidents occur frequently and have the potential to expose up to thousands of individuals simultaneously. The release of chemicals from their containment, either accidentally or initiated by an intentional act, is one of the most relevant risk scenarios in Europe. Prevention or mitigation of human health effects is often the major determinant underlying accident prevention policy and emergency response decisions. This requires an accurate and precise assessment of human health risk resulting from acute releases. Acute Exposure Reference Values (AERVs) are pre-eminently suitable for the public health assessment and are perceived as important cornerstones of the management of chemical incidents. AERVs are thresholds for multiple (often three) predefined levels of toxicity for multiple exposure durations. They aim to predict the occurrence of health effects resulting from a single airborne exposure in a heterogeneous human population. Consequently, AERVs are predictive and designate effect levels. A validated methodology with broad European consensus for deriving AERVs is a prerequisite for rapid and (cross-border) consistent health risk assessment of chemical incidents.

At present, however, no European guidance is available for risk assessment, risk management or risk communication purposes suitable for acute releases of chemicals in chemical incident scenarios. The required data and tools clearly differ from those needed in the regular risk assessment frameworks. Further, new chemicals (e.g. nanomaterials) as well as new applications of existing chemicals are continuously being developed and new technologies, for example for storage (e.g. carbon capture and storage) are being investigated. This underlines the need to explore whether the current common risk assessment paradigm is adequate to assess and manage the human health risks from single exposures in chemical emergencies. Uncertainty exists as to whether adjustments are required due to the specific needs of risk assessment for single exposures, of new and emerging chemical risks resulting from new technologies and industrial developments and/or progress in risk assessment methodologies such as those implemented under the Registration, Evaluation and Authorisation of Chemicals (REACH) or the Globally Harmonised System (GHS).

To determine the need for broadly accepted European guidance thirteen present methodologies for deriving AERVs were identified. Nine of these are currently applied. Six were selected for further methodology analyses and comparison. These include the Acute Exposure Guideline Levels (AEGLs), the Emergency Response Planning Guidelines (ERPGs), the Acute Exposure Threshold Level (AETL) methodology (the outcome of the FP5 ACUTEX (ACUTe EXposure) project) and the Dutch, French and Danish national methodologies. The Dutch and the French are the only two national methodologies currently in use, while the Danish methodology has been developed and tested but not yet further applied. The six frameworks were compared regarding how important toxicological endpoints (carcinogenicity, reproductive toxicity, sensitization, neurotoxicity and sensory awareness) are dealt with. In addition, differences between the level of protection for subpopulations, time scaling and dose-response modelling were addressed. The practical consequences of these differences for risk assessment, risk management and risk communication in an emergency situation were illustrated by comparison of AERVs derived by the different methodologies and their use in a fictitious chemical emergency situation.

The endpoints of carcinogenicity and reproductive toxicity were very differently addressed by the respective methodologies, ranging from not considering these endpoints as relevant for AERV derivation, to application as an endpoint for either AERV-2 or AERV-3 or, for carcinogens, via a separate risk calculation. Further, the methods for the calculation of the carcinogenic risk differed as well. Endocrine disruption is an important issue that has not yet been considered in any methodology. Its relevance for the derivation of AERVs should be verified and, if deemed necessary, specific guidance should be developed. Considering the importance of these two endpoints in risk communication, harmonization is urgently recommended to adequately address public concern.

Neurotoxicity encompasses different types of effects and it is recommended to develop guidance on how to address these various effects in the derivation of AERVs, including appropriate time scaling to multiple exposure durations. Regarding sensory awareness, the main issue for consideration is the inclusion of odour as an AERV-1 endpoint or to derive a separate value. For other endpoints, it suffices to state that clear guidance is needed on how to determine an appropriate point of departure for AERV derivation and how to define the respective tiers' critical effect sizes for the most important endpoints.

The six evaluated methodologies aim to protect different populations (i.e. healthy middle-aged (male) adults, susceptible subpopulations). For this reason and because the methodologies address toxicity endpoints differently, AERVs derived according to these methodologies are not interchangeable. However, in practice they are used as if they are which may lead to an overestimation or underestimation of the public health risks and hamper risk communication to the public. Such a situation is highly undesirable in chemical incidents with heavy time pressure on the decision-making process. Harmonization and clarification of the target population to be protected and the methodology to assure this protection are highly recommended to avoid inadequate risk management decisions and to improve risk communication in a chemical emergency.

Since AERVs are meant to be predictive for specific levels of health impact effects and are derived for multiple exposure durations, sophisticated tools such as physiologically based pharmacokinetic (PBPK) and dose-response modelling can be of importance to ensure appropriate AERVs. Therefore, the present state of the art regarding these modelling tools needs to be explored and practical guidance on the use of these tools for AERV derivation developed.

The methodological differences were reflected in large differences (up to 20-fold in individual cases) in the actual AERV values of six selected chemicals. These differences did not show any consistency. For four of these chemicals a fictitious incident scenario was also elaborated. Contours around the incident location were calculated to identify the area within which AERV-2 was expected to be exceeded. These contours determine the area within which specific actions need to be taken to protect the population from possible health risks or to communicate any possible health consequences to the potentially exposed population. As a consequence of the differences in AERV-2 values, large differences were observed in the surface areas of the calculated contours and consequently in the number of people potentially exposed. It depended on the methodology that underlay the AERV whether administrative borders were crossed or not. These observations clearly showed that AERVs derived by different methodologies indeed are not interchangeable.

At present, no specific European or globally harmonized legal framework exists that regulates or governs the principles of risk assessment in acute chemical incidents. A number of legal frameworks were reviewed to explore whether they provide any obligation or opportunity to produce acute toxicity data and/or guidance or other information relevant for human risk assessment in single exposure situations. These frameworks included the Seveso II Directive, the International Health Regulations (IHR), REACH, the UN ECE Convention for Transboundary Effects of Industrial Accidents, storage and transportation guidelines, the Globally Harmonised System (GHS) / Classification, Packaging and Labelling (CLP) Regulation, the EU Chemical, Biological, Radiological, Nuclear and Explosives (CBRNe) Action Plan (CBRN, 2009), the OECD Guidelines for acute inhalation toxicity testing and Occupational Exposure Guidelines.

The legislation pertaining to chemical safety is extensive in the EU and covers the principal facets of development and marketing of new chemicals, storage of hazardous chemicals at major industrial installations, occupational exposure and transportation of chemicals by road, rail, sea and air, application and subsequent waste disposal. A chemical may, therefore, be regulated within different regulatory frameworks depending on the stage of its life cycle, where each stage of a chemical may pose a potential chemical incident scenario. In addition, a chemical may often have multiple applications, each regulated within different frameworks. In most instances, there is no regulatory obligation to address human health risks from single exposures in a quantitative way.

The IHR, although not a basis for development of AERVs, may provide a tool for the international issue of alerts concerning major incidents of public health concern and thus facilitate international communication. Enhanced international collaboration as a consequence of mandatory notification may provide a vehicle for improved preparedness in other areas, including the development of AERVs. Exposure levels, such as Acute Reference Concentrations and acute Derived-No-Effect Levels, are of only limited value since they do not address topics important for AERVs (e.g. time scaling) and aim to be protective rather than predictive for different levels of toxicity. These exposure levels are, therefore, of limited value in chemical incidents. The newly developed $C \times t$ approach (part of OECD Test Guideline (TG) 403) to determine acute toxicity is an important new tool since it provides insight regarding the concentration-time relationship that is needed for adequate emergency planning, preparedness and response.

The importance of planning and preparedness for chemical incidents is acknowledged by the EC. Incidental release of chemicals into the air could happen during every stage of their life cycles. The extensive utilization of chemicals and their potential public health impact necessitates extensive planning and preparedness for chemicals of concern in the CBRNe arena prior to subsequent response. However, although current legislation in this arena recognizes the potential impact of chemicals, it does not specifically address toxicity. It is recommended that the potential for community exposure to chemicals due to incidental emergency exposure situations during the life cycle (as highlighted by the international regulatory framework) is explored and that a number of these scenarios are developed with a view to highlighting the toxicological data input requirement.

A special population to be addressed are first responders, who are by profession involved in the repression phase following a chemical incident and who are thus repeatedly but irregularly exposed to specific chemicals in extreme exposure scenarios. No specific guidance values exist to assess the health risk to these

first responders. Neither occupational exposure limits (OELs) nor AERVs are directly applicable and thus there is a special need for guidance to derive AERVs for first responders.

In conclusion, it is stated that the ability to perform a human health risk assessment is a prerequisite for effective chemical incident prevention, preparedness and response. This requires the availability of a validated and broadly accepted methodology to derive AERVs. An important feature of such a methodology should be the prediction of concentration thresholds for different health severity levels for a range of relevant exposure durations. The existing AERV methodologies differ in several important aspects, leading to the derivation of AERVs that are not interchangeable. However, the fact that they are often used in practice as if they are may lead to inconsistencies and inaccuracies in the chemical incident risk assessment, for instance in the case of transboundary incidents.

The present risk assessment paradigm does not provide the required information, tools and guidance to adequately support end-users in making risk assessments and risk management decisions in chemical emergency situations. In addition, the existing legislation does not provide incentives for derivation of AERVs and it is not expected that it will in the near future. This stresses the urgent need for harmonization of the present risk assessment paradigm aiming at single exposures from chemical incidents.

Several new and emerging chemical incident risk scenarios have been identified, often with a high level of uncertainty. A harmonized system for AERV derivation and guidance for AERV application should be developed such that these incident scenarios can be adequately dealt with. Especially if regular monitoring of new developments at an early stage is included, whether situation-specific adaptations or additions of risk assessment information, tools and guidance are required can be evaluated. This might require incorporation of a procedure, as a regulatory requirement, to identify and evaluate chemical incident scenarios during the life cycle of a chemical. In addition, specific attention should be paid to an approach dealing with exposure to mixtures in chemical incidents and also to derive AERVs for professional first responders.

Harmonization of a methodology and procedure for the derivation of AERVs is highly recommended. It has been noted that in this area several topics and methodological issues, identified in the present report, need further development. Further, specific attention should be given to exploring the possibilities of demanding a minimum data set for AERV derivation. In addition, it has been concluded that an overarching international committee responsible for the final AERV values is needed to ensure harmonized AERVs. Finally, to ensure successful implementation and adoption within Europe of harmonized AERVs and the underlying methodology, support from a broad European policy platform should be secured.

1 General introduction

The release of chemicals from their containment, either accidentally or initiated by an intentional act, is one of the most relevant risk scenarios in Europe. The information on the occurrence and public health effects of chemical incidents is fragmentary, however.

EU member states, in accordance with obligations of the Seveso II Directive, report on average 40 major accidents per year to the EU's Major Accident Reporting System (MARS) database. In accordance with Heinrich's pyramid theory, it is assumed that the number of smaller accidents occurring annually throughout Europe is substantially higher (Prem et al., 2010).

In England and Wales, a total of 1,040 chemical incidents were reported in 2005; 2,800–27,000 individuals were estimated to have been exposed. Between 600 and 3,400 persons were estimated to have experienced symptoms, and 8 fatalities occurred (Health Protection Agency (HPA, 2007). Comparable numbers were reported for 2008 (HPA, 2010a).
For 2009, a total of 967 chemical incidents were reported; 1,400 – 8,500 individuals were estimated to have been exposed. Between 400 and 2,500 persons were estimated to have experienced symptoms, and 22 fatalities occurred (HPA, 2010b).

The Hazardous Substances Emergency Events Surveillance registry (HSEES) of chemical incidents in 15 US States registered 8,603 chemical releases in 2005, causing 2,034 casualties including 69 fatalities, and giving rise to an unknown number of exposed individuals.

A comparison of the above chemical incident registries is difficult, because of the difference in the definition and coverage of chemical incidents. However, chemical incidents occur frequently and clearly have the potential to expose up to thousands of individuals simultaneously (WHO, 2009). Besides the often brief primary exposure in the acute phase of an incident, long-lasting secondary exposure can result from deposition on or contamination of soil, crops or groundwater (Pesatori et al., 2003). The health effects of exposure can be immediate, delayed or both, and may be permanent.

The burden of disease from chemical incidents has not been documented. WHO estimated the extent of disease due to environmental factors. The annual mortality in Europe from unintentional poisoning was 75,000 people in 2002, and the number of disability-adjusted life-years 1,461,000 (excluding asthma, COPD and cancers) (Prüss-Üsten and Corvalán, 2006). While this burden of disease is not all attributable to chemical incidents, it is reasonable to assume that the likelihood of chemical incidents and the resulting disease are equally related to the production, transportation and application of chemicals.

Prevention or mitigation of human health effects is often the major determinant underlying accident prevention policy and emergency response decisions. Irrespective of scenario or its underlying root cause (accidental, intentional, design, siting, flooding due to climate change), an accurate and precise assessment of human health risk resulting from acute releases is therefore a cornerstone of chemical incident prevention, preparedness and response. Public

health management's aim to reduce disease arising from chemical incidents is virtually impossible without health risk information.

1.1 Special case of acute chemical risk assessment

Risk assessment of industrial chemicals, pesticides and biocides for their intended use is a common European exercise supported by many formal arrangements and methods and is usually aimed at repeated exposures over exposure periods of up to a lifetime. Acute risk assessment in this context usually refers to estimation of safe exposure conditions, such as Acute Reference Concentrations.

At present, no European guidance is available for risk assessment, risk management or risk communication purposes suitable for exposure scenarios following incidental or intentional acute release of chemicals. Such an assessment requires specific data and tools that differ from those needed in the regular risk assessment frameworks.

In addition, technological developments in several areas are in a constant state of flux: new chemicals (e.g. nanomaterials), as well as new applications of existing chemicals, are being developed, and new technologies for storage for example (e.g. carbon capture and storage) are being investigated. These developments will lead to new, formerly unknown scenarios for incidental release of chemicals.

1.2 Underlying question of the present study

The observations on needs, scenarios and chemicals outlined above prompt us to explore the extent to which the current common risk assessment paradigm, tools and strategies are adequate to assess and manage the risk in humans of single exposure from acute chemical releases. In addition, uncertainty exists as to whether current practices may require adjustments due to the specific needs of risk assessment for single exposures, new and emerging chemical risks resulting from the above-mentioned new technologies and industrial developments and/or progress in risk assessment methodologies, such as those implemented under REACH or GHS.

1.3 Risk assessment defined

The term risk assessment is used in many different ways. In the process safety field, risk assessment refers to the overall process comprising a risk analysis (identification of hazards and risk estimation) and risk evaluation (procedure to verify if the desirable level of risk has been achieved in a certain situation) (Joint Research Centre (JRC), 2006).

In the present study the term risk assessment will be used in its toxicological sense (often referred to as 'consequence assessment' in the process safety context). An assessment of risk to human health is the process that characterizes the nature, severity and probability of adverse effects on the health of humans driven by the level of exposure in contaminated environmental media, now or in the future. Risk assessment is considered to be a four-step process (National Research Council, NRC, 1996), as outlined in Figure 1.1 (text and figure adapted from the US Environmental Protection Agency (http://www.epa.gov/risk/health-risk.htm).

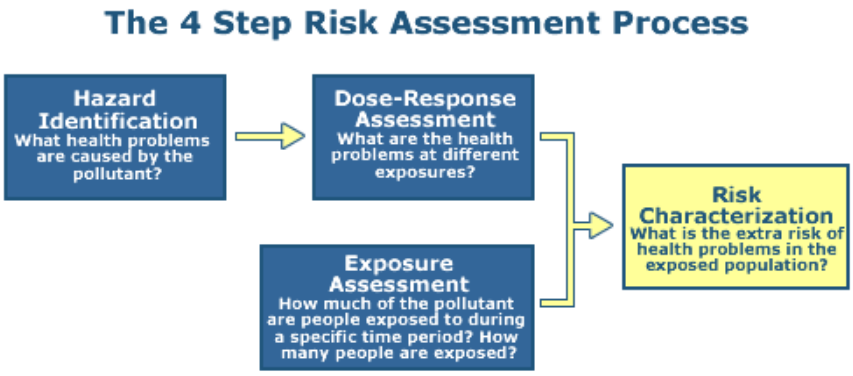

Figure 1.1 The four-step NRC Risk Assessment Model.

Step 1 – hazard identification: this aims to identify the types of adverse effects and to characterize the quality and weight of evidence supporting this identification. WHO defines this step as: 'Identification of the inherent capability of a substance to cause adverse effects' (WHO, 1999).

Step 2 – dose-response assessment: this documents the relationship between exposure or dose and the type and severity of the toxic effects. WHO defines this step as: 'Characterisation of the relationship between the dose of an agent administered or received and the incidence of an adverse effect.' For emergency response purposes, this information is often presented as Acute Emergency Reference Values for rapid risk assessment.

Step 3 – exposure assessment: this calculates a numerical estimate of exposure or dose relevant for the exposure scenario in question. WHO defines this step as: 'The qualitative and/or quantitative assessment of the chemical nature, form and concentration of a chemical to which an identified population is exposed from all sources (air, water, soil and diet).'

Step 4 – risk characterization: this summarizes and integrates information from the preceding steps in the risk assessment to synthesize an overall conclusion about risk. WHO defines this step as: 'The synthesis of critically evaluated information and data from exposure assessment, hazard identification and dose-response considerations into a summary that identifies clearly the strengths and weaknesses of the database, the criteria applied to evaluation and validation of all aspects of methodology, and the conclusions reached from the review of scientific information.' For chemical incidents, it may be useful to distinguish between the risks of acute and of delayed health effects.

Hazard describes the latent *potential* of a chemical to cause harm under conditions of exposure. Risk describes the likelihood that a health effect will occur and its incidence, endpoints and severity be given the exposure scenario.

1.4 Pivotally important role of risk assessment

The 'disaster management cycle' illustrates the continuous process by which governments, businesses and civil society plan for and reduce the impact of incidents by acting at different stages of an incident's life cycle. The nature of

activities that can be undertaken to reach the goal of impact reduction varies with the stage of this cycle. The five stages of the incident management cycle will be introduced briefly (Figure 1.2).

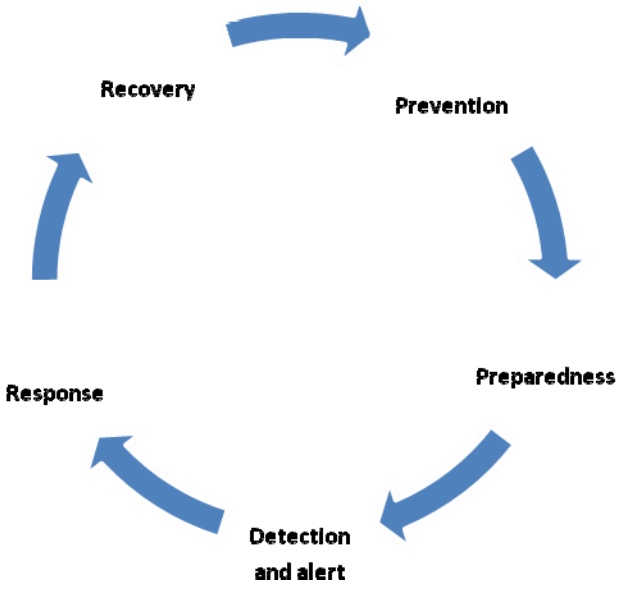

Figure 1.2 Stages of the disaster management cycle.

The first line of defence against the adverse consequences of chemical incidents is to prevent their occurrence. **Prevention** is aimed at reducing the likelihood of an incident occurring, but also includes all technical and organizational measures (taken before the incident occurs) to reduce the severity of any future incident, to ensure that its impact is reduced to a minimum and that it does not become a major event or incident.

Generally, a hierarchy of preventive measures is assumed. Risk reduction measures at the source have the highest priority; only operators can implement measures that actually prevent an accident. Other control (siting, licensing) and mitigation measures (e.g. land-use planning, alarm systems) follow in the hierarchy.

Risk assessment in the prevention stage is an element of risk analysis that the operator uses to prioritize risk reduction measures and identify unacceptable risks. In particular, operators will focus on reducing risks with potentially serious consequences that could involve any number of a variety of prevention measures. Risk analysis at this stage can help authorities in controlling risks through inspections, siting, licensing and land-use planning powers.

Despite the best efforts to eliminate risks or reduce the likelihood of their occurrence, some residual risk will remain that can materialize in an incident. The time taken during an incident to locate equipment and infrastructure, establish links and coordinate the actions of the various stakeholders, establish a response plan and gather general information about the pollutant(s) will reduce time spent in minimising the extent and consequences of a chemical incident. Hence, these tasks should be accomplished prior to the incident, in order to ensure that immediate efforts can really be focused on the response. Therefore, in the **planning and preparedness** stage an incident response system should

be designed, the roles, responsibilities and competencies attributed, and personnel selected, trained and exercised.. Risk assessment in this stage is an element of scenario analysis for consequence assessment and for emergency response capacity and capability planning.

Incident **detection and alert** is a continuous activity undertaken to pick up signals that a chemical incident has occurred, and to ensure rapid alert for an appropriate and timely response. One of the possible signals could be a rise in a substance's concentration above a critical threshold, based on a risk assessment.

When an incident takes place, the operator and various authorities may initiate the incident **response,** to terminate the incident and mitigate the consequences. In this stage dose-response information on the chemical, in conjunction with exposure information, provides the basis for setting incident response and mitigation priorities, for which accurate exposure information is often critical.

After the incident has been terminated the environmental, economic, social and cultural **recovery** may encompass years of clean-up, health monitoring, evaluation and other activities that aim to restore the situation to how it was prior to the incident and contribute to prevention of recurrence. Risk assessment plays a role in ensuring safe operations in the clean-up of released substances and also has a critical role in assessing the incident's potential long-term health consequences.

Clearly, an accurate and precise prediction of human health risk resulting from chemical incidents is a cornerstone of a strategy and policy (implementation) for all stages of the disaster cycle. Therefore, the effective implementation of incident control activities relies on the ability to make accurate risk assessments, tailored to the needs of each stage.

1.5 Risk assessment in the context of chemical incidents

Full exposure-response assessment requires the characterization of all possible toxicological endpoints for all relevant exposure routes. This may generate a large volume of data, which is impractical for the purpose of risk assessment, management and communication of chemical incidents. Particularly in a chemical emergency situation, time and resources are not sufficient to make adequate risk assessments. In addition, chemical incident planning, preparedness and response activities, including crisis communication, benefit from standardized risk information and the associated efficient use of resources, rather than relying on individual risk assessments. Therefore, this study will conform to existing practice by summarizing and presenting the exposure-response information as a set of Acute Exposure Reference Values (AERVs, thresholds for predefined levels of toxicity or severity of toxicity) or probit functions for a number of endpoints and exposure durations.

There is a clear distinction between such *predictive* AERVs and inherently *protective* guidelines such as Acute Reference Concentrations (ARfCs), Ambient Air Quality Guidelines (AAQGs) and acute Derived No-Effect Levels (acute DNELs). Such *protective* guidelines are designed to prevent any adverse health effect in a target population (not necessarily the general population) and, therefore, are often derived according to a so-called 'realistic worst-case'

approach, leading to conservative estimates. In contrast, *predictive* AERVs aim to provide guidance as to when an adverse health effect may occur.

1.6 European collaboration on risk assessment of single exposures

European collaboration on risk assessment of single exposures from chemical incidents, and in particular the development of AERVs, is a relatively recent activity. Even for high-volume chemicals European consensus on AERVs (or interpretation of exposure-response information) is absent, and none of the existing guidelines are universally endorsed.

On the other hand, in EU member states the history of the development of AERVs is limited. Unlike, for example, occupational threshold levels and ambient air quality guidelines, for which many member states already had their own guideline development programme when harmonization was considered, very few member states have well-established AERV development programmes and guideline values developed accordingly. Many member states have already indicated a need for such acute risk assessment guidance (OECD Workshops in Paris (OECD, 2001) and Varese (OECD, 2006) and at a JRC Workshop (Wood and Duffield, 2001)). The fact that a small number of EU member states has started developing such AERVs, without formal harmonization, also signals a clear need for them.

The FP5 ACUTEX (ACUTe EXposure) project represents the first time that EU scientists from both the public and private sectors have joined together to develop a European methodology in support of acute risk assessment. This represented a major step towards European collaboration on the subject (ACUTEX, 2006). After completion of the ACUTEX project, scientists from EU member states and the USA convened to discuss the project's results and to recommend a path forward (Post ACUTEX Workshop, 2006). Despite the significant progress on many scientific issues, a number of technical and methodological issues appeared to remain unresolved and it was recommended to resolve these in a follow-on project. These subjects included a toxicological methodology where the consensus methodology for chronic exposures was not applicable for single exposures (e.g. carcinogenicity and reproductive toxicity) and technical guidance specific for single exposures (e.g. time scaling, i.e. extrapolation of toxicity data to appropriate exposure durations). This recommendation was endorsed by the OECD in the OECD Workshop in Varese (OECD, 2006). These developments suggest support at the European level for harmonization in this field.
This history creates an ideal environment and an opportunity for European harmonization of acute risk assessment methodology, including the development of a methodology and AERVs for existing and new chemicals. In a web-based questionnaire survey on 'European methodologies in the risk assessment of single chemical exposures', policy-makers, toxicological scientists and end-users of risk assessment methodology clearly indicated a need for harmonized and accepted AERVs with broad European consensus (Heinälä et al., 2013).

1.7 Legislative context

An additional motivation for European harmonization of acute risk assessment practice originates from EU legislation.
The Seveso Directive[1] and the Agreement on Dangerous Goods by Road/Regulations concerning the International Transport of Dangerous Goods by Rail (ADR/RID))[2] require a risk assessment of single chemical exposures resulting from fixed sites and transportation. Risk assessment of industrial chemicals, pesticides and biocides for their intended use is a common European exercise supported by many formal arrangements and methods. In contrast, no harmonized and endorsed procedure is available at the European level to support the risk assessment of single exposure for lethal or non-lethal health endpoints. The absence of a harmonized and European endorsed methodology greatly hampers rapid and cross-border health risk assessment in single chemical exposure situations.

The implementation of the United Nations Economic Commission for Europe (UNECE) Convention on the Transboundary Effects of Industrial Accidents (http://www.unece.org/env/teia/intro.htm) and the International Health Regulations (IHR, 2005) would also greatly benefit from harmonization of risk assessment practices. To meet the IHR (2005) requirements, countries are required to establish a set of core capacities to include acute chemical risk assessment (Annex 1 of the Regulations).

1.8 Chemical risk assessment within the iNTeg-Risk project

The present study is part of a larger integrating FP7 project, iNTeg-Risk (Early Recognition, Monitoring and Integrated Management of Emerging, New Technology Related Risks). iNTeg-Risk aims to reduce time-to-market for the lead market EU technologies and to promote safety, security, environmental friendliness and social responsibility as a trademark of European technologies. The project will improve early recognition and monitoring of emerging risks, seeks to reduce accidents caused by these and to decrease reaction times if major accidents involving emerging risk happen.

For the iNTeg-Risk project, a framework for new and emerging risk has been developed consisting of two dimensions:

1. The Emerging Risk Management Framework (ERMF), originating from the FP6 SHAPE-RISK project;
2. The IRGC Risk Governance framework (Figure 1.3).

Risk assessment is one of the two elements (next to concern assessment) that comprise the risk appraisal stage of the IRGC framework, and is an intermediate step between chemical risk assessment and the pre-assessment and tolerability & acceptability stages.

Ideally, tolerability and acceptability criteria should be one of the forces driving the definition of effect severity levels for the acute exposure guidelines.

[1] Cf. section 4.2.

[2] European legislation regulating road and rail transportation of chemicals, cf. section 4.7.

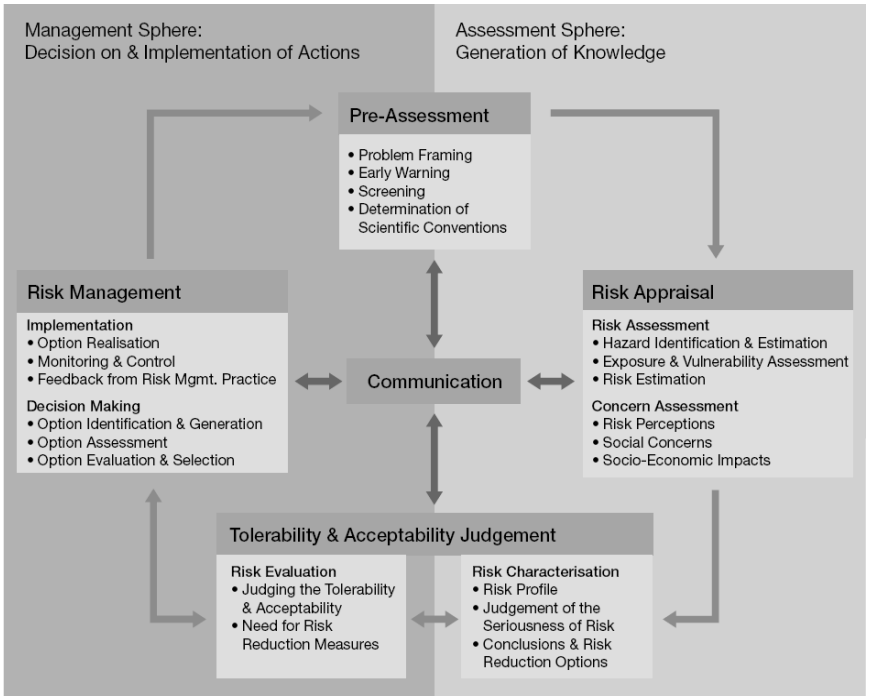

Figure 1.3. IRGC Risk Governance Framework.

1.9 Benefits of AERVs with broad European consensus

Currently, a wide variety of AERVs (mainly Acute Exposure Guideline Levels (AEGLs), Emergency Response Planning Guidelines (ERPGs) and Immediately Dangerous to Life and Health (IDLH)) are used for risk assessment of chemical incidents, including applications in the context of Seveso II (Wood et al., 2006). Joint European development and convergence of methods, tools and guidance for the derivation and application of AERVs would be beneficial to:

- strengthen the capacity of EU member states to deal with chemical incidents;
- improve the authority, validity and credibility of AERVs as a critical element in rapid risk assessment and the risk assessments based on them;
- enhance a level playing field and an equal level of protection for all European citizens and the environment;
- strengthen and improve the consistency of risk and crisis communication on acute chemical risk from different sources, such as authorities, industry and transport companies;
- facilitate a harmonized response to incidents with transboundary effects, where administrative boundaries may be within and between member states;
- improve European consistency in parameters used in generating risk assessments;
- assure consistency of the risk assessment methodology underlying the AERVs with other European risk assessment frameworks;
- avoid challenges from the public, policy- and decision-makers, and industry as well as accident investigators concerning differences in AERVs and in the consequence analyses based on such values;
- facilitate multinational companies and competent authorities in making consistent risk assessments Europe wide, thus avoiding duplication of effort;
- resolve open issues on toxicological endpoints and methodology, in order to develop AERVs;
- facilitate disclosure of the proprietary toxicological information;

- consolidate and maintain the scarce expertise, experts and experience in this toxicological field;
- create a network of experts for rapid risk assessments of single chemical exposures, even for scenarios involving a chemical without AERV values;
- provide a basis for planning and preparedness exercises on public health management of chemical incidents;
- facilitate a consistent fulfilment of regulatory requirements and international conventions.

The main obstacles to initiating a European programme on AERV methodology and levels are probably broad political support for a European harmonized approach, and organizational and financial aspects.

1.10 Objective and focus of the present report

Both in the web-based questionnaire survey that was part of this study (Heinälä et al., 2013) and elsewhere, the availability of European-wide harmonized AERVs and the easy access to the underlying risk assessment documentation was considered to be an important need. With that need as a starting point, the present study aims to explore the extent to which the current common risk assessment paradigm, tools and strategies are adequate to assess and manage the risk from and to derive AERVs for single human exposure from acute chemical releases.

The present study will explore the extent to which the current common risk assessment paradigm and strategy are adequate to assess and manage the risk of single exposure to humans from acute chemical releases. This current practice may require adjustments due to the specific needs of risk assessment for single exposures, new and emerging chemical risks resulting from new technologies and industrial developments and/or progress in risk assessment methodologies such as implemented under REACH or GHS/CLP.

This study will focus on the following aspects of risk assessment:

1. Risk assessment of human health effects. Effects on the environment will not be considered.
2. The population of concern is the general population, with all inherent variability in susceptibility.
3. Single respiratory exposures. Delayed effects of single exposures will be considered, exposures with a duration exceeding 24 hours will not.
4. Releases with airborne dispersion. Such releases entail the greatest time pressure to assess risks, and therefore the most urgent response and the largest potential for benefits of preparation. Other exposure routes will be mentioned when and where appropriate but are not an explicit part of the report.
5. The exposure-response assessment step of the risk assessment.

Chapter 2 will cover new and emerging risks, emerging from either newly introduced substances, scenarios or legislation. Chapter 3 will provide details about currently existing methodologies to develop AERVs, to draw up an inventory of the similarities and differences between the methodologies and the consequences thereof, to identify gaps in knowledge and to make recommendations to fill these gaps. Finally, since there is no specific guidance available to address risks from single exposures, Chapter 4 will address policies and guidelines that may have an impact on or provide some guidance for the

assessment of risk of new and emerging chemical incidents. Chapter 5 will provide conclusions on the adequacy of the current risk assessment paradigm to assess and manage new risks and will provide recommendations for improvements.

2 New and emerging risks

Chemical substances have been in the environment for centuries. Some have a long history of use and many of their toxic effects are well characterized, although for many chemicals the available information and knowledge regarding human health risk is still limited. New substances are constantly being developed for specific uses, and in addition new uses for existing substances. Although many possible risks of toxic effects from well-established uses of existing chemicals have been documented, new applications of existing chemicals may bring to light new risk scenarios that have not been previously described. In addition to the introduction of new substances and new incident scenarios for existing substances, changes in legislation due to other external factors may also influence the introduction of new risk scenarios and risk information for single chemical exposure. This chapter will explore the consequences of new and emerging chemicals and incident scenarios and the foreseen developments within several legal frameworks for the overall risk to human health from chemical incidents.

Only one study was identified that explored the external safety risk of new chemical substances and new applications of existing chemical substances in the Netherlands (Wijnant and Meulenbrugge, 2010). A survey consisting of a search of the REACH database and interviews with policy-makers, industry representatives and other experts at an invitational workshop failed to identify new chemicals that were anticipated to contribute significantly to external safety risks in the next few years (other than those involved in sustainable energy and new energy carriers). Possible new and emerging issues included:

- biofuels or other new formulations of liquid fuels;
- Liquefied Natural Gas (LNG) and LNG regasification, the main hazard being explosion;
- methane production from manure (biogas);
- carbon capture and storage (CCS).

2.1 Substances

Additional consultation of subject experts in the institutes participating in this study and consultation with other Emerging Risk Representative Application (ERRA) leaders in the iNTeg-Risk project produced the following list of possible new and emerging chemicals that may contribute to the overall human health risk from chemical incidents:

- nanomaterials (organic and non-organic). Risk scenarios include particularly manufacture, transport and application in products;
- biofuels or other new formulations of liquid fuels.

All other reported chemicals are new applications of existing chemicals and their new and emerging risks will be discussed under Scenarios in section 2.2.

An important finding of Heinälä et al. (2013) was that respondents believed that the most serious health effects due to chemical incidents were caused by irritating/corrosive chemicals, acutely toxic substances and combustion gases.

2.1.1 *Nanomaterials*

An important fast-growing field of potential concern is that of nanomaterials. Recently, a monitoring report to outline the present state of knowledge and developments in the field of nanotechnology, including possible human health risks, has been published (Zijverden and Sips, 2009). Nanotechnology was defined as the entirety of new, emerging technologies that use substances or structures on a nanoscale. At these dimensions, chemical substances sometimes acquire new, different properties, as a result of which they offer new possible applications and at the same time introduce as yet still unidentified risks to man and the environment.

Although this report does not address (risks from) accidental single exposures it demonstrates large data gaps regarding information about external (e.g. suitable measuring methods, appropriate dose metrics) and internal exposure (biokinetic characteristics), toxic potential and possible health risks of nanomaterials. Because of their fundamentally different physical and chemical properties from their non-nano counterparts, it appears reasonable to assume that nanomaterials may exert a different toxicological profile. This means that the risks posed by a nanoparticle cannot simply be derived from the risk profile of substances, neither in nano form nor in that of other nanoparticles.

A recent review by ENRHES (Engineered Nanoparticles, Review of Health and Environmental Safety (ENRHES, 2009) of the health and environmental safety of four classes of nanomaterials (fullerenes, carbon nanotubes, metals and metal oxides) also mentioned that the toxicity of particles is related to their size, so that as size decreases, toxicity generally increases, an effect considered to be driven by their surface area. It was additionally stated that other particle dimensions are also important drivers for toxicity. This report confirmed the conclusions that there are many data gaps for risk assessment of nanomaterials.

One of the concerns is that nanoparticles are more readily absorbed and have a higher bioavailability than their non-nano counterparts have. The standard solution to this uncertainty, as applied for chronic exposures (application of an additional assessment factor), is inappropriate for AERV derivation. Important endpoints in the derivation of AERVs are eye and respiratory tract irritation. If nanoparticles are more easily absorbed it may result in systemic toxicity at levels below which these particles cause irritation, meaning that the nano form might show a different toxicity profile than the non-nano form of the chemical. An additional assessment factor can never compensate for a health effect from a different mechanism of action.

Policy and legislation regarding nanomaterials
None of the existing regulatory frameworks have properly integrated nanomaterials, although they may be encountered in several of these frameworks, such as biocides. In the context of REACH, a nanomaterial (silver) was chosen and an attempt made to prepare a registration dossier (Pronk et al., 2009) in order to determine the problems that can be encountered with nanomaterials. Also, within the REACH framework three nano-specific REACH Implementation Projects (RIPs) are being drafted.

EU policy in the area of nanotechnology is set out in 'Nanosciences and nanotechnologies: an action plan for Europe 2005–2009'. This strategy covers several different areas, including research and development, public health, safety, and environmental and consumer protection. Within this last category,

the first steps being taken are testing the current regulatory frameworks on their applicability to nanomaterials, identifying different knowledge gaps and doing research, specifically in the context of determining safety risks and research on safety aspects, with the aim of supporting risk assessment at an early stage.

All the efforts being undertaken now are aimed at the risk assessment of scenarios covering normal, intended, foreseeable use. Considering the uncertainties even at that level, there have been suggestions to ban some specific products treated with or incorporating nanomaterials. As yet, the risk assessment of high airborne exposure of nanomaterials due to accidental release has not been subject of REACH, or any other legal framework.

2.1.2 Biofuels or other new formulations of liquid fuels

Biofuels are (currently) mixtures of fossil fuel and 4–5 per cent bioethanol or bioethyl-tert-butyl ether (ETBE) (Wijnant and Meulenbrugge, 2010). Alternative additives such as Fatty Acid Methyl Ester (FAME) and pure vegetable oil are also sold. Because of the perishable nature of these biofuels, the frequency of loading and unloading, maintenance and inspection of storage facilities is expected to increase. Depending on the composition, biofuels can be more corrosive than fossil fuels. Until all these possible risk factors have been accounted for, there may be an increased but most likely low extra risk of accidents.

With aviation, the viability of completely synthetic jet fuels is explored in the ALFA-BIRD project. Different mixtures of paraffinic, naphtenic and oxygenated compounds are selected and tested for safety and integration with aircraft systems before application as jet fuel (Starck et al., 2010).

Currently no tests of combustion products emerging from a fire in a storage tank of such alternative fuels are available, and therefore the human health risk associated with such events is difficult to assess. Before these chemical mixtures reach the high-volume production stage, such combustion and toxicity tests should be performed. This finding underscores the need for a methodology to derive AERVs for chemical mixtures, and to derive AERVs for relevant chemical mixtures, including combustion gases of large fires in alternative fuel storage facilities.

2.2 Scenarios

The TNO study (Wijnant and Meulenbrugge, 2010) produced the following new applications of existing chemicals with the potential to contribute to an increased external safety risk:

- biogas (methane/natural gas) production from manure;
- LNG storage, transportation and regasification;
- application of biofuels;
- carbon capture and storage (CCS).

Most issues appear to arise from applications associated with bulk energy carrier substances. Most of the accident scenarios involve mainly explosion risk, with the exception of CCS, which may produce toxicologically driven incident scenarios.

A review of new and emerging risks studied by other iNTeg-Risk ERRAs with the potential of human exposure to chemicals indicated the following possible scenarios:

- carbon capture and storage;
- extreme (underground) storage of hydrogen (H_2), for example;
- releases in underground hubs and other infrastructure (e.g. tunnels);
- increased risk of Natural-Technological incident scenarios;
- nanotechnology production and transportation, discussed in section 2.1.

Additional review of the literature for new and emerging scenarios involving human exposure to chemicals included:

- chemical terrorism;
- language problems in the working area, originating from increasing migration of workers.

2.2.1 Climate change related scenarios

The 2007 synthesis report of the Intergovernmental Panel on Climate Change (IPCC) indicates that climate change is ongoing (IPCC, 2007). Relevant effects of climate change that may influence the likelihood and consequences of chemical incidents include an increased likelihood of extreme weather events with high winds (including cyclones) and heavy precipitation, sea level rise and an increased risk of heat and drought, with the associated fire risk in subtropical land regions. Two iNTeg-Risk ERRAs have studied new and emerging risk issues related to climate change.

Natural-technological risks

Natural-technological accidents, or Natechs, reveal a particular exposure and vulnerability of industrial facilities to extreme, intense or more generally localized natural hazards. This has been confirmed, in the recent past, by events such as the 1999 Izmit earthquake, the 2002 floods in Southeast France, and the 2004 hurricane Katrina in the USA.

Climate change is likely to alter the intensity and/or frequency and/or spatial distribution of peak flood events, and the same potentially applies to lightning hazard. Social/market demand in developing or industrializing countries is likely to foster industrial development; in areas where land-use opportunities are limited, areas prone to natural hazards (e.g. earthquake) may be solicited for the building of new facilities – hence the calls for NaTech-specific approaches to facility design and accident risk assessment.

Emerging risks related to NaTechs include:

1. Unclear historical patterns of natural hazards threatening industrial facilities and lack of knowledge about whether and how climate change trends impact at local level.
2. Knowledge gaps in modelling of dynamic equipment response to external stresses (e.g. earthquake) and regarding organizational vulnerability and response to NaTechs.

From a chemical risk perspective, the ERRA concludes that the increased NaTech risk will mainly drive the likelihood of incidents, though not so much the nature of the incidents or the chemicals involved. Scenarios involving flooding may become more likely. This projection underscores that the risk of chemical incidents may not decrease everywhere, and that tools, guidance and information to properly assess human health risk will remain necessary.

Carbon capture and storage (CCS)
Carbon dioxide is by no means a new chemical. It is one of those that qualifies as a greenhouse gas (one of those held responsible for global warming), and it plays a crucial role in maintaining homeostasis in all mammals. CO_2 is handled extensively in industry in many applications, such as brewing, gas reforming and gas processing, as an inerting gas and fire extinguisher. It is also routinely manufactured and transported by industrial gas companies. Its properties are well understood in these industrial settings for the quantities and under the conditions involved.

With the advent of carbon dioxide capture and storage (CCS) technology the scale and extent of its handling is set to increase dramatically. Much larger inventories are envisaged as well as much higher pressures, possibly in combination with toxic materials such as H_2S and SO_2, especially if we consider the very high solvent capacity of CO_2 in dense phase. Furthermore, other substances such as hydrogen, oxygen and chemical absorbents are likely to be used in very large quantities. The processing plants are expected to be situated at power plants and other industrial facilities such as steel and cement works, which may be unused to handling such materials or operating the equipment required for CO_2 capture. In addition, CO_2 is likely to be transported through vessel-pipeline systems, which may run through non-industrial areas and cross/follow major features of the transport network such as roads and railways. Regulation of carbon dioxide hazards may need to change to take account of this new situation. The risks of CCS are studied by iNTeg-Risk ERRA A1.

Two scenarios have been identified that may pose risk to human health: groundwater contamination and massive ground emanation from a well or surface equipment. One of the main issues involved in this technology is that the concentration-time-response information for almost all human health endpoints has not been adequately determined (Wijnant and Meulenbrugge, 2010). In addition, gas dispersion from high-pressure storage is very ill defined and conventional gas dispersion modelling may not be adequate. This is clearly a situation where toxicological concerns are one of the main drivers of risk.

Chemical control of invasive exotic species
Biological invasions by non-native (or 'alien', ‘exotic’) species are a major threat to the ecological and economic well-being of Europe (Shine et al., 2009). Alien species can act as vectors for new diseases, alter ecosystem processes, change biodiversity, disrupt cultural landscapes, reduce the value of land and water for human activities and cause other socio-economic consequences for man. A number of reports have been published on the introduction of dangerous infectious diseases through invasive exotic disease vectors (Schwaiger and Bauer, 2009; Gale et al., 2010). Some of the important drivers of this new and increasing risk are climate change, international trade, travel and tourism, development of insecticide and drug resistance, and pollution (Harrus and Baneth, 2005; Jones et al. 2008).

The website of the FP6 EU project DAISIE (Delivering Alien Invasive Species Inventories for Europe) provides a 'one-stop shop' for information on biological invasions in Europe (http://www.europe-aliens.org/index.do). The DAISIE database behind this website is continually being updated. The ‘Impact and Management’ section of the species-specific fact sheets frequently mentions chemical management s. Currently preferred management options for a number of invasive exotic species are being developed (personal communication, expert

from the Dutch Centre for Monitoring of Vectors, Ministry of Agriculture, Nature and Food).

Although it is uncertain to what extent chemical and other (mechanical, biological) options will be used to control invasive exotic species, a substantially increasing use of chemicals for this application can be foreseen. This will inevitably lead to an increase in production, transportation, storage and application of such chemicals with an inherent increase in chemical incident potential.

2.2.2 Land-use related scenarios

Considering the population density in Europe, underground construction is a possible solution that makes efficient use of the limited land. The approaches that have been developed may produce new and emerging risks of acute chemical incidents. The risk involved with construction of facilities in areas prone to natural hazards has been discussed above.

Releases in underground hubs and other infrastructure
Urban public mass transportation systems rely to a large extent on efficient and effective underground lines that are well connected to all other means of public transport. Given the technological development in the underground construction field and in addition the increasing need for public transportation, increasing numbers of tunnels are being built and underground spaces are used for more than just transportation of passengers. The result of these developments in the use of the underground space is threefold:

1. New metro tubes must be built deeper and deeper.
2. Metro tubes are interconnected with other transport media in large underground constructions (hubs), including stations, car parks and shopping areas on different underground levels.
3. This results in longer access and escape routes, complex and hard to supervise structures split into several levels, used by ten thousand to hundreds of thousands of people every day, involving new risks for constructors, operators, passengers and users.

One of the most critical issues in the operation of deep tunnels and hubs is evacuation in case of emergency. The increasing length and depth of such infrastructure, in particular, complicate the escape of passengers, hamper orientation and make a successful escape more difficult. Furthermore, due to special ventilation conditions the dispersion of smoke may heavily influence or cut off escape routes.

In case of emergency, there are entirely new boundary conditions for the evacuation of passengers. For example: longer distances to reach the surface or safety structures underground, more demanding ventilation systems that must be adapted to the geometrical conditions as well as to the greater amounts of air to be managed, more interaction between different means of transport (suspension of traffic, emergency stops, evacuation of people etc.).

iNTeg-Risk ERRA A5 studies the associated risks to offer solutions to how manage such situations, increase the users' trust in underground infrastructures and facilitate the safe use and operation of underground transportation.

The most relevant emergencies are underground fires. This again underscores the need to develop methodology to derive AERVs for combustion gases and AERV values for such chemical mixtures, as identified by Heinälä et al. (2013). The composition of the combustion gases is determined by that of the material on fire and the available oxygen. Depending on the development of materials used in underground structures and the means of transportation (e.g. use of nanomaterials or carbon fibres in metro carriages), the composition of the combustion gases may be well known or highly uncertain. There is a clear potential for scenarios involving new chemicals, and those with longer exposure durations due to the extensive escape routes. The human health consequences of these scenarios have not yet been charted.

2.2.3 Energy-related scenarios

LNG regasification

Natural gas is an important part of the European energy market, for power generation, heating and domestic use. More than 50 per cent of the natural gas used in Europe is imported. Natural gas importation is expected to increase up to 70 per cent by 2020, and security of the supply is an important issue for the energy future of Europe. Import of LNG allows the supply of gas and the flexibility of the system to be increased, as a rigid pipeline link to a specific producing country is not required. In Europe, 13 LNG-receiving terminals are presently operating, and approximately 20 more are planned or are waiting for authorization by the competent authorities.

ERRA A4 has the objective of exploring the emerging risk related to the safety and security of new and alternative technologies for LNG regasification and of proposing solutions based on qualified and standardized approaches to risk assessment and management, while also addressing the land-use planning issue.

While many risk-related issues play a role in this new technology, the risk of LNG regasification is mainly fire and explosion. From a toxicological perspective, the risk is not new or emerging, unless the composition of the gas changes (more toxic ingredients) or the regasification plants move towards more inhabited areas.

Advanced storage technologies

Energy conversion and process technologies require storage capacities for fuels and products as well as for wastes. The larger the process units and their throughput become the larger the storage sites have to grow. New conversion technologies evoke new ways of storage, for example at extremely low temperatures, at high pressures or at extreme storage sizes. Besides LNG as discussed above, this applies especially to hydrogen as a prospective substitute for fossil fuels. In addition, conversion of fossil fuels requires separation of CO_2, which then has to be stored. This has been discussed under CCS above.

A third aspect is that even with the most environmentally friendly technology there will be some remaining waste, and past or current technologies have left and still leave numerous waste products, which accumulate to an emerging risk. The exact composition of the waste and exposure scenarios has not been well studied. Underground storage can have advantages, but there may also be drawbacks due to self-ignition, contamination of groundwater, lack of stability of the underground deposits in the long term and risk due to geological events such as earthquakes.

Also, for fossil fuels, especially for coal, improved conversion technologies lead to an increase in size of generation units and hence to a higher throughput of coal. Together with growing environmental concerns about storage in free heaps close to human settlements, large storage enclosures above – in one example – underground have recently been erected, and add to the growing concerns. However, densely packed solid fuel stored in tens or even hundreds of thousands of tonnes involves potential for auto-ignition and a fire that could be a major source of unwanted emissions and HSE risk, in addition to potential disruption of power and heating services for a large number of consumers.

Many of the possible new and emerging incident scenarios associated with such storage concern large fires. This underscores the result of the survey that AERVs for combustion gases are relevant (Heinälä et al., 2013).

Natural gas production from manure and waste
Driven by the incentive to be as energy efficient as possible, new ways to produce and utilize natural gas from waste are being explored. Natural gas can be produced in landfills, sewage and wastewater treatment plants, and manure. The RIVM identified the following risk issues concerning natural gas production from manure (Heezen, 2010):

1. The farmer's competency (knowledge, skill) to run the methane production plant. Due to the increasing size and complexity of such plants the farmer is becoming more and more of an operator.
2. The biogas contains the toxic gas hydrogen sulphide (H_2S). This is an additional source of risk that must be attended to.

Currently the energy of biogas is mainly used for power production or heat generation. In the future part of the gas is expected to be reprocessed to natural gas or motor vehicle fuel.

2.2.4 Other types of scenarios

Work area language problems
Due to the free movement of natural persons within the EU, an increasing number of foreign personnel are employed or (sub)contracted to work in the process industry. Language problems, however, do not apply only to workers with poor command of the local language, but also to workers with low literacy.

A study in the Netherlands has shown that workers with very limited Dutch language skills are put to work in dangerous jobs. Written safety instructions appear to be incompletely comprehensible for about half of the readers. This situation introduces an increased risk of misunderstandings, deviations from instructions, unknown situations, missed actions, misunderstood design and habitual errors (Lindhout and Ale, 2009).

Economic migration will most likely not decrease in the next decade, but is set to increase as long as the impact of the 2008–2010 economic crisis is more severe in some member states than in others. With that projection, language problems as a cause for mistakes and accidents must be considered an emerging risk.

Chemical terrorism
The European Council states that the Chemical, Biological, Radiological, and Nuclear agents (and Explosives) (CBRNe) threat from terrorism remains significant. Known terrorist groups and others without organizational

connections have shown interest in developing CBRNe capabilities. Chemical agents (C) and explosive chemicals (e) can be extremely hazardous agents for the mass destruction of materials, ecosystems and human populations. Whereas the focus has long been on terrorist attacks with chemical warfare agents (CWA), currently the threat of an attack involving toxic industrial chemicals /materials (TICs/TIMs) appears to be equally likely.

Two documents are central for further development. A key priority involving 'C terrorism' was adopted by the European Council on 1 December 2005, and the 'EU Strategy against proliferation of weapons of mass destruction (WMD) and their means of delivery' was adopted by Council on 12 December 2003. The EU JHA (Justice and Home Affairs) Council adopted specific conclusions in 2007 that called for further EU-level work on CBRN security.

The key priorities have to be achieved and each member state is responsible for considering the task. All EU countries have to consider:

1. Manufacturing, possession, acquisition, transport, supply or use of weapons, explosives or of nuclear, biological or chemical weapons, as well as research into, and development of, new biological and chemical weapons.
2. Release of dangerous substances, or causing fires, floods or explosions, the effect of which is to endanger human life.

As a conclusion, chemical terrorism is assessed to be a realistic threat. As with any type of terrorism, it is extremely difficult to predict when and where the threat will materialize.

2.3 Legislation

The (inter)national legal framework is a complex set of laws, directives, regulations and derivatives thereof. There is national law, and international law both at a European and at a global level. The extent of this project does not permit review of all the new developments in this area. The legislation that is now in force and has or should have any relation with single exposures to chemicals will be discussed in Chapter 4.

The present section describes a limited attempt to identify whether legislation and/or guidelines under consideration or development might be of interest within the near future to the subject of acute chemical risks. Experts from the fields of environment, public health, infectious disease control, chemical health risk assessment, climate change and chemical substances law have been interviewed to obtain relevant information. The main objective of these interviews was to find out whether there are new developments that may lead to new legislation in their respective working fields ultimately leading to or addressing new and emerging risk of acute chemical exposure scenarios.

Apart from discussions regarding the need for specific legislation for nanomaterials, no further indications for upcoming new legislation within these areas were identified. Within the public health framework, there are no indications that there is upcoming new legislation. Regarding climate change issues, no new legislation seems to be under development either. There is, however, much discussion about the spreading of viral vectors, such as the West Nile virus, Blue Tong virus and tiger mosquitoes, due to increasing global transport and travelling. The spread of such viruses around the world may

eventually lead to newly designed large-spread pest control measures with as yet unknown risks. Climate changes may cause insects and other disease-carrying animals to extend their habitat to areas where they previously could not survive. This may also lead to increased use or a shift in the use of pesticides, introducing new risks.

(Pre)legislative changes in the context of environmental issues on the European scale are predominantly developments regarding storage and transport, including the use of ballast water. These aspects are discussed in Chapter 4 and in other ERRAs in the iNTEg-Risk project (e.g. on CO_2-storage; ERRA A1). In this context, there is also an ongoing discussion on the temporary storage of LNG in old gas fields (subject of ERRA A4). The surplus of gas that becomes available in summer can be stored in the old gas fields until use in winter. This is, however, a national solution discussed in the Netherlands, which has no European coverage yet.

The Seveso II Directive is currently undergoing a revision. The implications of this revision will be discussed in section 4.2.

2.4 Conclusions

The aim of this chapter was to explore the consequences of new and emerging chemicals and incident scenarios and developments foreseen within several legal frameworks for the overall human health risk from chemical incidents. Information from the literature and expert consultation identified only two classes of chemicals that may contribute to new and emerging chemical risk: liquid energy carriers and nanomaterials. New chemicals are coming to the market all the time. These are expected to be registered and reviewed under REACH regulation (cf. section 4.3). Most of the new chemicals enter the market in small quantities, so the available toxicological database is in most cases limited.

The main drivers for new and emerging risks of chemical incidents may be new and emerging chemical incident scenarios. Climate change, land-use pressure and new energy technology all create new and emerging risks for chemical incident scenarios.

Based on developments described in this chapter the risk of chemical incidents is likely to increase for some chemical classes and chemical incident scenario categories. Little information is available to allow a quantitative assessment of the likely or possible increased risk of chemical incidents or their impact on ecology, economy and human health. In view of the potential threat, monitoring of the actual development of these risks and their impact seems reasonable.

3 Methodologies for risk assessment of chemical incidents

3.1 Introduction

Based on the results from a recent web-based survey designed to identify stakeholders' concerns, needs and gaps in available tools, and guidance and information to assess the risk of incidents involving acute chemical exposures, it appears that Europe would benefit from a harmonised methodology for deriving AERVs at a European level (Heinälä et al., 2013). Currently, there is no regulatory harmonized procedure for deriving such methodology and the respective AERVs, that meets the criteria and demands of European end-users and policy-makers. Therefore, this chapter will explore:

- information, tools and guidance required to develop AERVs;
- to what extent there is European consensus on the methodology to derive AERVs from toxicological data;
- which methods and procedures need to be further developed to reach the required consensus;
- relevant developments in the field of chemical incident exposure assessment, including sensor technologies and biomarkers.

3.1.1 Data and methodological requirements for AERV derivation

The design specifications of AERVs are determined by their intended application and, more generally, by the factors that determine the toxic response of a human or animal population to a chemical exposure:

- chemical substance;
- exposure route (inhalation, dermal, oral or parenteral);
- exposure concentration of the chemical in the contact medium (air, water, food, etc.);
- duration and repetitiveness of exposure (exposure pattern);
- species (test animals or human);
- toxicokinetics, including bioavailability;
- (patho-)physiological characteristics of the individuals in the exposed population, including genetic factors, different life stages, normal life events (e.g. pregnancy);
- socio-economic and cultural factors, including habitual co-exposure (e.g. alcohol consumption, smoking).

AERVs are used in support of the public health management of chemical incidents, which requires that AERVs should enable comparison of the public health impacts of the chemical exposure and of the possible emergency response measures such as shelter-in-place or evacuation. Therefore, AERVs should be designed to *predict* health effects in a heterogeneous human population resulting from a single brief (<24 hours) airborne exposure via inhalation and via the dermal route. Consequently, AERVs are *predictive* and designate *effect* levels.

There is a clear distinction between such *predictive* AERVs and inherently *protective* guidelines such as Acute Reference Concentrations (ARfCs), Ambient Air Quality Guidelines (AAQGs) and acute Derived No-Effect Levels (acute DNELs). Such *protective* guidelines are designed to prevent a target population (not necessarily the general population) from any adverse health effect and are of a conservative character to ensure protection. In contrast, *predictive* AERVs

aim to provide guidance as to when an adverse health effect may occur in a respective susceptible subpopulation.

For the purpose of this inventory thirteen methodologies to derive AERVs were identified and are presented in Table 3.1. Nine methodologies are currently applied to derive AERVs and four are either dormant or have not (yet) been applied in a formal AERV derivation context. Six methodologies (in italics) were selected for further methodology comparison and presentation of the current state of the art. AEGLs and ERPGs are the most applied worldwide and represent the existing American approaches. The Acute Exposure Threshold Level (AETL) methodology is the outcome of the ACUTEX project, which has been developed and tested but not further applied. The background of the ACUTEX project in which AETLs have been derived is described in detail by Wood et al. (2006). The Dutch Intervention Values (DIVs) and the French VSTAF (Valeurs Seuils de Toxicité Aiguë Françaises) are the only two national methodologies that are currently in use; the Danish Emergency Planning Exposure Guideline Values (EPEGVs) is a third national methodology that has been developed and tested but not further applied.

Table 3.1 illustrates that AERVs can be expressed as threshold values or as a function of concentration, time and incidence (usually a probit function). Probit functions are more informative and provide information for making a quantitative assessment of the incidence of a certain effect in the exposed population, but require much more substance-specific data to develop. Some frameworks have been specifically designed to produce AERVs for certain applications, such as EPEGVs for preparedness and DIVs for response. In practice, such nuances are lost and AERVs are used whenever an acute exposure guideline is required for any stage in the disaster management cycle (Heinälä et al., 2013).

Table 3.2 provides a basic overview of some essential characteristics of the six acute exposure guideline methods reviewed in this chapter, showing the different tiers applied, the different approaches with respect to the determined exposure durations, the basis of the derivation of the point of departure (PoD) and their respective guidelines or operating procedures.

Although many similarities exist between the methodologies presented, various disparities are evident. There are two driving forces behind such disparities:

1. The toxicological endpoints selected as a basis of the derivation of the PoD for each of the AERV levels.
2. The calculation of the AERV levels from the toxicological data (including methodological choices and tools used).

These discrepancies may result in major differences between AERVs for the same substance. This is demonstrated by Öberg et al. (2010), who compared the two most frequently used methodologies, AEGL and ERPG, in qualitative and quantitative terms. Despite the very comparable definition of the three tiers, the resulting AERVs varied by a factor of 3 in 40 per cent of the substances, indicating a need for broad international acceptance of harmonized values.

Many AERV methodologies have defined at least three tiers for AERV values, with roughly the following characteristics:

1. A threshold for discomfort or other minor, rapidly reversible health effects, such as slight eye and respiratory irritation.
2. A threshold for disabling (escape impairing) or otherwise serious health effects; these are not necessarily readily reversible. Examples are a moderate degree of intravascular haemolysis, serious eye or respiratory irritation with tissue damage, drowsiness, nausea.
3. A threshold for life-threatening effects or lethality.

In some frameworks an additional tier for sensory awareness is defined (mainly objectionable odour) and in some others a tier for supra-threshold lethality (AETL-3a and Seuil des Effect Létaux 5 per cent (lethal effects threshold – SELs) has been defined.

The value of any AERV tier can be based on any of the endpoints specified above. Respiratory and eye irritation or methaemoglobinaemia can be minor (qualifying for tier 1), disabling (tier 2) or life-threatening (tier 3).

Likewise, a chemical can produce more than one toxic effect that may qualify as a PoD for a particular tier. For example, reproductive/developmental effects and clinical signs of respiratory irritation/nasal lesions both qualify as points of departure for tier 2 of *n*-butyl acrylate. If effects of more than one endpoint qualify as a PoD for a particular tier, the endpoint that is lowest on the exposure-effect curve usually serves as a PoD for the AERV values. The process of AERV derivation from toxicological data is schematically presented in Figure 3.1.

Similarities and differences in the process steps outlined above will be explored in sections 3.2–3.4. This comparison will include only methodologies that produce AERVs for at least three tiers, and which are sufficiently documented, in order to compare approaches. Based on these criteria, the following methodologies will be compared: AEGL, AETL, DIV, EPEGV, ERPG and VSTAF. Table 3.2 provides an overview of the characteristics of these methodologies. Sections 3.2–3.4 describe the frameworks as accurately as possible. Section 3.5 illustrates the consequences of differences identified in these sections in definitions of AERV tiers and/or different evaluation of data for the resulting AERV values. Value judgements regarding any of the discussed subjects represent the opinion and methodology of the respective framework, and do not necessarily constitute consent of this study's authors.

Risk assessment of chemical incidents requires exposure-effect or exposure-response information (e.g. in the form of AERVs), and information on the actual exposure: contact medium, concentration and duration. Section 3.6 explores the current state and recent developments in methods to assess inhalation exposure resulting from chemical incidents, both during and before the incident.

Table 3.1. Overview of existing methodologies to derive AERVs.

Name	Responsible organization	Active	No. of (test) substances	Values	Endpoints
Acute exposure guideline level (AEGL)	US Environmental Protection Agency (EPA)	Yes. Since 1999.	60 finals 188 interims 24 proposed 46 on hold Total 318	4 severity levels 5 exposure times	Lethal and non-lethal
Acute exposure threshold levels (AETL)	ACUTEX project	No. Method developed.	20	5 severity levels 6 exposure times Lethality probit	Lethal and non-lethal
Dutch intervention value (DIV)	National Institute for Public Health and the Environment (RIVM), The Netherlands	Yes. Since 1993, updated in 2007.	313 (personal communicatio n, RIVM, The Netherlands)	4 severity levels 6 exposure times (revision)	Lethal and non-lethal
Emergency response planning guideline (ERPG)	American Industrial Hygiene Association (AIHA)	Yes. Since 1987.	142	3 severity levels 1 exposure time	Lethal and non-lethal
Emergency planning exposure guideline values (EPEGV)	Danish Institute of Food Safety and Toxicology, Denmark	No. Method developed in 1998, unpublished report.	11	3 severity levels 1 exposure time	Lethal and non-lethal
VSTAF	Institut national de l'Environnement industriel et des risques (INERIS), France	Yes. Since 1999. Methodology updated in 2001 and 2007.		3 severity levels Probit function	Lethal and non-lethal
Dangerous toxic load (DTL) for specified level of toxicity (SLOT)	Health and Safety Executive (HSE), UK	Yes. Since 1989.	247	2 severity levels Probit function	Lethal and non-lethal
Emergency exposure guideline levels (EEGL)/short-term public emergency guidance level (SPEGL)	US National Research Council (NRC)	No. Active in 1980s. Currently terminated.	Could not be publicly retrieved, probably due to cessation of project.	1 severity level 1 exposure time	Non-lethal

Name	Responsible organization	Active	No. of (test) substances	Values	Endpoints
Emergency exposure indices (EEI)	European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC)	No. Method developed in 1991.	3	3 severity levels 3 exposure times	Lethal and non-lethal
Immediately dangerous to life or health (IDLH)	National Institute for Occupational Safety and Health (NIOSH)	Yes. Since mid-1970s.	388	1 severity level 1 exposure time	Non-lethal
Predictive toxicity measures	US Department of Homeland Security (DHS)	Yes. Since 2009.	No values publicly available yet	4 severity levels Probit functions	Lethal and non-lethal
Quantitative risk analysis (QRA) lethality probit	RIVM, Netherlands Organization for Applied Scientific Research (TNO), The Netherlands	Yes. Since 1987 and updated 2008.	35, of which several are under review (personal communication, RIVM, The Netherlands)	Lethality probit	Lethal
Temporary emergency threshold limit (TEEL)	US Department of Energy (DOE)	Yes. From 1992.	3373; see Table 3.2.	4 severity levels 1 exposure time	Lethal and non-lethal

AEGL: http://www.epa.gov/opptintr/aegl/pubs/compiled_aegls_aug2010.pdf

DIV: http://www.rijksoverheid.nl/documenten-en-publicaties/publicaties-pb51/interventiewaarden-gevaarlijke-stoffen-2007.html

The DIV methodology and values are currently under revision. In the present report, the revised methodology is evaluated unless otherwise indicated.

DTL: www.hse.gov.uk/hid/haztox.htm

EPEGV: unpublished report dated 1998 (Nielsen, 1998).

ERPG: 2010 ERPG/WEEL Handbook by the AIHA Guideline Foundation (http://www.aiha.org/insideaiha/GuidelineDevelopment/ERPG/Documents/ERPG_Values2010.pdf).

IDLH: www.cdc.gov/niosh/idlh/intridl4/html

TEEL: www.atlintl.com/DOE/teels/teels.pdf. The Temporary Emergency Exposure levels (TEELs) dataset is renamed as the Protective Action Criteria (PAC) dataset. In this dataset the TEELs dataset is combined with the AEGL and ERPG dataset. This results in values for 3,373 chemicals.

VSTAF: http://www.ineris.fr/fr/rapports-d%C3%A9tude/toxicologie-et-environnement/fiches-et-rapports-de-seuils-de-toxicit%C3%A9-aigu%C3%AB (French).

Table 3.2. Methodological characteristics of current acute exposure guideline methods.

Subject	**AEGL**	**AETL**	**DIV**	**EPEGV**	**ERPG**	**VSTAF**
Tier 1	AEGL-1	AETL-1	VRW	EPEGV-1	ERPG-1	SER: threshold of reversible effects
Tier 2	AEGL-2	AETL-2	AGW	EPEGV-2	ERPG-2	SEI: threshold of irreversible effects
Tier 3	AEGL-3	AETL-3	LBW	EPEGV-3	ERPG-3	SPEL: threshold of lethal effect (1%)
Tier 4						SELS: significant lethal effect (5%)
Determined exposure duration	10, 30 minutes 1,4 and 8 hours	10, 30 minutes 1,2,4 and 8 hours	10, 30 minutes 1,2,4 and 8 hours	1 hour	1 hour	1, 10, 20, 30 minutes, 1,2,4 and 8 hours
Basis of the derivation of PoD	Predominantly single study	Single study (clear criteria adopted)	Weight of evidence	Predominantly single (acute exposure) study	Weight of evidence	Weight of evidence: predominantly acute effects
Unit	ppm	ppm	mg/m^3	ppm and/or mg/m^3	ppm	ppm and mg/m^3
Reference	NAS/COT, 2009 www.epa.gov/oppt/aegl/pubs/chemlist.htm	ACUTEX, 2006	Ruijten and van Doorn, 2006; currently under revision.	Nielsen, 1998	AIHA Guideline Foundation, Administrative Operating Procedures, 2010; ERP Committee, 2006	Pichard and Tissot, 2003

VRW: Voorlichtingsrichtwaarde (instruction guidance value); AGW: Alarmeringsgrenswaarde (alarm boundary value); LBW: Levensbedreigende waarde (life threatening value); SER: Seuil des Effets Réversibles (reversible effects threshold); SEI: Seuil des Effets Irréversibles; (irreversible effects threshold); SELS: Seuil des Effets Létaux 5% (lethal effects threshold); SPEL: Seuil des Premiers Effets Létaux (1%) (lethal effects threshold).

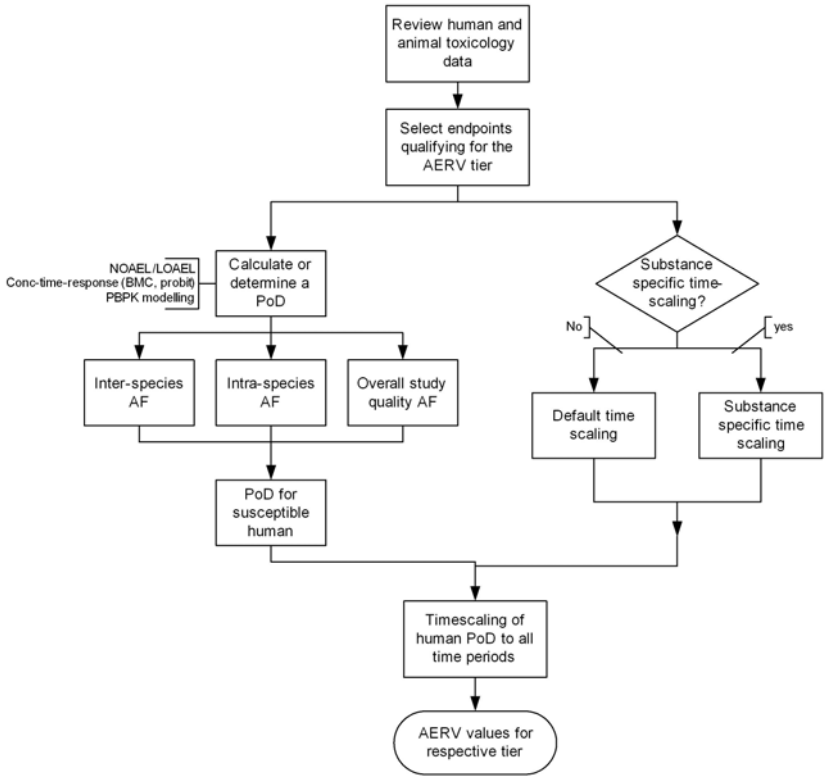

Figure 3.1. Flowchart for the derivation of AERVs from toxicological data. Depending on the model, the time scaling and PoD can sometimes be assessed in one integral step.

3.2 Toxicological endpoints

3.2.1 Introduction

Toxicological health endpoints that have been used as a point of departure for derivation of acute exposure guidelines include:

1. Respiratory and eye irritation (including sensory irritation);
2. Cardiac toxicity (e.g. cardiac sensitization);
3. Haematotoxicity (methaemoglobinaemia, haemolysis, aplasia, etc);
4. Hepatotoxicity;
5. Renal toxicity;
6. Carcinogenicity;
7. Reproductive toxicity;
8. Sensitization;
9. Neurotoxicity (e.g. narcosis);
10. Sensory awareness other than irritation (odour). Although this is not a toxicological health endpoint in a strict sense, it might also be an endpoint of interest in the context of AERVs.

There is relatively little debate concerning the use of toxicological data for the endpoints 1–7, which can be interpreted to mean that there is usually little controversy over the use of such data. However, there is little specific and quantitative guidance available on most of these endpoints and the procedures applied to derive AERVs from data on these endpoints were developed on an ad hoc, case-by-case basis. To determine the necessity to harmonize the use of these endpoints for AERV derivation methods, a review of individual documents

on the methodologies listed in Table 3.1 would be needed and, in some cases, authors or committees would need to be approached to find the rationale for the application of such data in the derivation process. This task is beyond the scope of the present study. Clearly, the accumulated knowledge about these endpoints (while not fully documented) provides an excellent starting point for a methodology to use data for the development of a PoD and AERVs.

Strictly speaking, the absence of documented guidance prohibits comparison of the listed methodologies and does not support the conclusion that a reasonable degree of consent has been reached. This assessment has been made from experience with review of the listed methodologies. The absence of well-documented specific and quantitative methodology for deriving AERV values, even for the less disputed endpoints 1–7 alone justifies the consideration of development of a harmonized European methodology for AERV derivation.

The present study will focus further on the endpoints for which obvious differences of opinion exist regarding their application in AERV development. In addition, the endpoints sensitization and neurotoxicity, which were identified as high-priority endpoints in the survey (Heinälä et al., 2013) will also be reviewed as an illustration of the extent to which the guidance for these endpoints has converged in the different methodologies.

Considerable debate and/or uncertainty appear to exist concerning the endpoints 7–10 (Post ACUTEX Workshop, 2006). This dissent prohibits the universal adoption of any of the existing sets of AERVs for application in a European context. Sections 3.2.2– 3.2.5 will explore the state of the art, identify the unresolved issues and propose a path forward towards their resolution.

For most of the endpoints listed above a particularly important tool is missing: classification criteria to assign effects to any of the AERV tiers. For instance, how much decrease in FEV_1 (a lung function parameter) is still considered to be below tier 2, and which absolute level or percentage decrease in FEV_1 is considered to be escape impairing. The definition of such critical effect sizes for the most frequently encountered measures of toxicity would greatly help to define values for AERV tiers. The ACUTEX project was the first to develop such criteria, albeit mostly qualitative. Quantification of critical effect sizes is a major task ahead.

3.2.2 Carcinogenicity

Background

Tumour development is the result of long processes resulting from the disruption of cellular function, e.g. following exposure to a carcinogenic chemical. Within the present context of single exposures, expert governmental committees suggest that such a carcinogenic risk is likely to be very small, as at low doses there may be significant DNA repair processes, a non-linear response may occur due to the complex carcinogenic processes, and genotoxic chemicals may exert different effects at high or low doses (i.e. at high doses cytotoxic mechanisms may promote tumour formation). However, the carcinogenic risk following a single exposure to a genotoxic carcinogen still needs to be considered after a chemical incident. As summarized by Verhagen et al. (1994), there is some evidence that a single exposure to some potent genotoxic substances can induce a cancer process during later life stages (demonstrated in animal studies). To estimate the cancer risk of a peak exposure relative to the cancer risk of the same total dose distributed over a lifetime, they defined a Dose-Rate Correction

Factor (DRCF) as 'a factor by which the tumour incidence caused by a specific dose of a chemical at low dose rates is multiplied to derive the tumour incidence at high dose rates'. They reported that DRCF values for genotoxic carcinogens calculated from experimental studies ranged from 0 to 8.3. Theoretical calculations, mainly based on computer simulations, revealed DRCF values ranging from 0 to 7.1. The latter values depended on the assumed number of stages in the carcinogenicity process in the simulation and on age at time of exposure. Verhagen et al. (1994) considered a DRCF value to be compound specific and proposed a default DRCF value of 10 if insufficient data were available to estimate a compound-specific value. Other suggested values for a DRCF include 1 (US EPA, 1986; 1996), 2.8 (COT, 1986) or 6 (NRC, 2001). A pragmatic approach how to deal with genotoxic carcinogens in single exposures is discussed in Bos *et al.* (2004).

If a substance is considered to be carcinogenic in the context of Regulation 1272/2008 EC for classification, labelling and packaging (GHS), the following hazard categories and hazard sentences are applicable: Hazard Category 1A, 1B are labelled with the hazard phrase H350 'May cause cancer (*state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard)*'and carcinogens in Hazard Category 2 (GHS08) with hazard phrase H351 'Suspected of causing cancer (*state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard)*'. Relevant in the context of AERVs is the mode of action of the carcinogen. Therefore, the categorization for mutagenicity is also of importance. The following hazard categories and sentences are applicable: Category 1A or Category 1B with hazard phrase H340 'May cause genetic defects (state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard)' and Category 2 with hazard phrase H341 'Suspected of causing genetic defects (state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard)'.

The different international methodologies considered in this chapter address this issue of carcinogenicity in accidental exposures in varying ways, as described below and summarized in Table 3.3 at the end of this section.

Methodology comparison

AEGLs

The issue regarding cancer risks has been considered in detail in the AEGL documentation and by the National Advisory Committee for AEGLs. In addition, guidance from the NRC in 1993 stated that the derivation of AEGLs should involve linear low-dose extrapolation from the upper confidence limit on excess risk for genotoxic carcinogens and for chemicals for which the mechanisms are not well understood. Moreover, it is suggested that multi-stage models could be useful for setting values, although it is acknowledged that data may not be available on the multi-stage process of the carcinogenesis.

The National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances (NAC/AEGL Committee) has evaluated excess theoretical risk levels of 10^{-4}-10^{-6} for a single exposure to known carcinogens by calculating the total cumulative lifetime dose then extrapolating to exposure periods of 30 minutes to 8 hours using Haber's law. Adjustment factors are then used with such doses to account for the multi-stage process of carcinogenesis.

The Committee assesses the methodology for setting the AEGL values for hazardous substances by considering carcinogenicity bioassay data, as well as epidemiological data, from which a causal relationship between exposure and health outcome may be defined. US EPA slope factors may be used as a basis to calculate cancer risk levels[3]. Alternatively, a single dose giving a cancer risk level of 10^{-4}–10^{-6} may be calculated using the linear rate model (RR = 1 + 0.0099X), by determining the cumulative lifetime dose, where X is the cumulative exposure in ppm-years. An appropriate point of departure is selected, appropriate adjustment factors applied and the concentration associated with a theoretical excess cancer risk of 10^{-4} calculated. By multiplying this concentration by 25,600 (the approximate number of days in 70 years) this concentration is converted from a 70-year exposure to a 24-hour exposure. This concentration is subsequently divided by a DRCF (called a multi-stage factor) of 6. Next, the 24-hour risk estimate is linearly extrapolated to the respective AEGL exposure durations. Finally, a 10- or 100-fold reduction of these concentrations reveals the corresponding 10^{-5} and 10^{-6} risk levels, respectively.

The NAC/AEGL Committee has decided not to establish AEGL-2 or -3 values using potential carcinogenicity as critical toxic effect. This is motivated by the uncertainties of assumptions used in extrapolation from lifetime exposures to 8 hours or less, the lack of single exposure inhalation data, the relatively small populations involved and the potential risks associated with evacuations. The Committee does not believe that the use of carcinogenicity data to derive AEGLs is justified at the present time.

Although AEGLs may not be based on carcinogenic endpoints, it is thought that information on human carcinogens should still be provided to emergency responders and the general public. Therefore, the NAC/AEGL Committee evaluates the available carcinogenic data on a chemical-by-chemical basis and provides the calculation in an appendix of the Technical Support Document. When the scientific data is sufficiently convincing to clearly support a relationship between a single short-term inhalation exposure and the onset of tumours that are likely to occur in humans, the carcinogenic risk will be given appropriate weight-of-evidence considerations in the development of the appropriate AEGL values.

AETLs

The methodology behind deriving AETLs in terms of using carcinogenicity as an endpoint was investigated as part of the ACUTEX project. Although little is known about the carcinogenic risk following a single exposure, it was concluded that carcinogenicity should be addressed when determining AETL values.

When considering carcinogenic compounds during AETL development, it was suggested that carcinogens should be differentiated into the four categories of increasing hazard after a single exposure to an AETL-2 or AETL-3 dose:

1. Non-genotoxic carcinogens with short half-lives;
2. Weak genotoxins and substances with short half-lives for which genotoxicity is not strongly related to carcinogenicity;
3. Highly genotoxic or potent carcinogens with short half-lives;
4. Established or suspected carcinogens with long half–lives.

[3] The EPA slope factors can be found at: http://www.epa.gov/IRIS.

The first two categories may be disregarded in terms of tumorigenic risk after a single exposure. For such chemicals, AETL-2 and -3 are based on conventional toxic endpoints that are also considered protective against cancer. The third category may be supported with mathematical risk calculations based on chronic bioassay data, from which a daily lifetime dose following a single inhalation exposure may be extrapolated. Acute carcinogenicity data should also be considered if available. Many chemicals in this category will have a very low risk after a single exposure. Group 4 chemicals may pose a considerable risk after a single exposure, although this should be compared with the total dose in a lifetime and with bioavailability data after a single exposure.

For genotoxic carcinogens, it is possible to extrapolate from chronic exposure to single exposure scenarios, once the level of excess cancer risk has been determined, i.e. 10^{-4}, 10^{-5} or 10^{-6}. For acute accidental releases, a higher risk, i.e. 10^{-4} or 10^{-5}, could be used and an additional uncertainty factor (analogous to a DRCF) of 10 is proposed to take into account enhanced susceptibility for the early life stages, in agreement with the US EPA methodology (US EPA, 2005a, 2005b).

The Guidance Document states that AETL-3 addresses potential life-threatening diseases and cancer may be encompassed in such a definition. If the AETL-3 for a genotoxic carcinogen is, however, based on acute lethal effects rather than carcinogenicity it should be verified whether AETL-2 adequately protects against carcinogenic effects. However, unfortunately carcinogenicity as an endpoint has not been elaborated in practice in any of the case studies.

DIVs
In the Netherlands, the methodology for the weighting of the carcinogenic potency is comparable to the AEGL philosophy, albeit with some adjustments. If, for a non-genotoxic carcinogen, a threshold value can be derived this will be used to derive the second level of DIVs, the *Alarmeringsgrenswaarde* (AGW). In that case, the derivation of the AGW is analogous to that for non-carcinogenic chemicals. For non-genotoxic carcinogens for which such a threshold value cannot be derived and for genotoxic chemicals, the derivation of a DIV is not based on carcinogenic potential. Instead, a quantitative risk estimate, the carcinogenic risk potential (CRP), is calculated if possible. The basis for the CRP is a unit risk estimate for an excess risk of 10^{-4} derived by (in order of importance) the US EPA, the Health Council of the Netherlands, the World Health Organization (WHO) and the National Institute for Public Health and the Environment (RIVM). As proposed by Verhagen et al. (1994), a DRCF is applied. Based on both experimental animal data and theoretical considerations, a DRCF of 10 can be chosen to ensure conservatism. However, since DIVs are meant for the estimation of actual risks, a median DRCF value is considered to be more appropriate. Therefore, in conformance with the ERPG methodology, a median DRCF value of 2.8 was selected, based on the maximal uncertainty in the multi-stage model.

The CRP is calculated by multiplying the concentration equivalent to an excess cancer risk level of 10^{-4} with the average lifetime in hours ($70 \times 365 \times 24 = 613{,}200$ hours) and subsequently dividing the outcome by the DRCF of 2.8.

EPEGVs
Within the Danish EPEGV proposal, it is mentioned that, if a substance is known or suspected to cause carcinogenic effects in humans or animals, the possibility that such effects may occur even after a brief exposure should be considered. If

the carcinogenic effects are considered to be the critical effects following a brief exposure, a cancer risk assessment may be performed. It is noted, however, that for most substances the risk of cancer arising from a brief exposure is not the critical endpoint. The carcinogenic effects are considered at the level of tier 2 but no further guidance is given.

ERPG
When deriving ERPG values, cancer data are reviewed but are only used in setting ERPG levels when the risk of developing cancer from a single exposure to a given concentration for the ERPG-2 would exceed a lifetime risk of 1 in 1,000,000 per year (AIHA, 2010). A robust inhalation dataset is necessary for the weight-of-evidence approach, although cancer bioassay or tumour mode of action data (qualitative evidence) and carcinogenicity dose response is deemed helpful rather than necessary.

An estimate of the potential for a carcinogenic response following short-term exposures will be developed based on the Committee on Toxicology, National Research Council (COT, 1986) approach. The estimate will be developed when a q_1* slope value has been published by the US EPA (IRIS database) or when appropriate data are available to calculate a q_1* value. The q_1^* calculation consolidates risk estimates derived from low-dose extrapolation of animal bioassay or epidemiological data into a single 1-hour exposure time-frame and assumes a 1 in 10,000 risk of cancer. The COT method uses a DRCF of 2.8 to account for uncertainties in extrapolation from long-term animal exposure to a single human exposure. The estimate from the COT calculation will then be compared with the derived value for the ERPG-2 based on other endpoints. Based on the Committee's assessment of the quality of the chemical's database, the ERPG-2 value may be based on the NRC estimate (AIHA, 2010). The Committee will make the final decision on the scientific appropriateness of the COT estimate based on the weight of the studies. The COT estimate will be included in the technical document.

VSTAF
In the French methodology (VSTAF), the potential carcinogenic effects are not taken into account when setting thresholds. However, a review paper has been written to discuss the inclusion of carcinogenic endpoints when deriving French acute thresholds, especially for 'one shot carcinogens'. The work is still in progress within the French expert group. If the chemical has known or suspected carcinogenic properties, then carcinogenic effects for this substance are evaluated and discussed in the report for the irreversible-effects level. As at September 2010, only vinyl chloride was encountered as a case study, in 2001.

Conclusion
Overall, it has been recognized that the theoretical risk from single exposure to a genotoxic carcinogen is probably low. Nevertheless, carcinogenicity was considered to be an important endpoint in most of the frameworks examined. Only VSTAF does not take this endpoint into account when deriving AERVs although the topic is presently under discussion by the French expert group.

The risk assessment of (genotoxic) carcinogenic chemicals is often the subject of debate, regarding the mechanism of action (genotoxic versus non-genotoxic) but also with respect to the derivation of an appropriate quantitative risk estimate for the targeted exposure situations. The latter issue is of special importance within the present context of estimating the carcinogenic risk for a single exposure. A distinction between genotoxic and non-genotoxic carcinogens

is not always clearly made. Further, some of the available guidance documents provide only very limited guidance (EPEGV) or are not always clear about how the guidance will work out in practice (AETL).
The methodologies of the frameworks show widely differing approaches to address carcinogenicity as an endpoint for AERV derivation. The approaches include:

- not considering carcinogenicity as endpoint (VSTAF);
- derivation of a separate risk estimate (AEGL; DIV (genotoxic carcinogens and non-genotoxic carcinogens without known threshold));
- consideration of endpoint at tier 2 (ERPG, EPEGV, DIV (non-genotoxic carcinogens with known threshold));
- consideration of endpoint at tier 3 or 2 (AETL).

Another important issue is the application of a DRCF. Of the frameworks that do address carcinogens no mention is made of the application of a DRCF (EPEGV) or different values are recommended, i.e. 2.8 (ERPG, DIV), 6 (AEGL) or 10 (AETL).

Single exposures to carcinogens appear to be an important issue of concern for risk communication, even if the actual risk is relatively low. Together with effects on reproduction, carcinogenicity is often the reason for extensive public concern when carcinogenic chemicals are released in the vicinity of residential areas. Therefore, risk managers and other end-users do need guidance and a communications strategy on carcinogenicity in the form of a quantitative risk assessment to adequately meet the public concerns. In this field of public information, the message has to be relayed to the public without causing stress, fear and/or panic. Therefore, even if AERVs are actually based on carcinogenicity as the endpoint for only a limited number of chemicals, it is important to be able to communicate that carcinogenic effects are being seriously considered in the specific exposure situation. On the other hand, any possible risk also has to be set against the risks of evacuation or other risk reduction actions. It can thus be concluded that a credible approach to carcinogenicity and mutagenicity for single inhalation exposure is needed in order to derive AERVs.

Considering the major differences in proposed and existing approaches to the endpoint of carcinogenicity and the need of risk managers and end-users for clear guidance, it is concluded that further elaboration is needed to develop an accepted Europe-wide guidance for the purpose of risk assessment, risk management and risk communication. It is noted that it is up to risk managers to define a level of acceptable risk based on the precautionary principle.

Within the context of future developments, reference is made to a workshop organized in December 2009 by ILSI Health and Environmental Sciences Institute (HESI). Forty-eight invited experts participated in discussing a proposed framework for estimating potential human cancer risk from less-than-lifetime exposures. The proposed framework provides a decision tree and guidance for cancer risk assessments for these exposures, using available toxicity and exposure data. A manuscript has been published that presents an overview of the foundation for the workshop, describes the proposed framework for assessing less-than-lifetime exposures to potential human carcinogens, suggests next steps, and reviews historical background (Felter et al., 2011).

Table 3.3. Summary of how carcinogenicity is addressed in the different methodologies.

Methodologies	**AEGL**	**AETL**	**DIV**	**EPEGV**	**ERPG**	**VSTAF**
Consideration/tier	Not incorporated in any tier, but discussed separately in an annex.	AETL-2 or AETL-3	AGW (non-genotoxic carcinogens with a known threshold) For other carcinogens, carcinogenicity is not incorporated in any threshold, but carcinogenic risk potential (CRP) is mentioned as a separate value.	EPEGV-2	ERPG-2	Not addressed specifically but might be used as case study for the derivation of the threshold for irreversible effects. A review paper has been written to discuss inclusion when deriving French acute thresholds. Still in progress.
Type of carcinogen	Genotoxic	Genotoxic	All carcinogens	All carcinogens	Genotoxic	One-shot carcinogens
Point of departure	Human virtually safe dose (VSD) or unit risk	Animal tumour risk	Unit risk estimate derived by (in order of importance) US EPA, Dutch Health Council, WHO or RIVM	EPEGV-2	Human Unit risk	-
Dose Rate Correction Factor	6	10	2.8	Not mentioned	2.8	-
Considered risk	10^{-4},10^{-5},10^{-6}	10^{-4},10^{-5}	10^{-4}	Not mentioned	10^{-4}	-

3.2.3 Reproductive toxicity

Background

Reproductive toxicity (including fertility and developmental toxicity) is an issue of major societal concern, even following single exposures. Developmental toxicants are defined as agents that can cause abnormal developmental effects in the developing organism, manifested as resorptions or death, structural abnormalities (teratogenic effects including malformations and variations), distorted growth (alterations in organ, bodyweight or size) or functional deficits (US EPA, 1991). Developmental toxicity generally occurs after repeated exposure, but may also result from single (short-term) exposure during a critical time window. Male or female fertility may be also affected.

If a substance is considered to be a reproductive toxicant in the context of Regulation 1272/2008 EC for classification, labelling and packaging (GHS), the following hazard categories and hazard sentences are applicable:

- Hazard Category 1A (known human reproductive toxicant) and 1B (presumed human reproductive toxicant);
- H360: May damage fertility or the unborn child (state specific effect if known; state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard);
- Hazard Category 2 (suspected human reproductive toxicant);
- H361: Suspected of damaging fertility or the unborn child (state specific effect if known) (state route of exposure if it is conclusively proven that no other routes of exposure cause the hazard);
- H362: May cause harm to breast-fed children (additional category).
-
- Hazard statements H360 and H361 indicate a general concern for both the reproductive properties related to fertility and developmental effects: 'May damage/Suspected of damaging fertility or the unborn child'. According to the classification criteria (Annex I, section 3.7) the general hazard statement can be replaced by the hazard statement, indicating only the property of concern, in the case that either fertility or developmental effects are proven not to be relevant.

The philosophy of addressing reproductive toxicity in relation to acute or short-term exposure varies between the different frameworks for setting threshold exposure levels. How different international methodologies address this issue of reproductive toxicity for accidental exposures is described below and summarized in Table 3.5 at the end of this section.

Methodology comparison

AEGL

Reproductive toxicity is addressed when deriving the second level: AEGL-2. Within the present procedure, the NAC/AEGL Committee has adopted the recommendations of the report by Van Raaij et al. (2003), which evaluated the different endpoints of fertility and developmental toxicity and whether a single exposure could induce such effects. It was concluded that fertility testing and multi-generation tests are generally not considered relevant for the present context since these tests address effects that only occur in repeated exposure situations. The main focus within the AEGL derivation is on effects that may result from a single exposure, such as embryotoxicity and foetotoxicity. Van Raaij et al. (2003) compared no observed adverse effect levels (NOAELs) and low observed adverse effect levels (LOAELs) from single and repeated developmental toxicity studies (OECD 414 test or comparable toxicity tests) for

a number of chemicals. They concluded that resorptions and foetal malformations/variants might be caused by single exposures and should be considered to be relevant toxicity endpoints, unless evidence becomes available to indicate otherwise. The relevance of foetal body weight should be evaluated on a case-by-case basis within the total context of developmental effects and maternal toxicity.

AETL
When deriving AETLs, the philosophy behind approaching reproductive toxicity differs considerably from the other frameworks. The largest difference is that the target population are healthy middle-aged (male) adults (see section 3.3). Consequently, susceptible subpopulations, such as the unborn child, are not protected by the AETLs by definition. Instead, the possibility for the existence of a susceptible subpopulation (e.g. the unborn child) is considered at each tier, and if such a subpopulation is determined, an additional factor is proposed by which the end-user can divide the AETL value to protect the regarding subpopulation. In the case of, for instance, ethylene oxide an additional factor of 3 was proposed to protect the unborn child from developmental effects (see section 3.5).

It is stated in the guidance document (ACUTEX, 2006) that for chemicals showing selective developmental effects at dose levels below maternal toxicity, the foetal NOAEL should be linked to AETL-2 or AETL-3, depending on the type and severity of the effect. The document also relates the evaluation of developmental effects to maternal toxicity, stating that for chemicals requiring maternal toxicity in order to exert adverse developmental effects, the unborn child will also be protected at AETL-2 levels based on subchronic No-Observed-Adverse-Effect Levels (NOAELs).

Fertility is also considered to be an endpoint that might be considered for application of an additional assessment factor at the AETL-2 tier. The Guidance Document stated that it has been shown that some chemicals induced adverse effects towards testicular/spermatogenic tissues following a single exposure. Therefore, subchronic studies in which relevant parameters, such as testes atrophy, are studied may also be used as a point of departure for the determination of AETL-2 values. Ovarian toxicity is considered to be comparatively rare and thus is seldom used as the critical endpoint.

For the evaluation of these endpoints tables are proposed in which relevant developmental reproductive toxic effects are crossed with severity, e.g. with level of thresholds (Table 3.4). The effects on the reproductive system are classified, depending on their (ir)reversibility. Both reversible and irreversible effects on male fertility are related to the AETL-2 level, but should be treated differently in terms of assessment factors.

DIVs
In the Netherlands, effects on offspring and fertility are evaluated in a similar way as in the AEGL framework (i.e. addressed on tier 2, based on the evaluation by Van Raaij et al. (2003). The methodology of how to deal with this issue has been developed in cooperation with the NAC/AEGL Committee. In summary, resorptions and foetal malformations/variants are considered relevant endpoints of developmental toxicity unless evidence is available to indicate otherwise. The relevance of foetal body weight should be evaluated on a case-by-case basis within the total concept of developmental effects and maternal toxicity. Fertility is not considered to be a relevant endpoint in single exposures.

Table 3.4. Reprotoxicity/developmental endpoints: grading of effects (ACUTEX, 2006).

Type of effect	Irreversible damage	Reversible effects
Slight and moderate testicular atrophy	-	+
Severe testicular atrophy	(+)	+
Ovarian toxicity	(+)	+
Decrease in fertility	-	+
Complete infertility	(+)	+
Hormonal effects in adults	-	+
Perinatal hormonal imprinting with sexual organs (related to developmental toxicity or brain regions persistently affected)	+	(+)

EPEGVs
Within the Danish EPEGV proposal, the possibility of the occurrence of teratogenicity and foetotoxicity, as well as reproductive effects is considered when deriving the second tier values but no further guidance is given.

ERPGs
The ERP committee considered effects on reproduction and developmental toxic effects for the ERPG-2 only if they were considered to be caused by a single exposure. No further guidance is given.

VSTAF
In the French methodology, reprotoxic effects are not taken into account when setting thresholds. However, a review paper has been written to discuss the inclusion of reproductive endpoints when deriving French acute thresholds, especially for chemicals classified as reprotoxic 1 or 2 (EU classification under CLP and REACH regulations). The work is still in progress within the French expert group. An update of the French methodology to include the reprotoxic effects when setting acute thresholds was scheduled for 2011.

Conclusion
Effects on the reproductive system clearly depend on the critical time window where chemicals can induce a certain reproductive toxic effect (Van Raaij et al., 2003). Although the number of pregnant women in an exposed population will generally be very small (and the number of pregnancies within the critical time window even smaller), each of the frameworks considers developmental toxicity of sufficient importance to be addressed. Two types of effects can be discerned: effects on the unborn offspring (developmental effects) and effects on fertility.

In summary, the differences between the frameworks are:
- Effects on unborn offspring
  - not addressed (VSTAF, but under discussion);
  - addressed, tier 2, guidance provided (AEGL, DIV);
  - addressed, tier 2, but no guidance provided (ERPG, EPEGV);
  - addressed, tier 2 or 3 (dependent on severity of effects) via proposal of additional factors to be applied by end-users (AETL; if the effects are independent of maternal toxicity).
- Effects on fertility

- not addressed (VSTAF, but under discussion);
- no endpoint for AERVs (AEGL, DIV);
- addressed, tier 2, but no guidance provided (ERPG, EPEGV);
- addressed, tier 2, via proposal of additional factors (dependent on (ir)reversibility of effects) to be applied by end-users (AETL).

Reproductive toxicity (including fertility and developmental toxicity) is of major societal concern, even following single exposures. Moreover, there are sufficient toxicity data available to indicate that adverse health effects in the offspring might occur after a single chemical exposure. Therefore, this endpoint should be seriously considered in the derivation of AERVs. As with carcinogenicity, adequate tools for ascertaining effects on reproduction are not only important for risk assessment purposes but also for risk communication. The possibility of health effects in the unborn child is an immediate cause of public anxiety and adequate risk communication is of the utmost importance. Therefore, first-responders do need appropriate information to communicate reproductive toxicity issues with the public, including the exposed population. Thus the fact that reproductive endpoints are included in the AERV derivation process may be of help in the risk management decision-making process and in the risk communication process to the exposed population.

Large differences exist between the different frameworks regarding how to deal with effects on reproduction. The endpoints of teratogenicity and foetotoxicity (effects on the unborn offspring) are acknowledged as an important issue in all frameworks, with the exception of VSTAF. The remaining frameworks address this endpoint at the tier 2 but when deriving AETLs it is an issue for either tier 2 or 3, depending on the severity of the effects. Since some effects can be considered to represent increased lethality (such as resorptions), it can be argued that they might be addressed at tier 3, which deals with life-threatening effects. However, AETLs themselves are derived for the healthy middle-aged man and effects on the offspring or on reproduction are addressed by additional factors, the application of which is in the hands of end-users. Two frameworks (AEGL and the current DIV approach) are based on a report by Van Raaij et al. (2003), while two frameworks do not provide any guidance.

Regarding fertility, the basic difference is whether this effect should be considered as relevant for single exposures, and thus for derivation of AERVs. The frameworks clearly offer different opinions on this issue, which needs to be further elaborated. Again, the AETL framework is distinguished from the others in that this endpoint is addressed by additional factors to be applied by end-users.

Considering the major differences in proposed and existing approaches on the endpoint of reproductive toxicity and that these effects are of large-scale public concern, it is concluded that further elaboration is needed to develop guidance with broad European consensus for the purpose of risk assessment, risk management and risk communication. First of all, it is essential, especially for this endpoint, that before considering harmonization of methodology, the basic philosophy regarding how to address the different kind of effects included in this endpoint (developmental, fertility) should be brought into line and at which tier these effects need to be addressed should be determined.

Table 3.5. Summary of how reproductive toxicity is addressed in the different methodologies.

Methodologies	AEGL	AETL	DIV	ERPG	EPEGV	VSTAF
Point of departure	Resorptions and foetal mal-formations/variants Foetal body weight case-by-case	Male fertility Unborn child*	Resorptions and foetal malformations/ variants Foetal body weight case-by-case	Effects on reproduction and developmental toxicity	Teratogenicity and foetotoxicity, reproductive effects	Not taken into account
Tier	AEGL-2	AETLs are derived for the healthy middle-aged man. Male fertility is addressed at AETL-2. The unborn child is addressed by additional factors applied at AETL-2 or -3.	AGW (level 2)	ERPG-2	EPEGV-2	Not taken into account
Reference	NAS/COT, 2009 (adoption of Van Raaij et al., 2003)	ACUTEX, 2006	In accordance with current AEGL approach, including recommendations by Van Raaij et al. , 2003	AIHA Guideline Foundation, Administrative Operating Procedures, 2010; ERP Committee, 2006	Nielsen, 1998	Pichard and Tissot, 2003. An update of the methodology to include reprotoxic effects is scheduled for 2011.

Another difficulty with developmental effects that needs further elaboration is that they may not be observed before childhood, i.e. some years after the exposure period (which could be an *in utero* exposition). Further, the proposal within the AETL framework to evaluate developmental endpoints in relation to maternal toxicity needs further discussion.

Finally, the topic of endocrine disruption needs special attention. Although there has been a lot of discussion about this endpoint it has not yet been addressed within any AERV framework. Recent publications suggest that exposure to an endocrine disruptor during a critical window might cause reproductive malformations, even after single exposure (Foster and Harris, 2005; Welsh et al., 2008). None of the current existing methodologies discusses whether this effect is a relevant endpoint for AERV derivation or, if appropriate, provides guidance on how to deal with it in the AERV derivation process. The substances with endocrine disruptor effects are considered of very high concern, in particular for REACH legislation. Until now, few tests have been validated or regulatorily adopted to evaluate these effects. Much work is in progress in the OECD framework. Two assays have been adopted to identify oestrogenic and anti-androgenic properties in rodents (TG 440 and 441). One of the challenges for the single exposure setting is to evaluate the relevance of taking into account endocrine disruption effects within the framework of AERV derivation, their extent and at which tier. The relevance and importance of this endpoint for human health effect assessment following single exposures needs to be evaluated.

3.2.4 Sensitization

Background

The immune system is critical in maintaining health. Immunotoxic responses may occur when the immune system is the target of an insult, e.g. by a chemical substance. This in turn can result in immunosuppression and a subsequent decreased resistance to infectious diseases, as well as some types of cancer, or immune dysregulation, which exacerbates allergy or autoimmunity. Alternatively, toxicity may arise when the immune system responds to an antigenic specificity of a chemical substance as part of a specific immune response (i.e. allergy or autoimmunity). In autoimmune diseases, the healthy tissue is attacked by the immune system as if it were a foreign compound. Both suppression and enhancement of immune function are therefore potentially harmful events, and chemical substances may exert immunotoxic effects of either type.

Sensitization is the process by which a person becomes, over time, increasingly sensitized (allergic) to a substance (sensitizer) through repeated exposure. Sensitization can occur both via inhalation (respiratory sensitization) as well as by dermal contact (skin sensitization). Respiratory hypersensitivity can be caused by immunological or non-immunological mechanisms.

Skin sensitization may be caused by agents that can activate the immune system with the consequence of an allergic response (Van Loveren et al., 2008). Following subsequent exposures of the skin, allergic contact dermatitis or atopic dermatitis may be provoked. Allergies are inappropriate or exaggerated reactions of the immune system to substances that, in the majority of people, cause no symptoms. Once an individual has become sensitised, the allergic response can be elicited by a single exposure and generally at exposure levels far below those at which non-sensitized individuals will respond. Thus, the

possibility that sensitization/elicitation of an allergic response may occur even after a brief exposure should be taken into consideration when setting AERVs.

In Western society serial prevalence studies have shown an increasing trend in the prevalence of childhood asthma and airway hyper-responsiveness (Von Mutius, 1998), contributing to the subpopulation for dermal and respiratory sensitization. Also, in adults the prevalence of allergic diseases, such as asthma and hay fever, has increased more than two-fold in 20 years (Upton et al., 2000). Asthma now affects an estimated 300 million people worldwide (Anandan, 2010). There is general consensus that this increased prevalence of certain allergic diseases is highest in industrialized countries, but there are indications that asthma symptom prevalence now is also increasing in Africa, Latin America and parts of Asia (Pearce et al., 2007). More knowledge is becoming available about the aetiology of allergic diseases, such as the various types of allergic reactions that may be more or less predictive for effects that can be exerted in unexpected exposure situations.

As this hypersensitive subpopulation is becoming larger over time and the health effects can be immediate or severe, varying from impairment to a life-threatening situation, it is a subject that also needs serious consideration in the context of the derivation of AERVs. If a substance is considered to be a respiratory or skin sensitizer in the context of Regulation 1272/2008 EC for classification, labelling and packaging (GHS) the following hazard categories and hazard sentences are applicable: Hazard Category 1 for respiratory and skin sensitizers are labelled with the hazard phrases H334 'May cause allergy or asthma symptoms or breathing difficulties if inhaled' and H317 'May cause an allergic skin reaction', respectively.

Methodology comparison
Sensitization is not specifically addressed in the AEGL, AETL, DIV, ERPG or VSTAF frameworks.

EPEGVs
In the EPEGV proposal it is mentioned that, for substances that are known or suspected to exert allergic effects, the possibility that such effects may occur even after a brief exposure should be considered in the setting of EPEGV values. Sensitising effects on the respiratory tract or skin are considered when estimating numeric values of EPEGV-2, but no further guidance is given.

Conclusion
Once an individual has become sensitized, an allergic response can be elicited by a single exposure and generally at exposure levels far below those at which non-sensitized individuals will respond. The significant increase in the prevalence of allergy and allergic diseases has become a major health issue in recent decades.

Most of the existing methodologies do not address this issue. However, considering the increasing prevalence of allergic diseases and the fact that an allergic response may occur even after a brief exposure, it is recommended to verify the relevance of this endpoint for the derivation of AERVs. Specific guidance is needed on how to address this endpoint and at which tier. In particular, chemicals classified as having a respiratory and/or a skin sensitizing potential should be considered.

3.2.5 Neurotoxicity

Background

Neurotoxicity can be defined as the induction of adverse effects in the central or peripheral nervous system, or in sense organs, by exposure to a chemical substance. Neurotoxicity may be indicated by morphological (structural) changes in the central or peripheral nervous system or, in special sense organs, by neurophysiological changes, e.g. electroencephalographic changes, by behavioural (functional) change, and/or by neurochemical changes, such as in neurotransmitter levels.

The complexity of the nervous system results in multiple potential target sites and adverse sequelae. No other organ system has the wide variety of specialized cell functions seen here. Different expressions of neurotoxicity are generally based on the different susceptibilities of the various subpopulations of cells that make up the nervous system. The status and role of the blood-brain barrier in the central nervous system (CNS), and similar structures in the peripheral nervous system, in modulating the access of some chemicals to the nervous system are also unique considerations in assessing neurotoxicity. In contrast to other tissues, the ability of nerve cells to replace or regenerate is severely constrained and is a limiting factor in achieving full recovery from neurotoxicity under conditions where cell death has occurred.

Signs of neurotoxicity are generally observed following repeated and prolonged exposure and thus are not considered relevant in the context of setting AERVs. Neurotoxicity may, however, also occur following a brief inhalation exposure to a chemical substance. For example, volatile substances may cause clear symptoms of acute CNS depression such as narcosis, drowsiness, reduced alertness, loss of reflexes, lack of coordination and vertigo. These narcotic/anaesthetic effects are assumed to be predominantly concentration dependent rather than time dependent, meaning that once the brain concentration of the toxic compound has reached a steady-state level no further increase in effect severity is expected with continuing exposure duration. This finding is important for time scaling (section 3.4). It has been stated that gases that are relatively insoluble in blood rise quickly toward equilibrium with the inhaled concentration and that the less soluble in blood, the faster the narcotic action of the gas. For instance, human and animal data show that for short-chain hydrocarbons that cause CNS depression, such as propane, butane, hexane and styrene, a rapid steady-state concentration in blood and brain occurs after approximately 30–60 minutes of exposure. Therefore, once this steady-state situation has been reached, AERVs for longer exposure duration may be set at similar concentrations, also called ‘flatlining’ (see the example of styrene in section 3.5).

Other examples include organophosphate pesticides and chemical warfare agents, of which many are potent acute toxic substances, which act by inhibiting the enzyme acetyl cholinesterase, which breaks down the neurotransmitter acetylcholine. Thus, the possibility that (delayed) neurotoxicity may occur even after a brief exposure should be taken into consideration when setting AERVs. Such substances are considered to be neurotoxicants in the context of Regulation 1272/2008 EC for classification, labelling and packaging (GHS). The following hazard category and hazard sentence are applicable: Hazard Category 3 (narcotic effects), hazard phrase H336 ‘May cause drowsiness or dizziness’.

Methodology comparison

AEGLs

Although neurotoxicity has not been addressed specifically in the AEGL standing operating procedure (SOP), it has been identified as a critical endpoint for the setting of AEGL-2 for a number of short-chain hydrocarbons that cause CNS depression, such as propane, butane, hexane and styrene. From practical experience it is known that the AEGL approach is known to flatline the different exposure times after a steady-state concentration has been reached, as indicated by toxicokinetic data (see the example of styrene in section 3.5).

AETLs

The AETL Guidance Document (ACUTEX, 2006) recognizes CNS depression as significant for single exposures. Depending on the severity of effects, they can be addressed by any tier. In general, the effects are considered reversible but irreversible effects may occur when CNS depression is accompanied by prolonged hypoxia and neuronal death. Acetylcholinesterase inhibition and delayed neurotoxicity through inhibition of a neuronal neurotoxic esterase is also described. The Guidance Document provides an overview of effects that are to be addressed at AETL-1, AETL-2 and AETL-3.

DIVs

In the DIV methodology the AEGL approach is applied, or at least conformity is searched for.

EPEGVs

In the EPEGV proposal, neurotoxic effects, including significant central nervous depression, are considered when estimating numeric values of EPEGV-2, but no further guidance is given.

ERPGs

Neurotoxicity has been used as endpoint in the derivation of ERPGs but no guidance is provided.

VSTAF

In the VSTAF approach, neurotoxicity is included in the threshold for irreversible effects (SEI), but no further guidance is given.

Conclusion

Different frameworks address the issue of neurotoxicity in different ways; however, a quantitative method of further approaching the subject is not provided in any of them. As neurotoxicity is an important toxicity endpoint following single exposures to a number of chemicals (e.g. volatile organic solvents, cholinesterase inhibitors, organophosphates) there is a need to develop specific guidance.

Neurotoxicity, particular CNS depression, can occur following a brief inhalation exposure to a chemical substance that has the potential of causing narcotic and/or anaesthetic effects. Neurotoxic effects were mentioned as being one of the most important endpoints in the web-based survey (Heinälä et al., 2013). It is therefore recommended to address this endpoint in the derivation of AERVs in a clear and transparent way, in particular for chemicals classified as having the potential of causing narcotic/anaesthetic effects (see below). The AETL Guidance Document (ACUTEX, 2006) might provide a basis for this. Although the main attention has been fixed on narcotic or anaesthetic effects, guidance is also

needed for acetylcholinesterase inhibitors and delayed neurotoxicity caused by inhibition of a neuronal neurotoxic esterase.

In this context it is of importance to bear in mind that symptoms of acute CNS depression are considered to be predominantly concentration dependent rather than time dependent, and therefore no increase in effect size with exposure duration is expected once a steady-state concentration in blood and brain has been reached. Data available for a number of CNS depressive short-chain hydrocarbons indicate that a steady-state blood concentration is reached in approximately 30–60 minutes. This aspect is not dealt with or is dealt with differently in the relevant frameworks and thus harmonized guidance is needed to adequately address this issue. Such guidance could be based on the available knowledge regarding neurotoxicity and the experience in deriving AERVs within the relevant frameworks (i.e. through study of the individual Technical Support Documents for known neurotoxicants).

3.2.6 Sensory awareness

Background

The Level of Distinct Sensory Awareness (LDSA) can be defined as the airborne concentration at which it is expected that a proportion of the general population could experience sensory stimuli that may lead to public complaints, concerns or requests for information on the incident. Examples of endpoints that meet this definition are odour awareness or annoyance, taste, vision and change of skin colour.
There is no harmonized approach on how to deal with sensory awareness in the context of AERVs, though the Post ACUTEX Workshop (2006) identified some critical factors and areas for further development.

Although not a toxicological endpoint, odour is of practical important in the immediate estimation of potential chemical concentrations. In chemical incidents, an exposed community is likely to interpret the presence of an unusual odour not common in the normal 'odour landscape' as a potential health risk. Recently a guidance document has become available on the derivation of a Level of distinct Odour Awareness (LOA) in a structured manner (Ruijten et al., 2009). For none of the other sensory endpoints mentioned above is a comparable methodology available.

Methodology comparison

AEGLs

Within the AEGL framework odour has been excluded as an endpoint for any AEGL level. The LOA is calculated according to Ruijten et al. (2009) and added as a separate value in the Technical Support Documents. Other types of sensory awareness are not considered.

AETLs

LDSAs are kept distinct from toxicological endpoints. In addition, it was considered important to provide unequivocal guidance on the derivation of threshold levels and systematic application (i.e. not to apply results for one chemical to others).

Furthermore, guidance should indicate where the LDSA lies relative to AETL values (much like for AEGLs) and further work would be needed to examine the possibility of representing the two different threshold levels including ranges. The AETL methodology permits calculation of a LOA, according to Ruijten et al.

(2009), and added as a separate value in the Technical Support Documents. For other endpoints, qualifying for LDSA no specific guidance is provided.

DIVs
At present, odour is considered as an endpoint for the VRW (tier 1). The methodology has been revised and provides guidance for deriving a LOA, based on the guidance by Ruijten et al. (2009). The derived LOA is included in the Technical Support Documents currently under review. No guidance is provided on LDSA qualifying endpoints other than odour.

EPEGVs
EPEGV-1 represents the threshold for recognition of adverse exposure, above which some individuals may perceive an objectionable odour or experience adverse health effects which do not pose a health risk as defined for EPEGV-2. The derivation of an EPEGV-1 value based on odour data has not been described in detail. No guidance is provided on LDSA qualifying endpoints other than odour.

ERPGs
Within the ERPG framework odour is considered and frequently applied as an endpoint for ERPG-1 but no further guidance is provided.

VSTAF
The French method has added a tier to incorporate this aspect as a perception threshold (SP). This threshold is defined as a sensory detection of the substance by an exposed population. The assessment of the sensory awareness is based on human data derived from epidemiological studies of occupational and/or accidental exposures, as well as from controlled experiments on healthy volunteers. The sensory effects observed mainly include visual and/or olfactory detection of the chemical substance. No further specific guidance is provided.

Conclusion
All compared frameworks address the issue of sensory awareness, but all in a different way. In some methodologies sensory awareness can be used as a PoD for tier 1 (ERPG-1, EPEGV-1), whereas in other frameworks the subject is addressed by deriving a separate number as LOA, LDSA or perception threshold (SP). Odour is the predominant sensory effect of concern (AEGL, revised DIV methodology, EPEGV, VSTAF). In some cases the sensory effect is not limited to odour (AETL) and room is left to include, for example, visual stimuli (VSTAF), although no practical guidance is provided to derive values for other endpoints than odour and data that can serve as a basis for such endpoints are scarce or absent. For a harmonized AERV methodology specific guidance on how to derive quantitative LOAs is already available (Ruijten et al., 2009).

No guidance is available on how to address the other sensory stimuli. The Post ACUTEX Workshop has defined several areas that can be of help for further development of this aspect, but in general, a completely new approach to addressing the other sensory stimuli needs to be developed.

3.3 Target population including assessment factors

The population of concern in a chemical incident is not limited to workers at an establishment and the people who are present in the direct vicinity of that specific accident site. The location of the incident (e.g. industrial area,

transportation route or residential area) and the airborne dispersion of the substance both determine the target population. For the purpose of AERV derivation, the eligible (target) population may either be restricted to relatively healthy workers or may be all- encompassing, to include susceptible subpopulations, such as the elderly, children and pregnant women (the unborn might be at extra risk).

Adverse responses to a given chemical do not occur at precisely the same exposure level for all individuals in a population, but can extend over a range of concentrations because of variability in individual susceptibility within a population. This is due to biological factors such as metabolic polymorphism, age and development (physiology, organ sensitivity), gender, health and disease status (diet, stress, lifestyle), and specific constitution and situation (weight, proportion of fat, pregnancy). These differences can be a result of genetic factors (enzyme polymorphisms, hereditary metabolic disorders) and genetic programming of developmental steps in particular in the newborn and in children up to young adulthood. The differences can also be caused by acquired susceptibility factors, as well as by environmental influences, e.g. previous or simultaneous exposure to multiple compounds (industrial chemicals, food additives, pesticides, drugs), all of which may have an impact on the susceptibility of different individuals in a population.

Some subpopulations may therefore be more susceptible to a chemical than the average person, i.e. showing adverse responses at exposure levels below those levels to which most individuals will respond. These subpopulations, often referred to as 'susceptible subgroups', include children and infants, elderly people, pregnant women and the unborn child, and individuals with pre-existing illnesses compatible with participation in normal daily activities. Examples of subpopulations with pre-existing illnesses include those with pulmonary, hepatic, cardiac, renal or immunological dysfunction, who would not ordinarily be considered in a severe or critical condition.

AERVs are derived to serve as a predictive tool to estimate risks of possible adverse health effects in an exposed population in a chemical incident. The exposed population may include people with a wide variability in susceptibility. However, the available toxicological database for a chemical rarely contains the information to address adequately the exposure situation and the exposed human population. For instance, one often has to rely on experimental animal data for the derivation of AERVs. Therefore, to derive appropriate AERVs, assessment factors (AFs, also called uncertainty or extrapolation factors) have to be applied to account for a possible higher susceptibility in humans compared with experimental animals and to account for differences in susceptibility within the exposed human population.

To take into account differences in susceptibility between individuals, intraspecies AFs are applied in risk assessments. When sufficient data are available a chemical-specific factor can be derived from the toxicological database, but generally one has to rely on default AFs (WHO, 2005; Stevenson et al., 1995). Default AFs applied to account for the interspecies differences vary from 1 to 10 and depend on the type of effect, consideration of the most sensitive species, chemical-specific aspects and the robustness of the overall toxicological dataset.

Default factors for intraspecies differences ranging from 1 to 10 are applied in most frameworks. The selected value will depend among others on the

toxicological endpoint (e.g. local versus systemic), chemical-specific aspects and most importantly the target population. In risk assessments for lifetime exposures a factor of 5 (ECETOC, 2003) to 10 is applied for the general population, including susceptible subpopulations such as infants and the elderly. For the working population less diversity is expected and a factor of 3 (ECETOC, 2003) to 5 (REACH framework) is therefore generally considered sufficient.

The philosophy concerning the target population for which AERVs are being derived and the application of interspecies and intraspecies AFs will determine to a large extent the final values of the AERVs. Therefore, the AFs used for intra- and interspecies extrapolation also raise a relevant issue in comparing the methodologies with regard to the subject target population.

In all populations, some individuals will show adverse responses at exposure levels far below those levels where most individuals will respond. These individuals, in most of the existing approaches, are referred to as 'hypersusceptible individuals', and include individuals with severely debilitating pulmonary, hepatic, cardiac, renal or immunological dysfunction. The AFs as described above are not applicable to these 'hypersusceptible individuals'. Although AERVs are designed to predict the threshold exposure for certain toxic effects, the text refers to the population 'protected by' rather than 'covered by' or 'predicted by' an AERV. This therefore refers to the inclusion or exclusion of certain subpopulations from the considerations underlying the AERV.

Table 3.6 at the end of this section summarizes how the reviewed methodologies address this issue of target population and AFs.

Methodology comparison

AEGLs

The AEGL values are designed to protect almost all people in the general population, including susceptible individuals; however, some hypersusceptible individuals might not be protected. In the AEGL SOP it is stated that the definition and intended application of AEGL values make distinctions between susceptible and 'hypersusceptible' individuals, which is important when selecting AFs, as well as for risk communication to emergency planners, emergency responders and the public. According to the SOP, 'hypersusceptibility' describes extreme examples of responses and may represent biological reactions that are unique, idiosyncratic and stem from determinants that are generally discontinuous with, and lie outside of, the range of distributions expected for the general population.

According to the SOP for AEGL derivation information bearing on the toxicokinetics and toxicodynamics of the chemical under consideration, as well as structurally related analogues or chemicals that act by a similar mechanism of action, will be used to deriving an appropriate interspecies AF that may range from 10 to 3 or to 1. In the absence of information on the chemical or on an analogous chemical, to set a data-derived AF, the use of a default AF of 10 is considered to be suitable in most cases. As always, all information on the chemical, its mechanism of action, structurally related chemical analogues and informed professional judgement will be used when determining appropriate AFs and evaluating the resultant AEGL values.

With regard to intraspecies differences, two questions need to be evaluated before establishing the correct AF: 1. distinguish between susceptible and hypersusceptible subpopulations; and 2. estimate the range of variability in a

human population. In general, in the absence of data or information to the contrary, the default value for the intraspecies AF is 10. However, an AF of 3, or even 1, may be used if credible information or data are available. Several guiding criteria to be taken into consideration when deriving (default) AFs for inter- and intraspecies differences are provided in the SOP.

Although an overall factor of 100 (a factor of 10 for both interspecies and intraspecies extrapolation) is theoretically possible according to the AEGL SOP, from experience it is known that such a high factor has been used only in incidental cases.

AETLs
The AETL values are derived for generally healthy middle-aged (male) adults. Hence, they do not take into consideration specific sensitive subpopulations. However, it has been decided to inform risk managers about possible sensitive subgroups. Thus, if information on susceptible subpopulations in relation to the substance of interest is available, these are to be identified. Where possible, the higher susceptibility of each subpopulation in question should be quantified. If quantification is not possible, a description of the subpopulation should be given, thus enabling risk managers to take decisions according to the local situation and the local needs.
In the ACUTEX methodology generally a default factor of 1 or 3 is applied both for interspecies as well as for intraspecies extrapolation. The selection of the default values is primarily based on whether the relevant health effect is a local or systemic type. For local effects a default interspecies factor of 1 and a default intraspecies factor of 3 are recommended. For systemic effects a factor of 3 is recommended for both extrapolation steps.

In addition to the factors above, an additional factor for differences in susceptibility between human subpopulations can be assigned. It is up to the end-user to determine the target population and the subsequent use of this additional AF in a chemical emergency situation. When the available data do not allow derivation of substance-specific additional AFs, default values to be used are described for four different scenarios: systemic effects due to the parent compound, systemic effects due to diminished oxygen supply, irritant/corrosive effects on mucous membranes of the lower respiratory tract and carcinogenic effects (mutagenic mode of action). The recommended values for the additional AFs vary from 2 to 10, depending on the type of effect and the susceptible subpopulation under consideration. (In section 3.5 practical examples are presented for six chemicals.)

DIVs
People with an increased sensitivity due to age, sex or pre-existing disease are taken into account in the derivation of DIV values. However, the effect of exposures to concentrations that are close to the limit value on very sensitive persons, such as terminally ill patients and sensitized persons is difficult to predict. For this reason, the thresholds are not primarily aimed at these types of individuals.

The methodology presently in force does not explicitly define AFs for inter- and intraspecies extrapolation. The revised version of the DIV derivation methodology is analogous with the AEGL approach with regard to this aspect.

EPEGVs
According to the EPEGV proposal, the differences in susceptibility within a population are considered to be essential and data for susceptible subpopulations should be included, if available, in the evaluation when setting a numeric EPEGV value. Susceptible subpopulations include children, elderly people, pregnant women and those with minor acute illness or chronic illness compatible with participation in normal daily activities, who may be more susceptible to a chemical substance than the average person. It is also noted that some individuals ('hypersusceptible individuals') may experience adverse health effects at the EPEGVs set for a given substance.'

'Hypersusceptible individuals' are stated to be seriously debilitated people such as those with pneumonia or myocardial infarction, who will show adverse responses at exposure levels far below those levels where most individuals will not respond.

The EPEGV proposal does not apply AFs to account for inter- and intraspecies differences as the numeric values of the EPEGVs are aimed as being predictive rather than protective (Nielsen, 1998).

ERPGs
The values derived for ERPGs should not be expected to protect everyone but should be applicable to most individuals in the general population because, in all populations, there are 'hypersensitive individuals', who will show adverse responses at exposure concentrations far below levels at which most individuals would normally respond. The use of AFs to account for intra- and interspecies differences are neither specified in the methodology nor transparently described in the ERPG derivation for specific chemicals.

VSTAF
The target population in the VSTAF approach is the general population, excluding 'susceptible and hypersusceptible individuals'. The VSTAF methodology is aimed at the general population in practice but usually does not apply AFs to account for intraspecies or for interspecies differences. However, it is stated that: 'Due to the lack of toxicological data or to the mechanism of action of the chemical substance, the group of experts may decide to use one or more uncertainty factors.' This includes a factor to account for the inter- and intraspecies variability. It is further stated that 'concerning the interspecies variability, the most relevant species (closest to the human in term of reactivity to the chemical substance) is usually retained. In the absence of such information, the most sensitive species will be considered.'

Conclusion
The AEGL, DIV, EPEGV and ERPG values are aimed at protecting the general population, including susceptible subpopulations, but not necessarily "hypersusceptible individuals'. However, these frameworks show methodological differences in accounting for susceptible subpopulations. While AEGL and DIV will be derived by transparently applying AFs, the EPEGV proposal does not apply AFs as the numeric values of the EPEGVs are aimed at being predictive rather than protective. In the VSTAF approach, the target population is the general population, excluding 'susceptible and hypersusceptible individuals'. The AETL values are meant for the general, healthy middle-aged (male) adults and thus do not take into consideration specific sensitive subpopulations. However, whenever possible susceptible subpopulations will be identified and additional factors will be recommended for their protection. In a chemical emergency

situation, it is up to the end-users to decide whether these additional factors need to be applied to the AETLs.

The distinction between susceptible subpopulations and 'hypersusceptible individuals' used in the described approaches to the derivation of numeric AERV values is generally not always clear and may differ from approach to approach. As individual susceptibility to chemical substances within a population exists, it is crucial to address this issue when setting AERVs. The philosophy behind the choice of how to account for the interspecies and intraspecies differences is clearly different, which also makes the derived values difficult to compare.

Considering the different levels of protection of the AERVs derived in the different frameworks (i.e. target population considered), the different AERVs are not interchangeable. The synchronous existence of AERVs that are predictive for different (sub)populations is undesirable. If it is left to the end-user to choose one of the existing AERVs, in the decision-making process of a chemical emergency situation it might lead to erroneous decisions, increasing the health risks of the exposed situations. Therefore, harmonization on the subject of the target population to be protected by the AERVs is highly recommended.

It is therefore recommended to further address the criteria for a differentiation between susceptible subpopulations as well as individuals, in order to, preferably, derive harmonized criteria on this issue and for the use of AFs for inter- and intraspecies extrapolation when setting AERVs.

3.4 Time scaling and dose-response modelling

As described in the introduction, the derivation of AERVs deviates from chronic exposure limits in several important aspects, such as addressing the full toxicity profile (i.e. identifying multiple boundaries between several severity levels ranging from minimal effects up to mortality), the level of protection (safety) and time scaling issues. These topics that are important in human health risk assessment in acute exposure situations play no or a less important role in chronic exposure situations.

1. AERVs are derived for different levels of toxicity, i.e. with an increasing health impact. This is in contrast with human limit values for lifetime exposures (e.g. the ADI), which are focusing on one exposure level, i.e. the level at which no adverse health effects are to be expected.
2. Time scaling. Since exposure following incidental or accidental release of chemicals can vary over time between incidents, AERVs are needed for multiple exposure durations and are derived for exposure durations ranging from 10 minutes up to 8 hours. Since data are often available only for a limited number of exposure durations these data have to be extrapolated to others.
3. Although AERVs are meant to be protective for the effects addressed by the respective tiers, they rather need to be predictive for the following reasons. Risk reduction measures (such as evacuation) in themselves may also introduce risks to the exposed population and should be avoided at exposure levels that do not pose actual health threats. Further, the AERVs at the different tiers need to be in coherence; AERVs for any tier cannot be lower than for a lower tier.

Table 3.6. Summary of selected target populations and the use of assessment factors to account for inter- and intraspecies differences within the respective methodologies.

Subject	**AEGL**	**AETL**	**DIV**	**EPEGV**	**ERPG**	**VSTAF**
Target population	Sensitive, but not hypersensitive (e.g. persons with breathing impairment)	Healthy middle-aged population	Sensitive, but not hypersensitive	Sensitive, but not hypersensitive	Sensitive, but not hypersensitive	Hypersensitive subjects are not considered (e.g. persons with breathing impairment)
Assessment factors:						
- *intraspecies*	1–10	1–3	Not specifically defined, current revision similar to AEGL	Not transparently defined	Not transparently defined	Usually not applied for local-acting substances; 3–10 for systemic ones
- *interspecies*	1–10	1–3*				
Reference	NRC, 2001; NAS/COT, 2009	ACUTEX, 2006	Ruijten and van Doorn, 2006, currently under revision	Nielsen, 1998	AIHA Guideline Foundation, Administrative Operating Procedures, 2010; ERP Committee, 2006	Pichard and Tissot, 2003

*Depending on target group additional intraspecies factors might be applied by the end-users to subpopulation effects. These factors vary from 2 to 10.

A major challenge within the framework of risk assessment in acute exposure situations is to define the different levels of toxicity that are addressed by the different tiers (e.g. AEGL-1, AEGL-2, AEGL-3). The three tiers comprise the dose-response relationship for the full toxicity profile, i.e. from a no-effect concentration to maximum effect size for various effects, including mortality. If the appropriate data are available it is preferred to determine the three tiers in a transparent and harmonized way using the best available tools.

Within some frameworks AERVs are derived only for one exposure duration, of 1 hour (ERPG, EPEGV). The other frameworks derive values for multiple exposure durations. It is noted that in an actual emergency situation the exposure duration might deviate from a 1-hour exposure and thus for an adequate risk assessment of the situation time scaling to the appropriate exposure durations is warranted.

Time scaling is based on Haber's Law, which states that the incidence and/or severity of an adverse effect is linearly related to the total exposure to a potentially toxic chemical, *i.e.*, $C \times t = k$ (where C is concentration, t *is* exposure duration and k represents a predefined toxic effect) (Haber, 1924). Miller et al*.* (2000) acknowledged the complexity of time as a contributor to toxicity and contended that Haber's Law is merely a special member of a family of power functions described by $C^{\alpha} \times t^{\beta} = k_1$ (viz. when $\alpha=\beta=1$) and that using this general power law will be more effective to study the relative contributions of the different time scales and dose. The general power law can be rewritten as $C^n \times t = k_2$ (with $n=\alpha/\beta$), which is the form used in emergency response planning and land-use planning frameworks. The exponent n is to be estimated from animal data if sufficient adequate data are available. If available these data are often limited to mortality data for multiple exposure durations (i.e. at the level of the tier 3). It is then assumed that this estimate for n is also applicable for the lower tiers. If no adequate data are available, default values for n are proposed. The default values used within the AEGL and AETL frameworks are similar: $n = 1$ for extrapolation from shorter to longer exposure durations and $n = 3$ for extrapolation from longer to shorter durations. It is noted that dose-response modelling and time scaling are also applied in the derivation of human limit values for lifetime exposures if only data on less than lifetime exposures are available. However, in those situations time scaling is applied on only one exposure level, i.e. the concentration or dose at which no health effects are to be expected. In these situations, scaling is in one dimension. Within the context of AERV derivation scaling is in two dimensions because the full toxicity profile (i.e. the entire dose-response curve) of a chemical needs to be scaled to additional exposure durations.

In recent years, modelling tools for improvement of the risk assessment process have been proposed. Many are under continuous development. The next section briefly explores the state of the art of existing modelling tools for their applicability within the present context, to identify still unresolved issues and gaps in knowledge and to propose a path forward towards their resolution. The subsequent section will address issues related to accounting for susceptible subpopulations.

3.4.1 PBPK-modelling

Physiologically-Based Pharmacokinetic (PBPK-) models are a description of the body, and processes within the body that affect the disposition of a chemical. Disposition, or pharmacokinetics, includes the processes of absorption,

distribution, metabolism and excretion of chemicals. PBPK-modelling provides a computational biology basis for certain extrapolations that need to be made in the course of the risk assessment. It translates, in a biologically adequate fashion, external doses of a chemical (e.g. concentration in the air) into a dose or concentration in a target tissue. PBPK-modelling provides estimates of concentration-time profiles, thereby reducing the sources of uncertainty (Barton et al., 2007; Loizou et al., 2008). Especially within the framework of AERV derivation PBPK-modelling can play an important role in both the interspecies extrapolation as well as in time scaling. It can also be used to estimate which combination of exposure duration and air concentration leads to internal concentrations in blood or target organs in humans that can be allocated to specific predefined health effects. In this way, PBPK-modelling is a powerful tool for non-linear time-scaling purposes. In some examples, PBPK-models have been extended to also include the pharmacodynamics of a chemical (e.g. the carboxyhaemoglobin formation from methylene chloride exposure using PBPK/PD-models) (Bos et al., 2006).

Within the AEGL-programme, a white paper has been written on the use of PBPK-models in the derivation of AEGLs has been written. AEGLs for several chemicals, such as toluene, methylene chloride and trichloroethylene, have been derived by PBPK-modelling; some of these models have been published in the open literature (Bruckner et al., 2004; Boyes et al., 2005; Bos et al., 2006). Also, within the ACUTEX research project the possibilities of the use of PBPK-modelling in deriving AERVs have been studied (Mielke et al., 2005; ACUTEX, 2006).

In addition, tissue dose metrics for certain chemicals can be significantly affected by increased ventilation, and altered blood flows can affect the distribution of the chemical. The basics of PBPK-models that have been used for workload physiology extrapolation can be used to model the effect of an increased inhalation of chemicals due to stress following attempts to escape from the incident location. Within the ACUTEX project, PBPK-modelling has been used to determine the part of the inter-individual differences in humans that is determined by differences in kinetics (Mielke et al., 2005).

In general, PBPK-models are developed for a specific chemical and are data demanding, which hampers the general application of this tool. However, there is ongoing research on possibilities of developing PBPK-based models that should have a more generic approach (Bois et al., 2010; Bosgra et al., 2012). The search for alternative testing strategies, among others within the context of REACH, that also focuses on *in silico* tools might provide interesting tools for the purpose of AERV derivation. It is recommended to closely follow these developments for their applicability within the present context.

3.4.2 Dose-response modelling

Dose-response modelling (DR-modelling) provides quantitative information on the relationship between a particular exposure and the estimated effect size at that exposure.

Within the AEGL-programme DR-modelling is only used at tier 3 if individual mortality data in animals are available. Acute toxicity studies in animals are mainly performed to determine the LC_{50} (i.e. the exposure concentration that is expected to cause lethality in 50 per cent of the exposed species), which is used for classification purposes. However, within the present context it is important to

determine the level at which no or a minimal effect size is expected. DR-modelling then is an important tool for deriving the dose for a pre-specified effect size for a predefined endpoint, e.g. mortality.

Within the AEGL programme the freely available Benchmark dose-modelling software (BMDS) of the US EPA is used to determine either an LC_{01} (lethal concentration; 1 per cent mortality) through probit analyses or a BMC_{05} (benchmark concentration with 95 per cent lower confidence limit; 5 per cent mortality). These values are used as a point of departure to derive an AEGL-3 through the application of AFs. Within the ACUTEX research project, other modelling tools have been developed (Diack and Bois, 2005) but this tool is still to be judged on its merits for the purpose of AERV derivation. It has nevertheless been used for the ACUTEX case studies (see also section 3.5).

DR-models have proven their value in estimating a benchmark dose representing a better estimate of a no-adverse-effect level for toxic chemicals than the traditional NOAEL. A NOAEL is the highest dose at which the observed effect size does not significantly differ from that in the control group, as is generally judged on statistical analyses. A benchmark dose derived by DR-modelling has the advantage that it is, unlike a NOAEL, not determined by the choice of dose-spacing and the number of animals per dose group, associated with a predetermined change or response in a toxicological parameter. DR-modelling thereby reduces the uncertainty in the estimation of an appropriate point of departure. Several DR-models, such as the BMDS software that is used within the AEGL-programme, address quantal data, i.e. the percentage of animals that shows a predetermined response (i.e. the percentage of animals that died). Therefore, up until now the application of DR-modelling within the derivation of AERVs has been limited to mortality data, thus at the level of tier 3. In principle, however, DR-models also have the possibility to be applied to other endpoints and data, including continuous data (Slob, 2002). Within the context of AERV derivation, where the focus is on three different levels of toxicity, it should be possible to apply DR-modelling at all three tiers. The challenge then is to adequately define the effect levels that are addressed by the individual tiers. While it is relatively easy to define a no-mortality threshold for tier 3, it will require more discussion to define the effect size related to levels of toxicity in tiers 1 and 2 and to reach consensus at an international level, especially for continuous data.

Slob and Pieters (1998) have introduced the term Critical Effect Size (CES) for dose-response modelling of continuous endpoints. The CES is expressed as a percentage change in the group mean as compared to the control group mean and reflects the quantitative change in a particular endpoint considered as non-adverse at the level of an individual. The dose associated with a particular CES is called the Critical Effect Dose (CED).

For the reasons mentioned DR-modelling is also suitable for estimations of concentrations associated with a predetermined severity of effect, as is needed to address the three tiers of an emergency response planning methodology. This means that not only should a CES be defined but also clear judgements in terms of the health impact of effect sizes addressed at tiers 2 and 3 are unavoidable. The challenge is to determine effect sizes for relevant toxicity endpoints that are addressed by the three different tiers. Although it was considered to be difficult to define even a CES (Dekkers et al*.,* 2001), let alone effect sizes at different levels of severity, the attempt to derive values for CES from the within-animal variation for some continuous parameters showed promising results (Dekkers et

al., 2006). The ACUTEX final report and the AEGL-SOP provide some guidance on the effect sizes or severity of effects that are to be addressed by the three tiers in emergency response planning. The information in these documents can serve as a basis for developing a clear, harmonized set of toxicity levels for a number of endpoints for the different tiers, after which time a DR-modelling tool can be developed that is suitable for deriving adequate 'thresholds' for the different levels of health effects, as addressed by the three tiers, including mortality.

A specific DR-modelling tool that is already generally applied, for both emergency response planning and land-use planning purposes, is probit analyses. Modelling of the proportional lethality in an exposed population can be assessed for each combination of exposure concentration and duration. The concentration-time-lethality relationship can be described with a number of statistical models, including (log) probit, (log) logit and Weibull models. All models mentioned make assumptions about the underlying statistical distribution of the concentration-time-response ($C \times t$) data, and usually describe the $C \times t$ relationship of acute lethality data equally well in the actual experimental exposure range (interpolation and limited extrapolation). The (log) probit model has been selected as the most simple and straightforward model to describe the human vulnerability distribution, for use in modelling acute lethality for external safety.

The probit model for concentration-time-lethality data is described as:

$$Pr = a + b_1 \times \ln C + b_2 \times \ln t$$

Where C is concentration and t is exposure duration.

A frequently used alternative presentation is:

$$Pr = a + b \times \ln(C^n \times t)$$

Where $b = b_2$ and $n = b_1/b_2$. The dose metric ($C^n \times t$) is also referred to as 'toxic load'.

If sufficient data of adequate quality are available containing information on the concentration-response for more than one exposure period, the parameters a, b and n can be calculated with available software such as DoseResp[4], which recently has been incorporated within BMDS of the US EPA[5].

DoseResp is presently used in the Netherlands in QRAs (Quantitative Risk Assessments) for land-use planning purposes. In cases of sufficient data LC_{01} or $BMCL_{05}$ values have been calculated with either DoseResp or the BMDS software to serve as the basis for AEGL-3 values and for DIV tier 3 (the LBW).

Within the ACUTEX project Bayesian dose-response software has been developed that can be run from the Institut National de l'Environnement Industriel et des Risques (INERIS) website[6]. However, the assumptions underlying this model cannot be clearly verified and parameter estimates produced by this model may differ from those of the above two models, particularly in data-poor circumstances.

[4] home.planet.nl/~wtberge/**doseresp**.html. A special version for probit calculations available on the RIVM website.

[5] www.epa.gov/ncea/**bmds**

[6] http://toxi.ineris.fr/programmes/acutex/tools/tools.php

The value of *n* is of importance for the estimation of the response for exposure durations other than those for which data are available. Often one has to rely on a default value for *n* (estimated to be between 1 and 3 for mortality (Ten Berge, 1986)). In some situations *n* can be derived from the available animal mortality data and this value is then also applied for time-scaling at the lower tiers. In principle, it should be possible to also perform probit analyses on non-lethal endpoints. However, lethality (expressed as percentage mortality) is a clear and well-defined response. It will be much more difficult to define clear effect sizes that can be used for the estimation of the appropriate parameters of a probit function. Especially with continuous data, where both the response and the severity of the effects increase with increasing exposure concentration and/or time, it will be a difficult task to perform such probit analyses. Nevertheless, some initiatives have been presented and are worth being further explored. An example of such an initiative is the development of Predictive Toxicity Measures (PTMs) for selected injury severity categories (Noblis, 2009).

Conclusions and recommendations

Specific issues need to be addressed within the process of derivation of AERVs, some of which are unique for this framework. Two main issues are that boundaries need to be determined between several severities of effect levels, ranging from minimal effects up to mortality and time-scaling issues.

Further, within the framework of AERV derivation scaling is in two dimensions since the full toxicity profile (e.g. the dose-response curve) of a chemical needs to be scaled to additional exposure durations, for which specific tools are required that are unique for the present framework. It is noted that the recently revised OECD TG 403 for acute inhalation toxicity testing includes the $C \times t$ test protocol that meets the demands required for AERV derivation (see section 4.5).

In addition, although these boundaries are meant to be protective for specific health effects addressed by the relevant tiers, they primarily need to have a predictive character. Because the available database is seldom adequate to address these topics, AERVs are generally derived by default approaches. This will be accompanied with several uncertainties that generally are accounted for by application of additional AFs. Use of defaults will often result in too conservative AERVs, leading to overestimation of the risks in emergency situations. Since some risk-reducing measures, such as evacuation, in themselves introduce risks to the population, overly conservative values are highly undesirable. Adequate PBPK-modelling tools and dose-response modelling tools, specifically developed for application in acute exposure situations, are needed to adequately address these issues.

Specific tools have been developed and applied both within the AEGL framework as well as within the ACUTEX project. These tools, though, differ in some aspects and need to be compared and evaluated (see also section 3.5). In addition, modelling tools have further been under development and papers have been published showing promising applications in single exposure situations. It is recommended to start from the AEGL White Paper on PBPK-modelling and the developments in the ACUTEX project (both dose-response and PBPK-modelling) and to compare the pros and cons and possibilities of the respective models. Further, recent publications on these modelling tools addressing issues that are of interest for AERV derivation (e.g. interindividual variability, interspecies extrapolation, time scaling, DR-modelling (of continuous data)) need to be screened for possible application in single exposure situations. It is recommended to investigate how the (combination of the) basic tools as

developed for the AEGL-programme or within the ACUTEX project can best be extended with more recent developments. Practical guidance needs to be developed as to how these tools can optimally be used to diminish the uncertainties involved in the risk assessment and to provide AERVs that are predictive for the boundaries between the different tiers. This should also include an inventory about gaps in knowledge that are still open and about which uncertainties remain. Tools with a probabilistic character can also be of help to quantify the remaining uncertainties, which is of importance in the decision-making process for risk reduction measures based on the AERVs.

3.5 Numerical comparison of methodologies to derive AERVs

The previous sections describe differences in the basic philosophies, methodologies and procedures of the different AERV frameworks; clear differences have been identified. The question then is how these differences will work out in practice, i.e. do they lead to significantly diverging values and, if yes, how will this affect the risk management actions to be taken after an incidental release of a chemical. The present section aims to provide answers to these questions by comparing AERVs derived within the respective frameworks for six chemicals (hydrogen sulphide, ethylene oxide, styrene, nitrogen dioxide, nickel tetracarbonyl and chlorine).

The frameworks being compared are AEGL, AETL, DIV, EPEGV, ERPG and VSTAF. Basic philosophical and methodological differences have been described in the introduction (section 3.1) and in section 3.2 (see Tables 3.1 and 3.2). In the tables below only those frameworks are presented that have values derived for the relevant chemical. DIVs, EPEGVs and ERPGs have only been derived for 1-hour exposure, although it is noted that the methodology for the derivation of DIVs is presently under revision and values for the same exposure durations as for AETLs will become available.

In contrast to the other frameworks, which are meant to be protective of the susceptible population, the target population for AETL derivation is the healthy middle-aged man. It is proposed that the AETL value may be divided by additional uncertainty factors by the end-user to protect susceptible subpopulations, if indeed such a population has been identified. For comparison, both the AETL value as well as the corresponding value for a susceptible subpopulation, are provided. The latter is derived after application of the largest possible additional uncertainty factor (called AETL+). For values derived within the VSTAF framework, SPELs are presented at tier 3. SPELs are associated with 1 per cent mortality in the animal, which differs from the other frameworks, where the tier 3 values are meant to protect (susceptible) humans from mortality or health-threatening effects. Within the ERPG framework a specific PoD is often not given, neither are details provided on time scaling (in case of PoD with an exposure duration different from 1 hour) or on extrapolation to (susceptible) humans.

The selection of chemicals used to compare the different frameworks in this report was to some extent hampered by the fact that only a limited number of chemicals have been evaluated in certain frameworks. Within the ACUTEX project AETL were derived for 21 chemicals (Trainor et al., 2006) and EPEGV for only 11 substances (Nielsen, 1998). These limited numbers of chemicals are due to the fact that these frameworks are under development and are not yet active. For the same reason it is stressed that the EPEGVs and AETLs presented in this

section have no formal status and should not be regarded as official values to be used for emergency response planning purposes.

When a chemical incident occurs, AERVs can be used to calculate contours around the incident location to identify the area within which the respective AERV is expected to be exceeded. This is of utmost importance in the decision-making process of risk management but also for risk communication. These contours determine the area within which specific actions need to be taken to protect the population from possible health risks or to communicate any possible health consequences to the exposed population. Contours have been calculated for a fictitious incident scenario for four of the chemicals (i.e. hydrogen sulphide, ethylene oxide, nitrogen oxide and chlorine). These calculations will illustrate the impact of the use of different AERV values on the dimensions of the area where people are expected to have an increased risk to health, and the number of people potentially exposed.

A fictitious incident scenario has been created to calculate the contours for all four chemicals using the 1-hour AERV-2 values of the respective frameworks. One-hour AERV-2 values are used because the tier 2 values are the most important ones in practice and some frameworks only have 1-hour values. The scenario consists of an accidental release of a chemical at the central railway station in a town in the centre of the Netherlands (Amersfoort). The scenario considered is an instantaneous release of 50 tonnes of a chemical present as 'saturated liquid' in a rail tank, resulting in a liquid pool of approximately 300 m^2. Wind direction is approximately northwest and measures 3 m/sec.

The example chemicals have been selected just for illustrative purposes and are by no means meant to be representative. For the same reason differences are presented without expressing value judgements. The AERVs for each chemical are presented in tables below with brief statements outlining the main observations and possible explanations for any differences observed. Furthermore, the impact of the AERV during a chemical incident is illustrated for each chemical.

Hydrogen sulphide

Comments on AERV-3 (Table 3.7)

- Despite a different PoD and a different *n*-value (for time scaling according to $C^n \times t$; AETL: n=8.29, AEGL: n=4.4; both based on lethality data but calculated with different modelling tools). AETL and AEGL values are comparable but the application of the additional uncertainty factor to protect susceptible populations results in much lower values within the AETL-framework.
- The SPEL values are approximately 3- to 10-fold higher than corresponding values within the other frameworks because no uncertainty factors are used and the values are predictive for 1 per cent mortality in the mouse. The AETL values for the susceptible population are up to 50-fold lower than the SPEL values.

Table 3.7. AERV-3 values for hydrogen sulphide (ppm).

	AETL		AEGL-3	ERPG-3	LBW	SPEL
	AETL-3b	AETL-3b+[a]				
10 min	60	12	76			688
30 min	53	11	59			472
60 min	50	10	50	100	140	372
120 min	45	9				-
240 min	41	8	37			-
480 min	38	8	31			-

[a] An additional uncertainty factor of 3 is recommended for ethanol consumption, newborns and infants, and in case of critical oxygen supply. A factor of 5 is recommended for respiratory insufficiency. The values presented are calculated with an additional uncertainty factor of 5.

Comments on AERV-2 (Table 3.8)

- The same PoDs are used for the derivation of AETLs and AEGLs but different values of the exponent *n* for time scaling are applied. Within both frameworks, similar interspecies and intraspecies factors are applied, leading to comparable values, but application of the additional uncertainty factor to protect susceptible subpopulations provides much lower values within the AETL-framework.
- The SEI values are approximately 3- to 5-fold higher than for the other frameworks because no uncertainty factors are used. The AETL values for the susceptible population are up to 50-fold lower than the SEI values.

Table 3.8. AERV-2 values for hydrogen sulphide (ppm).

	AETL		AEGL-2	ERPG-2	AGW	SEI
	AETL-2	AETL-2+[a]				
10 min	29	6	41			150
30 min	25	5	32			100
60 min	22	4	27	30	36	80
120 min	21	4				--
240 min	19	4	20			--
480 min	18	4	17			--

[a] An additional uncertainty factor of 3 is recommended for ethanol consumption, newborns and infants, and in case of critical oxygen supply. A factor of 5 is recommended for respiratory insufficiency. The values presented are calculated with an additional factor of 5.

Comments on AERV-1 (Table 3.9)

- No SER values were derived because of lack of adequate data.
- The AETL values are approximately 20-fold higher than the corresponding AEGL values and the 60-min value is two orders of magnitude higher than the ERPG-1 and VRW, which are, in contrast to AETL-1, based on odour. (Odour is not an endpoint for AETL-1).
- Reasons for the differences between AEGL and AETL values are differences in PoD (AETL: 3-hour exposure data in the rat with an interspecies factor of 1; AEGL: 30-min exposure data in (asthmatic) humans), endpoint (odour was considered for AEGL-1 next to headache, increased airway resistance; AETL: alteration of respiratory and olfactory mucosa), different *n*-values (see ARV-3 comparison).

Table 3.9. AERV-1 values for hydrogen sulphide (ppm).

	AETL		**AEGL-1**	**ERPG-1**	**VRW**	**SER**
	AETL-1	**AETL-1+[a]**				
10 min	14.1	--	0.75			NR[b]
30 min	12.4	--	0.60			NR
60 min	11.4	--	0.51	0.1	0.04	NR
120 min	10.5	--				NR
240 min	9.7	--	0.36			NR
480 min	8.9	--	0.33			NR

[a] No susceptible subpopulation could be identified.

[b] NR – Not recommended due to insufficient data.

Additional comments

One of the last steps in the process of AERV-derivation is the comparison of the three tiers to observe whether they are in coherence. For obvious practical reasons AERV values for a specific tier cannot be set at lower concentrations than the corresponding values of a lower tier. When this occurs in the process of the AERV-derivation no values will be recommended for the lower tier. It is remarked that the coherence step within the AETL framework is at the level of the AETLs before application of additional uncertainty factors. For hydrogen sulphide, susceptible subpopulations have been defined for tiers 2 and 3, but not for tier 1. Comparison of the AETL values for the three tiers show that after application of the additional uncertainty factor for protection of susceptible subpopulations, the values for both tiers 2 and 3 are all lower than the corresponding AETL-1 values.

Figure 3.2 clearly shows the differences between the contours of the fictitious chemical incident scenario, as calculated for the respective 1-hour AERV-2 values for hydrogen sulphide. The lower the respective value, the larger the area where this value is expected to be exceeded.

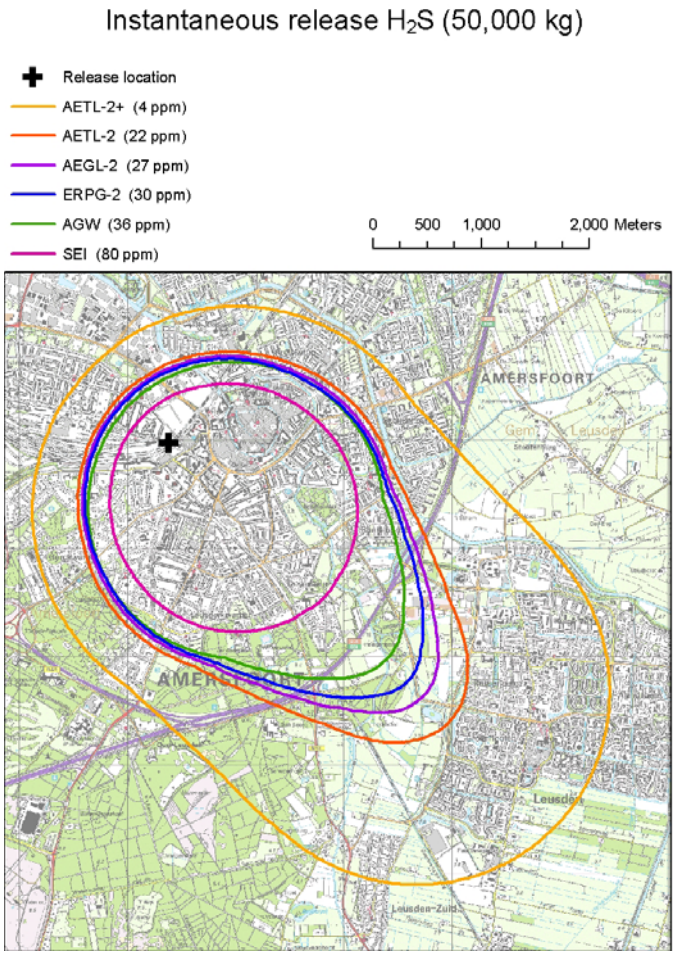

Figure 3.2. Contours of areas where the respective AERVs are calculated to be exceeded, following a fictitious incidental release of hydrogen sulphide.

The distance downwind from the incident location where people might be at increased risk is approximately 2 km for the SEI contour but approximately 5 km for the AETL-2+ contour. The latter contour stretches out over a large area, crosses a highway over a length of approximately 4 km and extends over a large part of the residential area of a neighbouring community to the southeast of Amersfoort, thereby crossing an administrative border. Starting from the AETL-2+ contour, other local authorities have to be informed and inter-community cooperation in risk management and communication is needed to protect people suffering from respiratory insufficiency (being one of the defined subpopulations for AETL-2+) within this area. The contours for AEGL-2, AGW and ERPG-2, whose values intend to be protective of susceptible subpopulations such as those defined for AETL-2+, are much smaller than the AETL-2+ contour and also somewhat smaller than the AETL-2 contour aimed to protect healthy middle-aged males.

Ethylene oxide

Comments on AERV-3 (Table 3.10)

- Although the AEGLs and AETLs are comparable for the shorter exposure durations, an up to 6-fold difference is present for the 8-hour exposure period. The same PoD is used in both frameworks (4-hour study in rats) but no interspecies uncertainty factor is used for AETL derivation (a factor of 3 is used for AEGL derivation) and a different *n*-value is used for time scaling

(AEGL: n = 1.2; AETL: not specified, but estimated from the AETL values to be approximately 5.4).
- The AETL values for the susceptible population are lower than the AEGL values for the shorter exposure durations but up to 2-fold higher for the longer exposure durations, due to the different n-values used.
- The SPEL values are approximately 3- to 30-fold higher than for the other frameworks because no uncertainty factors are used and the values are predictive for 1 per cent mortality in the rat.
- The 1-hour ERPG-3 and the LBW value (the latter is based on the same PoD as the other frameworks) are approximately 2- to 5-fold higher than the corresponding 1-hour AETL and AEGL values, respectively.
-

Table 3.10. AERV-3 values for ethylene oxide (ppm).

	AETL		AEGL-3	ERPG-3	LBW	SPEL
	AETL-3b	AETL-3b+[a]				
10 min	386	129	360			12,550
30 min	347	116	360			5465
60 min	326	109	200	500	550	3233
120 min	263	88				1913
240 min	237	79	63			1132
480 min	213	71	35			670

[a] An additional factors of 3 is recommended for children and patients with respiratory deficiency.

Comments on AERV-2 (Table 3.11)
- The AEGL-2, ERPG-2 and AGW values are based on developmental toxicity data. Since these effects are not an endpoint for AETL-2 and SEI these values have been derived by dividing the tier 3 values by a factor of 3. For derivation of the SEI an additional intraspecies uncertainty factor of 3 is applied. AETL-2 values for the unborn child and the SEI values are derived from the AETL-3 (or AETL-3+) and SPEL, respectively, and thus (indirectly) based on mortality data (although developmental toxicity data are available).
- The AEGLs and AETLs for the shorter exposure durations are of the same order of magnitude but a 10-fold difference is present for an 8-hour exposure, due to the use of different n-values (see AERV-3 comparison).
- The SEI for an 8-hour exposure is comparable to the 8-hour AETL value but approximately 10-fold higher for a 10-min exposure.

Area contours for ethylene oxide (Figure 3.3)
Although the areas within the contours for ethylene oxide are much smaller than those calculated for hydrogen sulphide, clear differences between the respective AERVs can still be observed. The distance downwind from the incident location, where people might be at increased risk is more than 1.5 km larger for AETL-2+ than when calculated with the SEI, and includes a large residential area. The AETL-2+ value is expected to be exceeded at twice the distance downwind than for the AETL-2 value. The difference between the last two contours is the area for which the end-user has to decide whether the AETL-2+ needs to be applied

Table 3.11. AERV-2 values for ethylene oxide (ppm).

	AETL		AEGL-2	ERPG-2	AGW	SEI
	AETL-2	AETL-2+[a]				
10 min	129	43	80			1394
30 min	116	39	80			607
60 min	109	36	45	50	55	359
120 min	88	29				213
240 min	79	26	14			126
480 min	71	24	7.9			74

[a] AETL-2 values are derived by AETL-3. An additional factor of 3 is recommended for the unborn child.

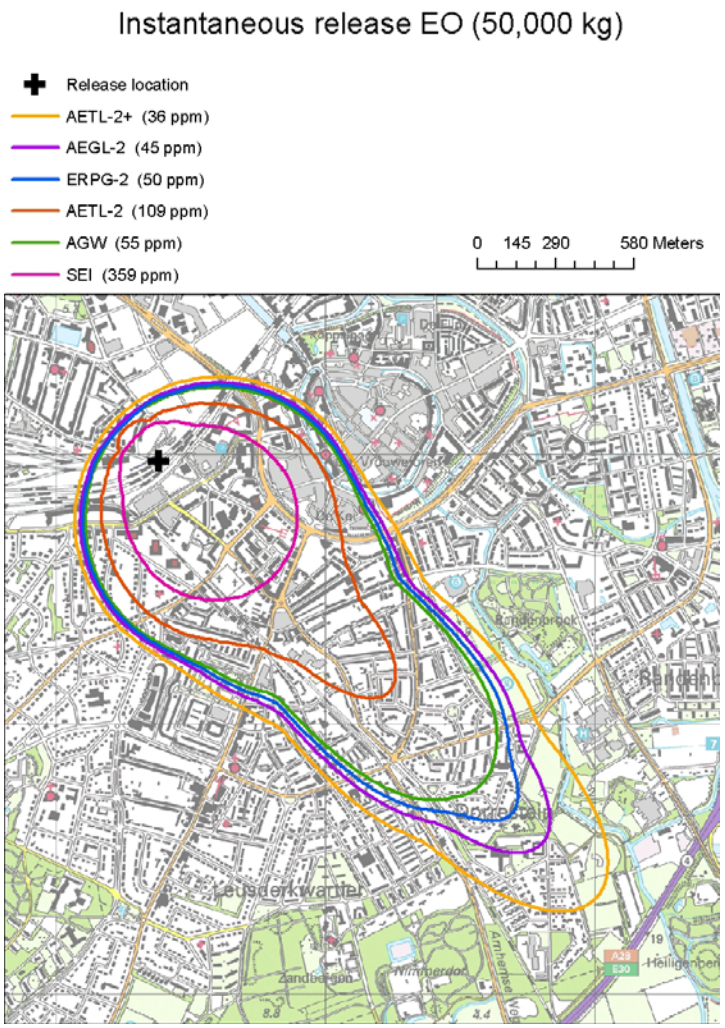

Figure 3.3. Contours of areas where the respective AERVs are calculated to be exceeded, following a fictitious incidental release of ethylene oxide.

to protect the unborn child here. The AETL-2+ contour is somewhat larger than the AEGL-2 contour, which, in contrast to the AETL-2+, is based on actual teratogenicity data.

Styrene

Comments on AERV-3 (Table 3.12, Figure 3.4)

- The AEGLs and AETLs are based on the same PoD (4-hour exposure in rats) but different calculations with different modelling tools are applied (AETL: LC_{01} calculation and time scaling with default *n*-values (1 and 3); AEGL: $BMDL_{05}$ calculation and n = 1.2).
- The AEGL-3 values for 4- and 8-hour exposures are similar for kinetic reasons (mortality is dependent on the styrene concentration in tissues, which does not significantly increase after 4 hours of exposure).
- There is no consistent difference between the AETLs and AEGLs. Predominantly the 30- and 60-min AEGL and AETL values differ by approximately a factor of 2.
- The AETLs for the susceptible subpopulation are up to approximately 8-fold lower than the corresponding AEGLs.
- The SPEL has been based on 8-hour exposure data in the mouse and the ERPG-3 value. The SPEL values for the 10- and 30-minute exposures are higher than the AETLs and AEGLs but more comparable to the corresponding AETLs and AEGLs for exposure durations of longer than 60 minutes.

Table 3.12. AERV-3 values for styrene (ppm) (see also Figure 3.4).

	AETL		**AEGL-3**	**ERPG-3**	**LBW**	**SPEL**
	AETL-3b	**AETL-3b+[a]**				
10 min	1200	240	1900	--	--	5000[b]
30 min	800	160	1900	--	--	2500
60 min	650	130	1100	1000	1200	1000
120 min	500	100	--	--	--	500
240 min	400	80	340	--	--	250
480 min	200	40	340	--	--	250

[a] An additional uncertainty factor of 3 is recommended for newborns and infants; an additional factor of 5 is recommended for people with an impaired respiratory function. The values are calculated with an additional factor of 5.

[b] Value for 15-min exposure.

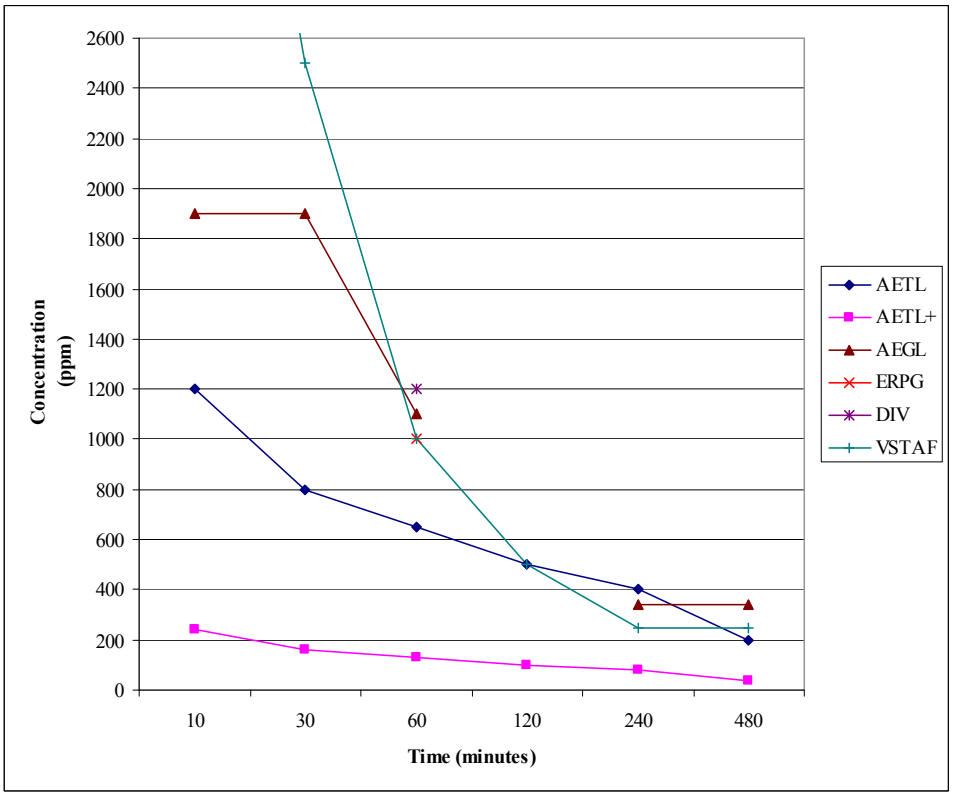

Figure 3.4. AERV-3 values for styrene.

Comments on AERV-2 (Table 3.13, Figure 3.5)

- The AEGL-2 values for 1-, 4- and 8-hour exposures are similar for kinetic reasons (toxicity is dependent on the styrene concentration in tissues, which does not increase significantly after 1 hour of exposure). This results in an almost 10-fold difference from the AETL value for an 8-hour exposure, but an approximately 25-fold difference from an 8-hour AETL value adjusted for infants.

Table 3.13. AERV-2 values for styrene (ppm) (see also Figure 3.5).

	AETL		AEGL-2	ERPG-2	AGW	SEI
	AETL-2	AETL-2+[a]				
10 min	230	77	230			800[b]
30 min	160	53	160			500
60 min	130	43	130	250	230	250
120 min	60	20				200
240 min	30	10	130			100
480 min	16	5.3	130			100

[a] An additional factors of 3 is recommended for newborns and infants.

[b] Value for 15-min exposure.

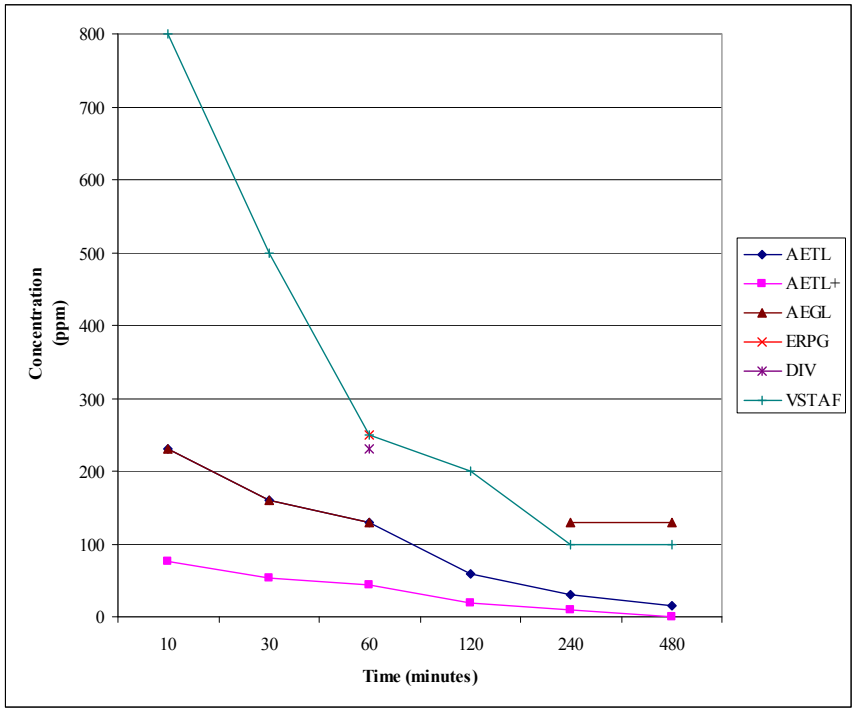

Figure 3.5. AERV-2 values for styrene.

- The SEI values are based on multiple data, including a 30-minute IDLH (700 ppm) and the ERPG (and including the same study as for the AETLs and AEGLs). No further detail on time extrapolation is provided. The SEI values for the 10- and 30-minute exposure durations are more than 3-fold higher than the corresponding AEGL and AETL values.
- The ERPG, AGW and 1-hour SEI are comparable and 2-fold higher than the 1-hour AETL and AEGL.
- It is noted that the AETL-2 values for a susceptible subpopulation (children, infants) for exposure durations of 30 minutes and longer are lower than the corresponding AETL-1 values (see Table 3.14).

Comments on AERV-1 (Table 3.14)

- Different human studies form the basis of AETLs and AEGLs (much lower concentrations as PoD for AEGL derivation); for the AETLs, an intraspecies uncertainty factor of 3 is applied; for AEGLs this uncertainty factor equals 1. This leads to AEGLs that are approximately 3-fold lower than the AETLs.
- Because of the type of effect (concentration-related irritation), it is not expected within the AEGL and AETL framework that an increase in effect severity will occur with prolonging exposure duration.
- The SEI values are based on multiple data, including (indirectly) a 30-minute IDLH (700 ppm) and the ERPG (including the same study as for the AETLs). No further detail on time extrapolation is provided.
- The VRW is based on odour; the ERPG-1 is based on objectionable odour and irritation.

Table 3.14. AERV-1 values for styrene (ppm).

	AETL		AEGL-1	ERPG-1	VRW	SER
	AETL-1	AETL-1+[a]				
10 min	72		20			200[b]
30 min	72		20			100
60 min	72		20	50	2.3	50
120 min	-[c]					50
240 min	-[c]		20			20
480 min	-[c]		20			20

[a] No susceptible subpopulation could be identified.

[b] Value for 15-min exposure.

[c] No value is recommended because the AETL-1 of 72 ppm would be higher than the corresponding AETL-2.

Nitrogen dioxide

Comments on AERV-3 (Table 3.15)

- The differences in AERVs between the respective frameworks are overall relatively small for nitrogen oxide, although different PoDs are used (e.g. AETL: rat study; AEGL: monkey study) and different probit analyses tools are used.
- AETLs for the susceptible subpopulations are 5-fold lower than the corresponding AEGLs.
- The SPELs are based on the same PoD as the AETLs but are higher than the values in other frameworks because no uncertainty factors are used and the values are predictive for 1 per cent mortality in the rat.

Table 3.15. AERV-3 values for nitrogen oxide (ppm).

	AETL		AEGL-3	ERPG-3	EPEGV-3	LBW	SPEL
	AETL-3b	AETL-3b+[a]					
10 min	36	7.2	34				100
30 min	25	5.0	25				80
60 min	21	4.2	20	30	53	26	70
120 min	17	3.4					--
240 min	13	2.6	14				--
480 min	11	2.2	11				--

[a] An additional factors of 5 is recommended for young children, people with lung diseases or with pre-existing critical oxygen supply.

Comments on AERV-2 (Table 3.16)

- AETLs and AEGLs have been derived following a similar procedure (PoD: human data for 2-hour exposure), with the exception that AETL for shorter exposure durations were set equal to the 2-hour value because of the possibility of mortality at higher concentrations.
- AETLs for the susceptible subpopulations are 5- to 10-fold lower than the corresponding AEGLs.

Table 3.16. AERV-2 values for nitrogen oxide (ppm).

	AETL		AEGL-2	ERPG-2	EPEGV-2	AGW	SEI
	AETL-2	AETL-2+[a]					
10 min	10	2	20				60
30 min	10	2	15				50
60 min	10	2	12	15	26	10	40
120 min	10	2					-
240 min	8.1	1.6	8.2				-
480 min	6.5	1.3	6.7				-

[a] An additional factors of 5 is recommended for young children, people with lung diseases or with pre-existing critical oxygen supply.

- SEI values are 3- to 6-fold higher than values in the other frameworks (with the exception of the EPEGV-2). SEI values have been based on monkey data, in contrast to, for example, the AETL, AEGL and AGW, which are based on human data.

Comments on AERV-1 (Table 3.17)
- AERVs differ up to a factor of 10 between the different frameworks.
- AETLs and AEGLs are based on different studies (AETL: human data, intraspecies factor of 3; AEGL: human data (asthmatics), intraspecies factor of 1).
- AETLs for the susceptible population are similar to the AEGLs.

Table 3.17. AERV-1 values for nitrogen oxide (ppm).

	AETL		AEGL-1	ERPG-1	EPEGV-1	VRW	SER
	AETL-1	AETL-1+[a]					
10 min	2.5	0.5	0.5				5
30 min	2.5	0.5	0.5				5
60 min	2.5	0.5	0.5	1	-[b]	0.5	5
120 min	2.5	0.5					-
240 min	2.5	0.5	0.5				-
480 min	2.5	0.5	0.5				-

[a] An additional factor of 5 is recommended for young children, people with lung diseases or with pre-existing critical oxygen supply.

[b] No EPEGV-1 has been derived as it is not considered by the Danish competent authorities to be relevant for practical purposes in emergency planning programmes.

Area contours for nitrogen dioxide (Figure 3.6)
The differences between the contours of the fictitious chemical incident scenario as calculated for the respective 1-hour AERV-2 values are large (Figure 3.6). The difference in distance downwind between the SEI contour and the AGW and AETL-2 contours is approximately 1 km. The downwind distance within which the AETL-2+ is calculated to be exceeded is extensive, and stretches up to approximately 4 km from the incident location. As with hydrogen sulphide, this contour crosses a highway and reaches the residential area of a neighbouring community, meaning that other local authorities have to be informed and cooperation in risk management and communication is needed if young children (being one of the defined subpopulations for AETL-2+) are to be protected. However, the contours for AEGL-2, AGW and ERPG-2, whose values intend to be protective for susceptible subpopulations such as young children, are much smaller than the AETL-2+ contour and similar to or somewhat smaller than the AETL-2 contour aimed at the healthy middle-aged man.

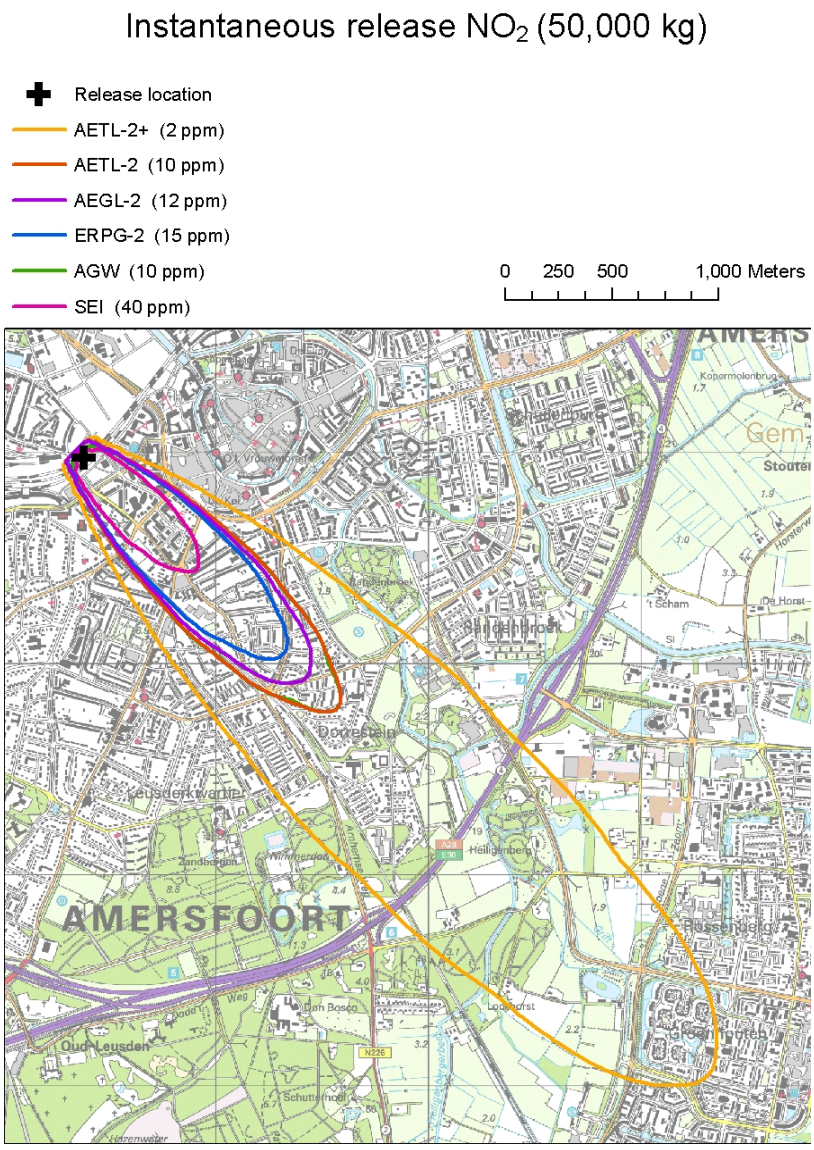

Figure 3.6. Contours of areas where the respective AERVs are calculated to be exceeded, following a fictitious incidental release of nitrogen oxide (the AGW contour is similar to the AETL-2 contour).

Nickel tetracarbonyl

Comments on AERV-3 (Table 3.18)

- AETLs are approximately 10- to 20-fold lower than the corresponding AEGLs; after application of the additional factor for subpopulations the difference is 100- to 200-fold.
- Different PoDs form the basis for the AETLs (calculated LC_{01}; 15-min rat data) and AEGLs (30-min mouse data). Application of extrapolation factors and choice of default values for *n* are similar.
- No comparison has been made for the first and second tier because no AETL-2, AETL-1 or AEGL-1 values are recommended due to insufficient data.

Table 3.18. AERV-3 values for nickel tetracarbonyl (ppm).

	AETL		AEGL-3	LBW
	AETL-3b[a]	AETL-3b+[a]		
10 min	0.035	0.0035	0.46	
30 min	0.015	0.0015	0.32	
60 min	0.008	0.0008	0.16	0.28
120 min	0.004	0.0004		
240 min	0.002	0.0002	0.04	
480 min	0.001	0.0001	0.02	

[a] A modifying uncertainty factor of 3 is added for lack of data.

[b] An additional uncertainty factor of 10 is recommended for newborns; an additional factor of 5 for people with pre-existing lung diseases; an additional factor of 3 for 2–15 year old children and people with a critical oxygen supply. The values are calculated with an additional factor of 10.

Chlorine

Table 3.19. AERV-3 values for chlorine (ppm) (see also Figure 3.7).

	AETL		AEGL-3	ERPG-3	EPEGV-3	LBW	SPEL
	AETL-3b	AETL-3b+[a]					
10 min	336	112	50				280
30 min	117	39	28				160
60 min	60[b]	20[b]	20	20	20	17	110
120 min	31	10					-
240 min	16	5	10				-
480 min	8	3	7.1				-

[a] An additional uncertainty factor of 3 is recommended for elderly people and people with pulmonary or liver/kidney diseases.

[b] The 60-min AETL-3b in the ACUTEX document appeared to be incorrect and has been recalculated.

Comments on AERV-3 (Table 3.19, Figure 3.7)

- Although the 8-hour AETL and AEGL values are similar, an increasing difference with shorter exposure durations is present, resulting in a more than 6-fold difference for 10 minutes of exposure.
- AEGLs are derived from the same study as the AETLs, but with data from a second study included. Different values of *n* (AETL: *n*=1.04 (calculated by probit modelling tool based on animal mortality data); AEGL: *n*=2 (based on human irritation data) and different extrapolation factors (AETL: 3 for extrapolation of LC_{01} to non-lethal concentration; AEGL: 10 (combined factor for interspecies and intraspecies extrapolation) were used.
- SPELs are calculated by probit analyses of mouse data (among others the same study as for AETLs and AEGLs); no extrapolation factors are applied. The 1-hour SPEL is 2-fold higher than the corresponding AETL, and approximately 5-fold higher than the corresponding AERVs of the other frameworks.

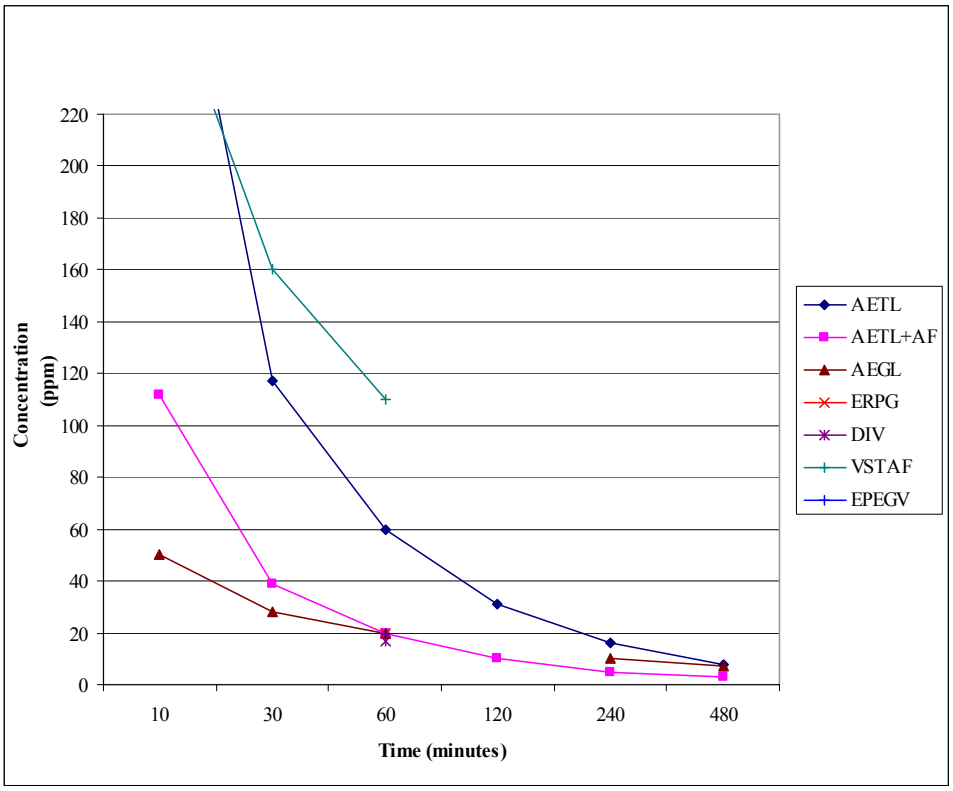

Figure 3.7. AERV-3 values for chlorine.

Comments on AERV-2 (Table 3.20, Figure 3.8)

- The AETLs are 4- to 40-fold higher than the corresponding AEGsL. Different PoDs and *n* values are used (AETL: 2-minute rat study, *n*=1.04; AEGL: human data for 4 hours of exposure, *n*=2). The AETLs for susceptible subpopulations are approximately similar to the corresponding AEGLs for the longer exposure durations but up to 12-fold higher for the shorter exposure durations.
- The 1-hour AEGL is in line with the ERPG-2, EPEGV-2 and AGW. The 1-hour AETL is similar to the 1-hour SEI.
- The derived SEI values are approximately 10- to 15-fold higher than the corresponding AEGLs. SEIs are based on human data (published in 1946)

that were considered imprecise and not suitable for use within the AETL framework and not evaluated within it.

Table 3.20. AERV-2 values for chlorine (ppm) (see also Figure 3.8).

	AETL		AEGL-2	ERPG-2	EPEGV-2	AGW	SEI
	AETL-2	AETL-2+[a]					
10 min	106	35	2.8				41
30 min	37	12	2.8				25
60 min	19	6	2	3	2	1.7	19
120 min	10	3.3					-
240 min	5	1.7	1				-
480 min	3	1	0.71				-

[a] An additional uncertainty factor of 3 is recommended for elderly people and people with pulmonary or liver/ kidney diseases.

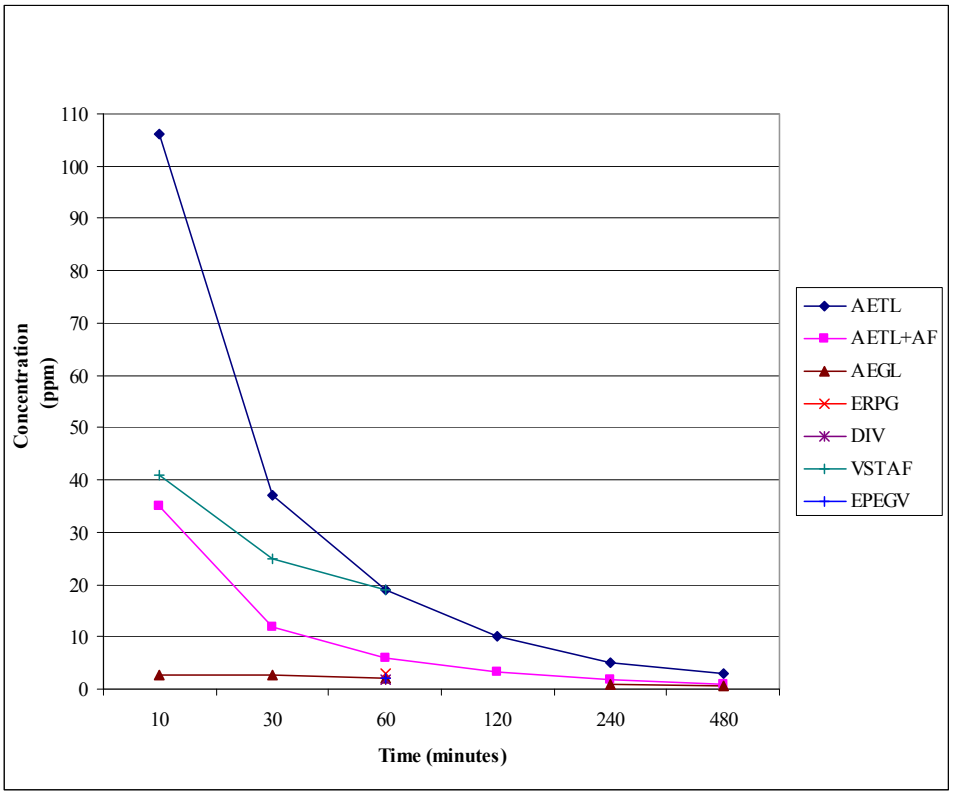

Figure 3.8. AERV-2 values for chlorine.

Area contours for chlorine (Figure 3.9)
Figure 12 shows the respective AERV-2 contours for chlorine. The AETL-2 contour for chlorine is similar to that for SEI and the boundaries for both are within one community. The contours of the other frameworks stretch out over the residential area of a neighbouring community. The contours for AGW, AEGL-2, EPEGV and ERPG-2 are approximately similar. In contrast to the simulations for the three other chemicals, the AETL-2+ contour stretches out over a smaller area than do the AGW, AEGL-2, EPEGV and ERPG-2 contours.

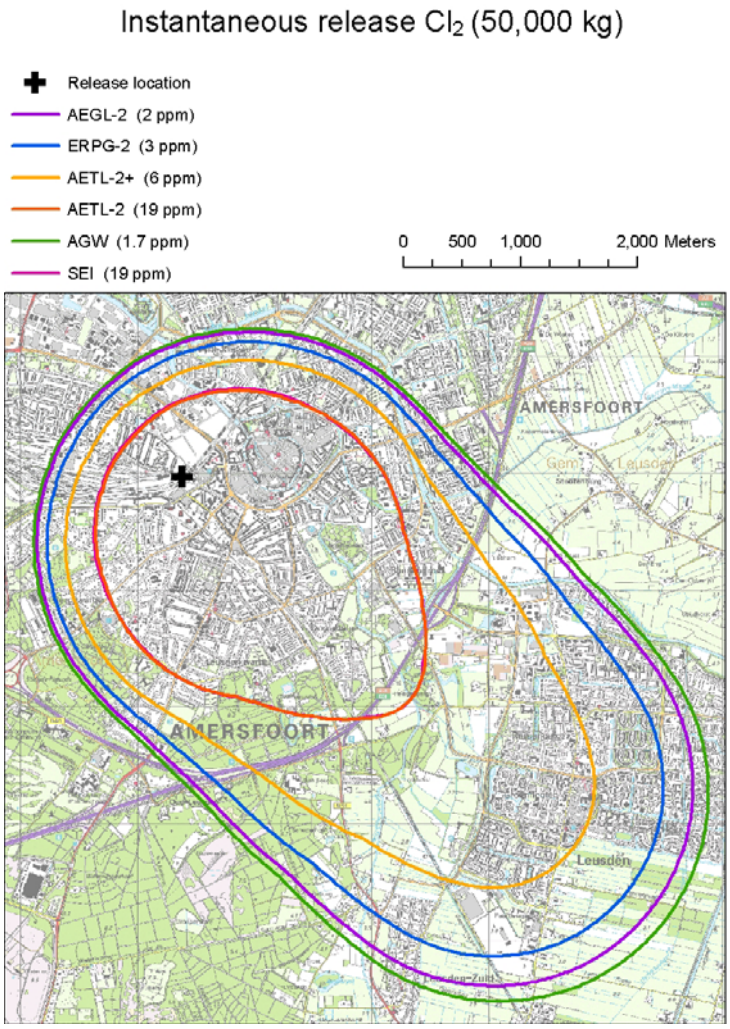

Figure 3.9. Contours of areas where the respective AERVs are calculated to be exceeded following a fictitious incidental release of chlorine. The EPEGV contour has not been calculated but is similar to the AEGL-2 contour and the SEI contour is similar to the AETL-2 contour.

Discussion
From the six examples discussed it can be concluded that large differences in the actual values do occur and that these differences are not showing any consistency. For instance, the AETL-1 values for hydrogen sulphide were approximately 20-fold higher than the corresponding AEGLs but AEGL-3 values for nickel tetracarbonyl were up to 20-fold higher than the corresponding AETLs. A comparison of all 21 AETL cases with the corresponding AEGLs (unpublished data) showed that in general the values will differ 2- to 6-fold to either side.

The VSTAF values (SPELs and SEIs) are generally much higher than those in other frameworks, as a result of a different basic philosophy on the purpose of these values and their level of protection. Extrapolation factors accounting for interspecies and intraspecies extrapolation are generally not used for SPEL or SEI derivation. However, for certain chemicals the SPEL and SEI values are at comparable levels to AEGLs (e.g. AERV-3 for styrene) or AETLs (e.g. AERV-3 and AERV-2 for chlorine), where AFs are applied.

Differences were also caused by issues related to time scaling. For instance, the AETL and AEGL frameworks each have their own modelling tools for probit analyses and DR-modelling. This sometimes results in different estimates for the value of *n*, as illustrated by the AERV-3 comparison for ethylene oxide. The ratio of the 10-minute and 480-minute value is 1.8 for the AETLs but 10 for the AEGLs. Another issue regarding time scaling is illustrated by the example of styrene, where AEGL-2 and AEGL-3 values were set equal after a specific exposure duration at which tissue steady-state concentrations were expected to have occurred. Finally, in the example of chlorine the value of *n* was based on human irritation data at tier 2 but also at tier 3, in contrast to the AETL framework, where the value of *n* was calculated by probit analyses of animal lethality data.

Basic philosophical and methodological differences also contribute to the observed differences. An example is the choice of target population to be protected. It is noted, that although the AETLs are aimed at the healthy middle-aged man, they still can be equal to or lower than the corresponding values in the other frameworks that are derived for susceptible subpopulations (e.g. AERV-2 for hydrogen sulphide, AERV-2 and AERV-3 for styrene, AERV-3 for nickel tetracarbonyl). Another important issue is that developmental toxicity (effects on the unborn) is not an endpoint for AETLs and SEIs, although an additional uncertainty factor is proposed within the AETL framework in case the unborn are defined as a susceptible subpopulation. However, the question remains whether an uncertainty factor applied to an AETL-2 value based on an endpoint that has no relationship with developmental toxicity (e.g. respiratory tract irritation) will provide sufficient protection for the unborn. Furthermore, as illustrated by the example of hydrogen sulphide, the method of choice for protecting the susceptible subpopulation as within the AETL framework may result in difficulties in risk communication. For hydrogen sulphide, application of the additional uncertainty factor for the susceptible subpopulation resulted in AERV-2 and AERV-3 levels that were lower than the corresponding AERV-1 levels.

Within some frameworks odour is recognized as an endpoint at tier 1 (e.g. ERPGs), while in others it is addressed separately. For compounds with a strong objectionable odour (such as hydrogen sulphide) this might lead to large differences in AERV-1 values.

To illustrate the consequences of applying different AERVs in a chemical emergency situation a fictitious incident scenario was simulated for four out of the six chemicals. Large differences were observed in the surface area where AERV-2 levels were calculated to be exceeded and consequently in the number of people potentially exposed. It sometimes depended on the AERVs used, whether administrative borders were crossed or not. These differences showed no consistent pattern. It is noted, that the differences between AERVs will sometimes be larger for other exposure durations than one hour and thus larger differences in the contours can then be expected.

Overall, this illustrates that the AERVs derived within the respective frameworks are not interchangeable and result in different outcomes in emergency response situations. Considering the consequences in terms of health risk for the exposed population and the number of potential victims, this is of large concern. Application of unsuitable AERVs or inadequate application of suitable AERVs might lead to an unnecessary increased risk to health for the exposed population, especially as decisions have to be made within a very short time period (minutes) immediately after the onset of an incidental release. This stresses the need for international harmonization regarding the derivation and application of AERVs in order to assure adequate risk management decisions and risk communication to the public.

Summary and conclusions

Öberg et al. (2010) made a thorough comparison between the 1-hour AEGL values and the ERPG values for all substances evaluated within these frameworks (as on January 2009). They concluded that the values differed by a factor of 3 or more for almost 40 per cent of the substances for which both an AEGL and ERPG evaluation were available. These differences could be explained by differing selections of critical effect or study and choice of PoD. Time-scaling issues were not addressed.

Large differences exist between the methodologies used to derive AERVs, leading to major discrepancies in values and level of protection. AERVs derived by different frameworks are often used in combination, depending on which value is most easily available. Without proper knowledge of the level of protection these values will be considered interchangeable, which may result in inappropriate measures or actions for risk reduction and may hamper risk communication to the public, leading to unnecessary concern or unjustified reassurance. As Öberg et al. (2010) concluded, major discrepancies may affect the communication and trust between diverse stakeholders (think tanks, experts, journalists, politicians and governmental officials) engaged in the process of establishing a legitimate definition of risk.

The observed differences resulted from several causes:

- differences in PoD (different criteria in selection of data);
- differences in basic philosophy/methodology regarding
  - target population and use of assessment or extrapolation factors,
  - level of protection,
  - considered endpoints (developmental toxicity, odour);
- use of different DR modelling tools (including probit analyses tools).

The examples show that harmonization is needed for all these factors. Furthermore, the simulations of a the fictitious chemical incident scenario for four chemicals showed large differences in estimation of the areas where AERVs are expected to be exceeded and, consequently, the number of people at risk. Since unsuitable AERVs or inadequate application of suitable AERVs might increase risk to human health, especially in chemical incidents with a heavy time pressure on the decision-making process, there is an urgent need for international harmonization on the derivation and application of AERVs.

3.6 Exposure assessment

Introduction
Risk assessment of chemical incidents requires exposure-effect (or -response) information in the form of AERVs, and information on the actual exposure: contact medium (in this case: air), concentration and exposure duration. This section explores the current state and recent developments in methods and strategies to assess airborne exposure resulting from chemical incidents at all stages of the disaster management cycle.

Exposure assessment can be performed under two circumstances:
1. As a part of the actual incident response, with the main objective to provide decision support and enable a rapid health risk assessment. To be of practical value, such exposure assessment must be done in a given time frame, and used in conjunction with toxicological considerations such as AERVs to determine the actual risk.
2. Aimed at scenario analysis for prevention, planning and preparedness. The main objective in these cases is to provide prognostic capabilities for chemical incidents (including CBRN events) in tactical and strategic planning and training/exercise.

These two categories of application put very different demands on the methodology, which will be discussed briefly below.

Methods for immediate response
In acute emergency situations it is important to have exposure assessments, thereby enabling actions to take place quickly, e.g. identification of risk areas and appropriate measures of protection for first responders.

Currently, the only feasible methods of rapid exposure assessment are model-based template methods, requiring very little input data, to assess risk areas and make informed decisions regarding appropriate levels of personal protection, feasible mitigation techniques etc. Template methods are based on the identification of 'dimensioning scenarios' and exposure assessment with more advanced models, based on these dimensioning scenarios. Examples of tools of this kind are the US Emergency Response Guidebook (ERG; PHMSA, 2012) and the NATO ATP-45 templates.

Depending on the duration of the release and dispersion, actual concentration measurements may be feasible. At the least, these can be used to fine-tune and validate modelled concentration assessments.

Methods for aftermath analysis
In the aftermath of a release, a more refined estimation of the dispersion process and the exposure is necessary, e.g. for localization of a source with an unknown position, for reducing the initially huge risk areas, determining safe areas and decontamination areas etc. For this purpose, a combination of environmental measurements and models should be used. Measurements alone give local, highly significant estimates at the sampling point, whereas dispersion models give overall estimates of the past and future development of the event.

Future methods
The next step for exposure assessment is to use individual sensors on exposed people and/or biomarkers. Person-carried passive dosimeters have been used for a long time in occupational hygiene. However, the turnaround time is long

because of the laboratory analysis needed. There is emergent technology applicable in emergency situations for both environmental exposure assessment and biomarkers.

3.6.1 Environmental exposure assessment

To determine or estimate exposure one has to use a combination of models and measurements, depending on the situation, the available resources and the available time to deliver an exposure estimate.

Modelling approaches

The single most important advantage of exposure models over exposure measurements is that the former can be used to predict future exposure and to estimate exposure where measurements are lacking, if there is sufficient information about the release and the circumstances determining airborne dispersion. Often crude, inexpensive and fast methods are used for fast exposure estimates, which is refined in an iterative way if necessary, with more sophisticated, time- and resource-demanding methods. Sophisticated models may or may not deliver more precise results, since they need more input data, which may not always be available or accurate, causing larger errors than crude models with few but relatively certain input data.

The exposure estimation can be divided into estimation of the source release, dispersion and human exposure. The present report focuses on inhalation, but a considerable additional exposure can occur through skin uptake and/or gastrointestinal uptake after the mucociliary clearance of particles from the respiratory tract. The inhalation step depends on the behaviour and individual characteristics of the exposed individual, and assumptions must be made about 'worst case' or 'dimensioning' behaviour. In occupational hygiene, worst case scenarios are usually considered, whilst, in chemical incident preparedness and response, dimensioning scenarios are defined, reflecting the amount of acceptable risk in the decision process. Such assumptions that fit the chemical incident scenarios can be accounted for in the derivation of AERVs.

In the source release modelling physico-chemical properties of the substance, as well as the nature of the release (formation of pools, aerosols, dense gas effects etc.), are considered. The worst case scenario is usually an instantaneous release of all available material.

To estimate the dispersion (e.g. the concentration), a range of modelling techniques of increasing complexity is available, from simple zero-ventilation models based on physico-chemical properties alone, to dispersion models of growing sophistication – well-mixed stationary or portable box models, Gaussian dispersion models, eddy diffusivity models, Lagrangian stochastic particle models.

In the acute phase of an emergency response a simple model with few input data must be used to obtain a rapid exposure estimate. Models that are more complex give a more detailed description of the dispersion process, provided correct input data are available, for example taking terrain and urban geometry into account. However, complex models require more expertise from the user, more input data and a longer time to deliver a response. More precise dispersion estimates are useful in emergency preparations (what-if scenarios, exercises) and in emergency aftermath assessments. An overview of dispersion modelling

for emergency management may be found in Borysiewicz and Borysiewicz (2010), and a model database in EIONET (2010).

The results from Heinälä et al. (2013) indicate that a large number of air dispersion models are used in Europe. Frequently used programs are ALOHA, PHAST and Effects. The long list is a clear indication that harmonization of air dispersion modelling has not yet been achieved in Europe. A major need was found for atmospheric air dispersion modelling tools and training in their use.

Environmental monitoring
Environmental monitoring does not permit prediction of future exposure per se, but provides information on current concentrations of the chemical in the contact medium (air) at best and usually only provides information on past exposure after field or laboratory analysis.
Environmental monitoring in the acute phase of a chemical incident is usually restricted to quick and simple direct reading techniques such as gas detection tubes, Photo Ionization Detection (PID) and infrared spectroscopy. Under these circumstances, the accuracy and validity of the environmental monitoring are limited due to the personnel involved, the available detection and analysis equipment and the time necessary to fit the personnel with appropriate protective equipment to enter the site or the downwind area. While air sampling could be performed quickly, and the analysis and interpretation performed post hoc, this environmental monitoring strategy has not yet been applied frequently (Bonger et al., 2008).

To measure exposure more accurately, passive dosimeters (e.g. diffusion samplers) may be used, either carried by an individual or placed at a fixed position in the environment. Passive dosimeters are commercially available for a variety of chemicals, including laboratory analysis. This approach is only helpful if the dosimeters have been pre-installed or can be installed by sufficiently protected personnel early on in the incident. Results do not become available until after the incident and therefore do not contribute to the acute risk assessment. Therefore, none of these methods are suitable for emergency situations.

An alternative is to measure the concentration of the chemical in air with active sensors. There is no universal sensor technology that can detect all toxic industrial chemicals; to handle several chemicals, it is likely that different sensor types must be combined.

All above methods only provide an estimate of the concentration of the released chemical in the contact medium (air). The personal exposure or the inhaled and/or dermally absorbed dose must still be estimated by modelling. A number of the assumptions that are necessary to make risk assessments based on such crude exposure data can be integrated in the methodology to derive AERVs, so that personal air concentrations will suffice to make the risk assessment.

The miniaturization of sensor technology makes person-carried active sensors feasible. An interesting example is the US DHS programme for Cell Phone Chemical Sensors, a prospective ubiquitous sensor network activated when an emergency situation occurs. Four main types of sensors can be distinguished: IMS sensors (ion mobility spectroscopy: portable); FTIR sensors (Fourier transform infra red: not portable, but remote sensing); electrochemical sensors (portable); and PID (photo ionization detector: portable). Typically, highly sensitive but broad (non-specific) sensors are used for detection (PID), and then

more specific sensors for classification or identification (e.g. IMS). A description of the sensor technologies may be found in Sferopoulos (2010). An additional 'sensor' is the measurement of chemical elements by XRF (X-ray Fluorescence) (Kalnicky and Singhvi, 2001), frequently used portable in the field (Wingfors et al., 2005). However, the optimal choice of sensors is highly dependent on the compound agent, the situation and the available personnel and equipment.

3.6.2 Determination of exposure in biological samples

Biomarkers of exposure have been used historically in forensic toxicology, internal medicine and pharmacology. Clinical symptoms as well as other biomarkers were established to follow the actual chemicals or their metabolites that can be measured in the body, or after excretion from the body, to determine different characteristics of a person's exposure (WHO, 1993). Four main sampling strategies are implemented:

1. Body fluids (sweat, tears, urine, saliva, spinal fluid);
2. Exhaled air (sac sampling);
3. Integument (hair, nails, skin);
4. Tissue (blood, lymph, target tissue).

Most sample analyses require time-consuming reprocessing for the exact identification and quantification of agents. However, in recent years the detection of hazardous agents has improved by utilizing techniques developed for field use and even by real-time surveillance of the individual medical status, cf. Ausen (2010). This may provide opportunities for quick exposure assessments at the incident scene and the downwind affected areas. For example, drugs in exhaled air can in principle be detected in drug addicts by Raman techniques. Other examples are given in a report from the EU 'MASH' project (Göransson Nyberg et al., 2010). The field detection of biomarkers may be implemented in suitable disaster management stages, e.g. triage-management.

Methods for rapid decision-making on the usefulness and feasibility of using biological monitoring are needed. Recently, a stepwise procedure for taking such a decision has been proposed (Scheepers et al., 2011).

3.6.3 Conclusions

The task of determining human exposure to hazardous chemicals requires maintaining a set of source and dispersion models and measurement techniques, and assumptions about dimensioning or worst-case scenarios must be determined. As Heinälä et al. (2013) clearly demonstrated, there is no harmonized procedure for exposure assessment (modelling, environmental or biological monitoring) for chemical incident response in Europe. However, within the European REACH framework, the Advanced REACH Tool (ART) (ART, 2010; Fransman et al., 2009) is available for occupational exposure assessment, where simple dispersion models are used (box and Gaussian models). This may be a starting point for further development.

3.7 Summary, conclusions and recommendations

3.7.1 Summary

Chapter 3 explored the present approaches for risk assessment of chemical incidents. A total of 13 frameworks dealing with derivation of AERVs have been identified, of which nine are presently active. Six of these 13 frameworks were

selected for comparison based on the criteria that they are sufficiently documented to be compared and had AERVs for at least three tiers. The selected six frameworks are AEGL, AETL, DIV, EPEGV, ERPG and VSTAF. The AEGL and ERPG frameworks are both approaches from the USA. The DIV, VSTAF and EPEGV are national approaches in the Netherlands, France and Denmark, respectively. The AETL methodology has been developed within the 5th EU Framework project ACUTEX as a first step towards a harmonized European approach. These frameworks were compared as to how important toxicological endpoints are addressed and the differences between the level of protection for different subpopulations, time scaling and dose-response modelling. The practical consequences of the identified methodological differences for risk assessment, risk management and risk communication in an emergency situation were illustrated by comparison of AERVs and their use in a fictitious chemical emergency situation. Finally, some issues on exposure assessment, being the second pillar of risk assessment, were highlighted.

In the Appendix, the specific characteristics of the six compared frameworks are summarized. Although there is general consensus about which issues and topics are important in the derivation of AERVs, critical differences in methodologies are identified regarding how these topics are dealt with, as summarized below.

Toxicological endpoints

Carcinogenicity

- Although the theoretical risk from single exposure to a genotoxic carcinogen is considered to be probably low, it was recognized in most frameworks that carcinogenicity is an important endpoint that should be addressed, considering the societal perspective on carcinogenicity and the potential public health impact.
- The compared frameworks treated carcinogenicity very differently, ranging from not considering carcinogenicity as relevant to AERV derivation, to application as an endpoint for either AERV-2 or AERV-3 or via a separate risk calculation.
- Different methods were applied in the calculation of the carcinogenic risk.

Harmonization is needed on this endpoint since release of a carcinogenic chemical in an incident will lead to substantial public concern that requires adequate risk communication; an authoritative carcinogenicity risk assessment is an essential prerequisite for this purpose.

Reproductive toxicity

- The frameworks differed as to the application of developmental toxicity and fertility effects as endpoints for AERV derivation. There was no consensus on how to address these effects and at which tier. Approaches ranged from not considering reproductive toxicity as a relevant endpoint to regarding developmental toxicity as an endpoint for AERV-3.
- Within the AETL framework, this endpoint is not addressed at a specific tier but identification of a susceptible subpopulation such as the unborn child is possible. End-users have to decide about the protection of this subpopulation via an additional assessment factor. Leaving the choice to the end-user may not help end-users who indicated that the use of existing AERVs is complicated enough as they are (Heinälä et al., 2013).
- Issues for which no guidance is available include endocrine disruption and effects that may not be observed until childhood, i.e. years after the exposure period.

- Considering that reproductive toxicity can generate substantial societal concern, risk assessment of chemical incidents requires appropriate information in order to communicate reproductive toxicity issues with the public, including the exposed population. Harmonization is therefore urgently recommended, both for effects on fertility and developmental toxicity as well as for delayed effects and endocrine disruption.

Sensitization
- Because of a significant increase in the prevalence of allergy and allergic diseases, sensitization has become a major health issue.
- Most of the existing methodologies do not address this issue and none of them provides adequate guidance.

It is recommended to verify the relevance of this endpoint for the derivation of AERVs and if appropriate to develop specific guidance if necessary.

Neurotoxicity
- Neurotoxicity is recognized as an important endpoint for AERV derivation and includes different type of effects such as CNS depression (narcosis), acetylcholinesterase inhibition and delayed neurotoxicity.
- None of the frameworks provides a quantitative method to address this endpoint.
- Guidance is needed on time scaling of acute CNS depression, especially for longer exposure durations.
- Guidance may be obtained from the technical support documents for known neurotoxic substances.

It is recommended to develop guidance on how to address the different neurotoxic effects as endpoints in the derivation of AERVs in a clear and transparent way, including time scaling to multiple exposure durations.

Sensory awareness
In chemical incidents an exposed community is likely to interpret the presence of an unusual odour not common in the normal 'odour landscape' as a potential health risk. Therefore, sensory awareness of an incident, even without toxicity, is an important trigger for crisis communication with the affected population.

While in theory all sensory awareness might occur through all sensory modalities, only odour awareness and annoyance are chemical specific and can be quantified on the basis of existing information.

Objectionable odour is an endpoint for ERPG-1 and EPEGV-1. In the other frameworks a separate 'odour' value is calculated based on existing methodology.

For odour awareness, a relatively recent methodology is available and used in a number of frameworks. The main issue to be resolved is about the inclusion of odour as an AERV-1 endpoint, or the derivation of a separate value.

Target population
- The six studied frameworks all aim to protect a different population, and at a different level of protection. Five different approaches can be distinguished:
  - The AEGL and DIV values are derived to protect the general population including susceptible subpopulations, but not necessarily 'hypersusceptible

individuals'. AFs to account for interspecies and intraspecies differences are transparently applied to calculate the values.
    - ERPG values also aim at protecting the general population including susceptible subpopulations, but not necessarily 'hypersusceptible individuals'. Instead of using extrapolation factors, a weight-of-evidence approach is applied to derive values.
    - EPEGV values are also aimed at protecting the general population including susceptible subpopulations, but not necessarily 'hypersusceptible individuals'. AFs are not applied as the numerical values of the EPEGVs are aimed at being predictive rather than protective.
    - In the VSTAF approach, the target population is the general population excluding the susceptible and 'hypersusceptible individuals'.
    - AETL values are aimed at generally healthy middle-aged (male) adults, so do not take specific sensitive subpopulations into consideration. If susceptible subpopulations can be defined, additional factors are proposed to protect them. The decision whether to apply this additional factor is the responsibility of the end-user.
- The distinction between susceptible subpopulations and 'hypersusceptible individuals', used in the described approaches to the derivation of numeric AERV values, is not always clear and may differ from approach to approach and from substance to substance.
- The AERVs derived via the different methodologies are aimed at different target populations and are therefore not interchangeable, although they are used as such in practice. Use of AERVs without sufficient insight into their level of protection may result in risk management decisions that may either increase or overestimate health risks and hamper risk communication to the public. Synchronous existence of AERVs with different levels of protection is highly undesirable.

Harmonization regarding and clarification of the target population to be protected and regarding the methodology to assure this protection is highly recommended to avoid inadequate risk management decisions and to improve risk communication in a chemical emergency situation.

Time scaling and dose-response modelling

- Derivation of AERVs requires specific tools for time scaling (to derive values for different exposure durations, particularly those for which no data are available) and dose-response modelling (AERVs are set at multiple levels of toxicity).
- The different tiers are meant to be predictive for the health effects addressed by the respective tiers. Adequate PBPK- and dose-response modelling tools are needed to achieve this.
- Often default approaches have to be applied, increasing uncertainty in the AERVs derived. Different modelling tools have been occasionally used within the AEGL and AETL frameworks, providing different end results in values and time scaling.
- The use of probabilistic tools, e.g. to quantify uncertainties in the AERV values, should be explored.
- Sophisticated PBPK- and dose-response modelling tools are important to derive predictive AERVs at multiple health impact levels and for multiple exposure durations. The present state of the art for these modelling tools (including probabilistic tools) needs to be explored for their applicability in AERV derivation. Practical guidance is needed on how these tools can optimally be used to diminish the uncertainties involved in the risk

assessment and to provide AERVs that are predictive for the boundaries between the different tiers.

Numerical comparison of AERV methodologies

- Major differences were observed between the methodologies for AERV derivation, leading to major discrepancies in values and level of protection.
- The observed differences in AERV values were inconsistent and resulted from multiple causes:
  - differences in toxicological PoD;
  - differences in basic philosophy/methodology:
  - target population and use of assessment or extrapolation factors;
  - level of protection (e.g. population protected);
  - considered endpoints.
- Use of different dose-response modelling tools.
- Simulations of a fictitious chemical incident scenario showed large differences in the estimated area of concern calculated for the respective frameworks and, consequently, the number of people at risk.

The numerical comparison and the fictitious chemical incident scenario show that AERVs derived in the respective frameworks lead to different risk assessments and thus to different risk management decisions that will not always be of sufficient quality to protect the public health. It is therefore unavoidable that this situation might increase human health risk, especially in chemical incidents with a heavy time pressure on the decision-making process. There is an urgent need for international harmonization of the methodology to derive AERVs and practical guidance on the application of AERVs.

Determination of exposure

The task of determining human exposure to hazardous chemicals requires maintaining a set of source and dispersion models and measurement techniques, and assumptions about dimensioning or worst case scenarios must be determined. As Heinälä et al. (2013) clearly demonstrated, there is no harmonized procedure for exposure assessment (modelling, environmental or biological monitoring) for chemical incident response in Europe, while there is a great need for more harmonization in this field.

3.7.2 Conclusions and recommendations for harmonization

In a chemical incident, risk assessment is the basis for emergency response decisions that have to be taken under great time pressure. The simultaneous availability of different AERVs, which appear but in fact are not equal, is then confusing. Immediately after the onset of a chemical incident there will be no time to compare the underlying considerations and the level of protection of the different AERVs. In practice, the different AERVs are considered to be interchangeable (Heinälä et al., 2013). End-users will use whatever is available. Application of AERVs without knowledge of their basis and level of protection will unavoidably lead to inadequate risk management decisions, either too strict or insufficient. This was illustrated by the simulations of a fictitious chemical incident scenario for different chemicals in section 3.5, showing large differences in estimated areas of concern where risk reduction actions are warranted.

The present methodologies were evaluated and compared to answer the following questions:

- Which information, and what tools and guidance are required to develop AERVs?

- To what extent is there consensus on the methodology to derive AERVs from toxicological data?
- What methods and which procedures need to be further developed to reach the required consensus?

Öberg et al. (2010) defined three general key factors for broad international acceptance, i.e. transparency of the decision-making process, agreement on the definition of toxicological tiers and a clearly described target population, including susceptible subpopulations. The present comparison shows that there is a general agreement on which issues are of importance for AERV derivation (see Table 3.7) and on the information and tools needed to properly address these issues. However, there is little consensus on how to use the available information and the different frameworks utilize their own tools. However, for some issues differences already exist at the level of the basic philosophy on AERVs and their purpose, for example on the target population to be protected by AERVs.

Within all frameworks AERVs are defined for three tiers, although no EPEGV-1 values were derived for the 11 case studies, because the Danish competent authorities at that time did not consider EPEGV-1 to be practically relevant to emergency planning programmes. The relevance of AERV-1 values was also questioned within the web-based survey (Heinälä et al*.,* 2013).

ERPGs and EPEGVs are derived only for 1-hour exposures. As described in section 3.7.1, differences between methodologies exist on most of the issues described in Table 3.7. Harmonization is still to be achieved in defining the relevant toxicological effects within the toxicological endpoint (e.g. within reproductive toxicity: developmental effects, fertility, endocrine disruption), defining critical effect sizes for the respective tiers or addressing specific endpoints separately form AERVs (as is for instance proposed for odour, for example, or carcinogenicity within the AEGL framework). In addition, no guidance exists in any methodology for certain toxicological endpoints, such as for sensitization. Whereas for other toxicological endpoints, such as neurotoxicity, practical experience is available and is already described in individual technical support documents for the relevant chemicals. The existing consensus on these endpoints only needs to be laid down in a protocol.

Endpoints such as carcinogenicity and reproductive toxicity may in general not pose a large health risk in a chemical emergency situation but incidental release of carcinogenic or reprotoxic chemicals will give rise to major public concern. Transparent guidance on a communication strategy for these endpoints can be of great help in risk communication to the public.

Comprehensive guidance documents for derivation of AERVs exist within the AEGL and AETL framework. These documents can form the basis for further harmonization that should be laid down in a Guidance Document on the derivation of European AERVs. In conclusion, the following actions are recommended to achieve harmonization:

Toxicological endpoints

- Carcinogenicity:
  - Agreement is needed on how to deal with this endpoint (tier 2, tier 3, separate quantitative risk estimate) and the DRCF to be used.
  - Development of guidance for a communication strategy.

- Reproductive toxicity:
  - Agreement on the relevance of the different endpoints (developmental toxicity, fertility) and at which tier these effects are to be addressed.
  - Verification of the relevance of endocrine disruption as endpoint for AERVs and, if yes, development of guidance.
  - Development of guidance for a communication strategy.
  - Sensitization:
  - Verification of the relevance of sensitization for the derivation of AERVs and if yes, development of guidance.
- Neurotoxicity:
  - Guidance quantitatively addressing the different neurotoxic effects (narcosis, acetyl cholinesterase inhibition, delayed neurotoxicity) as endpoints in the derivation of AERVs.
  - Guidance on time scaling for concentration-related neurotoxic effects such as narcosis.
  - Guidance can probably be derived from practical experience, as can be found in the technical support documents in the case of neurotoxic chemicals.
- Sensory awareness:
  - Definitions of endpoints to be included.
  - Agreement on how to deal with this endpoint (tier 1, separate (quantitative) estimate).
- Other endpoints:
  - Guidance on how to determine the PoD for AERV derivation.
  - Agreement on the endpoints to be addressed by the respective tiers.
  - Defining critical effect sizes for the respective tiers for the main endpoints.
  - Guidance can be derived from practical experience, as can be found in the technical support documents for relevant chemicals.

Target population
- Definition and transparent description of the target population (general population, susceptible subpopulations or 'hypersusceptible individuals') to be protected and guidance on the methodology to assure this protection (i.e. to account for interspecies and intraspecies differences).
- Guidance on the derivation of AERVs for the target population and how '(hyper)susceptible' subpopulations are to be addressed.

Time scaling and dose-response modelling
- Agreement on the number of exposure durations for which AERVs are to be derived.
- Agreement on the number of tiers to be derived.
- Definition and derivation of critical effect sizes for the respective tiers for endpoints that are most common for AERV derivation.
- Evaluation of the present state of the art regarding PBPK- and dose-response modelling tools (including probabilistic tools) and their applicability for AERV derivation.
- Development of and guidance for use of harmonized modelling tools for the derivation of AERVs for multiple exposure durations that are predictive for the respective tiers.
- Agreement on the application of default approaches for time scaling.

Exposure assessment
The task of determining human exposure to hazardous chemicals in chemical incidents requires maintaining a set of dispersion models and measurement techniques, and assumptions about dimensioning or worst case scenarios have

to be determined. A large variety of exposure, or dispersion, models and exposure measuring devices are available. This was also demonstrated in the web-based survey (Heinälä et al., 2013). However, there appears to be no harmonized approach to which methods and models should be used in given situations. Aspects such as, among others, the required accuracy, chemical specificity and portability may play a role in the selection. A harmonized, tiered approach or guidance should be developed to ensure consistency in measurements and model calculations in transboundary exposure incidents.

International harmonization: additional steps
If a European harmonized approach for AERV derivation is developed, after consideration of all the practical, jurisdictional, political and scientific issues, further steps will still need to be taken. The second step in the process concerns the actual derivation of AERVs according to the future harmonized methodology with broad European consensus. A harmonized methodology and description of how to derive AERVs will still not be sufficient to assure harmonized AERVs. This was illustrated by the principle of proof within the Emergency Exposure Index (EEI) methodology development process in 1991 (ECETOC, 1991). Eleven different industrial organizations were approached to propose EEIs according to the developed methodology and guidance. Large differences in proposed EEIs were observed, although it was expected that many of these differences could have been resolved by discussions leading to mutual agreements. This demonstrates that one international interdisciplinary organization or committee should be made responsible for deriving the definitive AERVs in order to assure harmonized values. In addition, to ensure successful implementation and adoption within Europe of harmonized AERVs (including the methodology for derivation), the support from a broad European policy platform should be secured.

A third step includes appropriate training of first responders and other end-users on the application of AERVs in emergency response situations, application of AERVs in the risk assessment process and in risk communication (including risk communication strategies for specific endpoints). The end-user needs sufficient knowledge of the background and the purpose of AERVs and their limitations in order to enable adequate application of these values in chemical incidents. For this purpose an international training course should be developed. Risk assessment courses are generally focused on risks from lifetime exposures to chemicals, and not on single exposures in chemical incidents. In these courses topics that are typical and specific for risk assessments following single exposures in chemical incidents, such as time scaling and multiple health effect levels, are not addressed.

4 Existing policies, legislation and guidelines

4.1 Introduction

Currently, there is no specific European or globally harmonized legal framework regulating or governing the principles of risk assessment in acute chemical incidents. A number of national regulations already exist, covering for instance land-use planning and (acute) occupational exposure levels. These national frameworks are either not yet harmonized at the European level or member states are yet to implement EU regulations that cover aspects of risk assessment. In the absence of a specific and comprehensive European or a globally harmonized regulatory framework, this chapter will explore which of the existing international or inter-governmental regulations affect chemical incident risk assessment and, in particular, the subsequent derivation of AERVs.

The aim of this chapter is to explore the extent to which existing international legislation may actually directly or indirectly provide an obligation or an opportunity to produce acute toxicity data and guidance or other relevant information that can be used for acute human risk assessment in chemical emergency situations. The focus is whether provisions are made for guidance on risk assessment in such chemical emergency response scenarios and if any possible data requirements include toxicity data that are of interest for acute, single exposure scenarios. In addition, the influence of the global policy on reduction of the use of laboratory animals on the toxicological data requirements is an essential part of the exploration and thus acceptance of *in vitro* testing methodologies and *in silico* methods, such as Quantitative Structure-Activity Relationships (QSARs).

The body of international regulatory frameworks with a possible impact on risk assessment for chemical incidents is potentially huge. Therefore, a selection of applicable regulatory frameworks is discussed. The following selection criteria were applied:

1. Legal frameworks for this chapter were based on the regulatory life cycle of a chemical substance. Chemicals undergo different subsequent stages, during which different exposure situations may arise. The evaluation of chemical exposure scenarios in the different stages include, for instance, the use of exposure scenarios in the specified regulatory framework for end/intended -usage (e.g. pesticides, biocides, REACH chemicals, veterinary or human pharmaceuticals, etc.), the production stage (including land-use planning), transportation and storage, occupational exposure, misuse (e.g. terrorism) and chemical incidents/accidents. For that reason, any chemical may be evaluated in more than one legal framework. For instance, the exposure of workers in the production stage of a pesticide is regulated under REACH, whereas the exposure of operators applying the pesticides or workers being exposed by re-entry is evaluated within the framework of the registration of pesticides. The present chapter focuses on those regulations and guidelines that deal with chemicals in situations where single, high and acute exposures might occur and where it is anticipated that information of interest for the present project might be available. Regulations that deal with exposures as a result of foreseeable use (e.g. operator exposure) or application (e.g. consumer products) are not included.
2. Applicable regulatory frameworks must be at an international level, at least European.

3. The regulatory frameworks must have a human health risk context. The (acute) human health risk had to be the main subject or at least be part of the legislative or guidance document. Environmental legislation, including also air and water quality regulations, was excluded.
4. In addition to the legal frameworks, the impact of the changes in EC or OECD guidelines for toxicity studies, which can be used for risk assessment purposes in existing regulatory frameworks, is considered relevant in terms of data needed for the derivation of AERVs.

Based on the criteria outlined above, the following legal frameworks were selected for review:
- Seveso II Directive;
- International Health Regulations;
- REACH;
- UN ECE Convention for Transboundary Effects of Industrial Accidents;
- Storage and transportation guidelines;
- Globally Harmonized System (GHS) – CLP Regulation (Classification, Labelling and Packaging);
- EU CBRNe Action Plan;
- OECD Guidelines for Acute Inhalation Toxicity Testing;
- Occupational Exposure Guidelines, as an example of a methodology developed by the European Commission.

Each of the selected legal frameworks will be described systematically in the following section, specifically addressing the following points:
- The primary goal and/or history and the general contents of the selected legal framework.
- An assessment of whether the regulatory framework provides guidance on toxicological data requirements that are also of importance for risk assessment purposes in single acute inhalation exposure scenarios (as described in Chapter 3).
- Differences (if any) between the data requirements as required by the selected legal framework and for the risk assessment of acute chemical incidents.
- Discussion as to whether the respective frameworks provide a statutory obligation to submit acute risk scenarios and/or a risk or exposure assessment for acute inhalational risk scenarios (including guidelines on how to perform them).
- An assessment as to which elements from the existing framework can be used to support the need for AERVs.
- An assessment as to whether individual legislation or regulation makes referral or provisions for applicability in the context of new and emerging risks.
- Conclusions and recommendations.

4.2 Seveso II Directive 96/82/EC

History and background

Many chemical substances are produced and stored in large quantities at major installations, a reflection of societal need for a myriad of purposes. Accidents in such locations can therefore produce widespread environmental contamination and subsequent exposure, with consequent significant human health risks (number of people exposed, intensity of exposure and frequency of exposure). Two major accidents in the 1970s form the basis for the development of

European legislation on major chemical industrial installations. In 1974, an accident occurring at a chemical processing plant in Flixborough, United Kingdom, released 40 tonnes of cyclohexane. It formed a vapour cloud 100-200 metres (320–650 feet) in diameter. The accident killed 28 people and seriously injured 36. Around 1,800 buildings within a mile radius of the site were damaged. The leaking of large amounts of dioxins from a factory in Seveso, Italy occurred in July 1976. Twenty-two thousand persons have been exposed (estimation), distributed across 11 townships. The contamination of soils was estimated at 2,000 ha. More than 250 cases of chloracne were diagnosed and 81,000 animals died or were slaughtered. Decontamination of the area began 6 months later and has lasted 5 years. The amount of dioxins released was estimated at up to 40 kg.

Consequently, the European Community put into force a Directive in order to prevent major accidents with dangerous chemicals or to limit the consequences thereof; this became the Seveso Directive. In 1997, this Directive was updated to the current Seveso II Directive. Since this is the only legislation specifically aimed at chemical accidents, its role in the derivation of health-based emergency response values is discussed in this section.

Legislation
The aim of the Seveso II Directive is two-fold. Firstly, it seeks to prevent major accidents involving dangerous substances. Secondly, as accidents do continue to occur, the Directive aims at the limitation of the consequences of such accidents, not only for humans (safety and health aspects) but also for the environment (environmental aspect). Both aims should be achieved by ensuring high levels of protection throughout the EU in a consistent and effective manner.

The scope of the Seveso II Directive deals solely with the presence of dangerous substances in establishments and thus does not cover transportation (see section 4.2.2). It covers both industrial installations as well as the storage of dangerous chemicals. Categories of dangerous substances covered under the Directive are defined by Directive 67/548/EEC (classification and labelling of dangerous substances) and Directive 1999/45/EC (classification and labelling of dangerous preparations). Establishments are considered covered by the regulation if they have quantities in excess of the threshold quantity indicated in the Directive of substances falling in one or more categories defined by the Directive. The categories include both a ‘toxic’ and very toxic’ category, as defined by 67/548/EEC. In addition, Annex 1, Part 1 contains a list of substances identified by name whose threshold quantities supersede the thresholds given for the categories to which they belong.

The Directive can be viewed as providing for three levels of proportionate controls (‘thresholds’) in practice, where larger quantities mean more controls. A company which holds a quantity of dangerous substance less than the lower threshold level given in the Directive is not covered by this legislation, but will be proportionately controlled by general provisions on health, safety and the environment provided by other national legislation that is not specific to major-accident hazards.

Companies that hold a larger quantity of dangerous substance, which is above the lower threshold, but below the higher threshold contained in the Directive, will be covered by the lower tier requirements. Companies that hold even larger quantities of dangerous substance (upper tier establishments), which are above the upper threshold contained in the Directive, will be covered by all the

requirements contained within the Directive. The Directive specifically excludes nuclear safety and carriage by pipeline.

The principal general and specific obligations are:

- The introduction of safety management systems with the development of new managerial and organizational methods. One of the main objectives underlined by this obligation is to prevent or reduce accidents with management-related causes, which have proven to be significant causative factors in over 90 per cent of the accidents in the European Union since 1982.
- Notification: The Directive includes an obligation to notify, under the principle that it is illegal for enterprises to hold large quantities of dangerous substances without informing the authorities.
- Major accident prevention policy and safety management systems: Operators are also required to establish major accident prevention policies and upper tier sites are further required to demonstrate implementation of the major prevention policy through a safety management system. The safety management system should include the part of the general management system that includes the organizational structure, responsibilities, practices, procedures, processes and resources for determining and implementing the major-accident prevention policy[7]. The risk assessment can be used to identify critical elements of the organization that contribute to accident prevention, such as communication between various actors involved in the process, training of key personnel, documentation of procedures and equipment parameters, budgeting resources for maintenance and upgrades, and other areas that depend on the management function.
- Safety report: Member states must require the operator to produce a safety report for the purposes of demonstrating that they are taking all necessary measures to control major hazards in accordance with the aim of the Directive. In particular, the operator must demonstrate that major-accident hazards have been identified and that the necessary measures have been taken to prevent such accidents and to limit their consequences. The operator is expected to conduct a risk assessment of the site and explain how measures for prevention, mitigation and emergency response are effective in reducing the risks identified in the assessment.
- Emergency plans: The Directive requires operators to establish internal emergency plans for response measures to be taken inside establishments. These plans must be supplied to the local authorities to enable them to draw up external emergency plans. Emergency plans have to be reviewed, revised updated and tested.
- Land-use planning: The land-use planning implications of major-accident hazards should be taken into account in the regulatory process. Member states are obliged to pursue the aim of the Directive through controls on the sitting of new establishments, modifications to existing establishments and new developments such as transport links, locations frequented by the public and residential areas in the vicinity of existing establishments. In the long term, land-use planning policies ensure that appropriate distances between hazardous establishments and residential areas are maintained. Risk assessment is a necessary component in land-use planning decisions in many member states.
- 'Domino effects': Member states are obliged to identify and facilitate exchange of information between establishments or groups of establishments

[7] Annex III of the Directive.

where the likelihood, possibility or consequences of a major accident may be increased because of the location and the proximity of such establishments, and their inventories of dangerous substances. Often the risk assessment is used as a tool for identifying 'domino effect' establishments.
- Information to the public: The SEVESO II Directive gives rights to the public in terms of access to information as well as consultation. Operators and competent authorities are expected to be pro-active, for example through the distribution of leaflets or brochures informing the public about what to do in the case of an accident.
- Accident investigation and reporting: Operators and competent authorities are required to analyse the causes leading up to major accidents, defined as accidents meeting one or more of the criteria listed in Annex VI. Subsequently, member states are obliged to report major accidents to the EC that fulfil one or more of the criteria defining a major accident (Annex VI). In order to fulfil its information obligations towards the member states, the Commission has established the Major-Accident Reporting System (MARS) and the Community Documentation Centre on Industrial Risks (CDCIR) at the Major-Accident Hazards Bureau established within its Joint Research Centre (JRC) in Ispra, Italy.
- Inspections: Competent authorities are obliged to organize an inspection system, which can either consist of a systematic appraisal of each establishment or of at least one on-site inspection per year. Inspectors will often check the risk assessment described in the safety report and also use it as a guide for planning inspection strategy.

A review of the Seveso II Directive 96/82/EC, the provisions of which have remained essentially unchanged since its adoption, is currently ongoing. The Directive will have to be amended due to changes to the EU system of classification of dangerous substances, to which the Directive refers. The EC Regulation No. 1272/2008 on classification, labelling and packaging of substances and mixtures (the 'CLP Regulation', published on 31 December 2008, will repeal Directives 67/548/EEC (DSD) and 1999/45/EC (DPD) by 1 June 2015. This classification system represents the EU adoption of the GHS classification into the European classification system (EU, 2010a).
This realignment was necessary because the GHS assigns different measures, categories and threshold levels from 67/548/EEC for a number of chemical hazards, both acute and long term. The Seveso II Directive acutely dangerous substance categories are derived directly from 67/548/EEC. Therefore, it has also become necessary to review the substance categories in Annex 1, Part 2 of the Seveso II Directive and adapt them to the new classification system. In 2008, the Directorate General for the Environment (DG-Environment), the policy secretariat for this Directive within the EC, began a series of initiatives as part of this process. In particular, it formed a Technical Working Group on Seveso and GHS to perform this exercise. Within this group, experts from member states, industry and other stakeholder groups assessed the options for realignment. The Technical Working Group explicitly aimed to find solutions that would impose the least changes to the current coverage of establishments. It delivered its proposals for a revised Annex 1, Part 2 to DG-Environment in April 2010. The DG is currently considering how the findings and options presented in this document may be reflected in its formal proposal for a revised Directive.

In addition, in preparation for revision of the Directive, DG-Environment launched a study to assess the impacts of various options for realigning Annex 1, Part 2 with the new CLP Directive. The final report, *Impact Assessment Study into possible options for adapting Annex I of the Seveso II Directive into*

the GHS, presents the results of the work, which will be taken into account in the ongoing process of reviewing the Seveso II Directive within DG-Environment (EU, 2010b).

Guidance on hazard and risk assessment for acute exposure scenarios
The SEVESO II Directive requires upper tier establishments to demonstrate that they have applied a systematic approach to identifying risks and associated appropriate prevention and mitigation measures within the safety report. This requirement essentially obligates upper tier sites to conduct a comprehensive risk assessment of the chemical hazards on site. Estimates of acute effects from exposure to individual toxic substances are commonly used in risk assessments of hazardous installations in order to evaluate the potential consequences of particular accident scenarios, and more generally, to support risk management decisions in relation to the application of appropriate preventive, mitigation and emergency management measures.

In addition, the potential consequences of different scenarios, as estimated within the risk assessment, and in particular in terms of residual risk, are of primary importance in the implementation of provisions within the Directive related to land-use planning (Article 12) and emergency planning (various Articles[8]). As a result, civil protection authorities at various levels of government are increasingly seeking to base their emergency preparations, as well as actions in the field[9], on risk assessments, which include estimates of the effects from single exposure to particular substances.

The acceptability of various risk assessment approaches, and how and when to apply acute exposure values, are not subjects addressed at European level and may or may not be specifically addressed at national or local level. Consistent with the principle of subsidiarity within the Treaty of the European Union, the detailed implementation aspects of the Seveso II Directive are left to local actors. Results from a survey of Seveso II competent authorities identified a wide range of acute toxic thresholds accepted in Europe for land-use and emergency planning activities associated with requirements of the Directive. Some member states assign the type of acute exposure value that should be used, through legislation or practical guidance, in risk assessments associated with land use and emergency planning. However, the majority of member states will accept the operator's choice provided that it is a well-known value and its use is justifiable. Values cited included many types of existing values (mainly of US origin), such as AEGLs, ERPGs and TEELs or nationally developed acute thresholds, as is the practice in France, the UK and the Netherlands.

In order to promote a more unified approach to land-use and emergency planning in Europe, a scientific collaboration to develop acute exposure thresholds for chemicals was established within the EU ACUTEX project (2002-2005). The goal of the project was to develop a methodology to determine AETLs. Although the project achieved its objective, some technical

[8] Several articles within the Directive contain emergency planning requirements, including Article 8 (domino effects), Article 10 (internal emergency planning in the context of safety reports) and Article 11 (external emergency plans).

[9] This paper uses the term 'risk assessment' to include not only the formal methods of risk assessment that are in place for prevention, mitigation and land-use planning purposes, but also 'rapid risk assessments' that support decisions that emergency responders are obliged to take on-the-spot in the event of a major incident.

aspects remained unresolved by the end of the project. Moreover, the lack of a European process to oversee or verify the values has stalled it except for broad application of EU values at European level (ACUTEX, 2006).

In terms of the potential revision to the Seveso II Directive, a key finding from the Technical Working Group's assessment related to the current Seveso toxic categories. The differences between the 67/548 toxic categories and the toxic categories of the CLP Regulation are substantial for some exposure pathways and types of substance. Thus, indirectly through the REACH regulation described later in this chapter, a revised Seveso could give more urgency to having good quality toxicological data, and European consensus on how these data are analysed, particularly for certain substances on the margins of new toxic categories as defined in a revised Seveso Directive.

Need for AERVs
The Directive highlights the need to assess major chemical installations and to record the hazards posed by chemicals utilized and/or stored on site if given amounts are exceeded. There is therefore a need for AERVs to support decision-making for emergency and land-use planning related to the control of major-accident hazards, underlining the need for identifying a Europe-based team, such as a development or validation/approval centre, dedicated to the development of acute exposure levels.

The development of AERVs for such high production volume/ toxic industrial chemicals would enhance planning and preparedness and emergency response, thereby reducing community impact.

Emerging threats
Currently, no policy decisions have been taken following ACUTEX to promote further harmonization of risk management measures for land-use and emergency planning. Convergence of acute exposure levels and stronger collaboration on their development are still important questions at EU level and in an international context. The Directive only covers hazardous chemicals if they exceed a given threshold. Therefore, emerging threats would be covered by this legislation only if a chemical substance were sufficiently hazardous and produced at sufficient volume.

Conclusions and recommendations
In summary, application of the Seveso Directive in Europe implies:
- a need for generally accepted AERVs to support decision-making for emergency and land-use planning related to the control of major-accident hazards;
- a benefit from sharing, at a European level, scientific data and common principles of extrapolation for producing AERVs;
- the importance of identifying a Europe-based team, such as a development or validation/approval centre, dedicated to the development of acute exposure levels.

At this time, no policy decisions have been taken following ACUTEX to promote further harmonization of risk management measures for land-use and em ergency planning. Convergence of AERVs and stronger collaboration on their development are still important questions at EU level and in an international context.

4.3 REACH

History and background
In the EU, the regulation 2006/1907, called REACH for Regulation, Evaluation, Authorization and restriction of Chemicals, was adopted on 18 December 2006 and entered into force on 1 June 2007.

Legislation
The regulation aims to:
- improve the protection of human health and the environment from the risks that can be posed by chemicals;
- enhance the competitiveness of the EU chemicals industry, a key sector for the economy of the EU;
- promote alternative methods for the assessment of hazards of substances;
- ensure the free circulation of substances on the internal market of the EU.

In principle, REACH applies to all chemicals: not only chemicals used in industrial processes, but also in everyday life, for example in cleaning products and paints as well as in articles such as clothes, furniture and electrical appliances. REACH places greater responsibility on industry to manage the risks that chemicals may pose to health and the environment. The system is coordinated by ECHA (European Chemical Agency), which has been created within the implementation process of the regulation.

REACH replaces about 40 previous pieces of legislation with an improved regulation. Other legislation regulating chemicals (e.g. cosmetics, detergents) or related legislation (e.g. health and safety of workers handling chemicals, product safety, construction products) not replaced by REACH will continue to apply. REACH has been designed not to overlap or conflict with the other chemicals legislation.

REACH is closely linked to CLP Regulation (see section 4.4) and regulation 2008/440 on EU test methods, which should be followed to fulfil the information requirement described in annexes VII to X of REACH.

All manufacturers and importers of chemicals must identify and manage risks linked to the substances they manufacture and market. For substances produced or imported in quantities of 1 tonne or more per year per company, manufacturers and importers need to demonstrate that they have done so appropriately by means of a registration dossier, which shall be submitted to the Agency.

Once the registration dossier has been received, the Agency may check that it is compliant with the Regulation and shall evaluate testing proposals to ensure that the assessment of the chemical substances will not result in unnecessary testing, especially on animals. If appropriate, competent authorities may also select substances for a broader substance evaluation to further investigate substances of concern.

REACH also foresees an authorization system aiming to ensure that substances of very high concern are adequately controlled, with progressive substitution by safer substances or technologies or only used where there is an overall benefit for society. These substances will be prioritized and over time included in Annex XIV. Once they are included, industry will have to submit authorization applications to the Agency for continued use of these substances. In addition, EU

authorities may impose restrictions on the manufacture, use or placing on the market of substances causing an unacceptable risk to human health or the environment.

Manufacturers and importers must provide their downstream users with the hazard and risk information they need to use the substance safely. This will be done via the classification and labelling system (CLP Regulation) and Safety Data Sheets (SDS), where needed.

Substances can be exempted from all or a part of the obligations under REACH. For example, substances described in Annexes IV and V are exempted, as well as radioactive chemicals. The overall exemptions are pharmaceuticals, farm-produce substances, biocides, pesticides, substances used for national defence etc., as described in Article 2.

Guidance on hazard and risk assessment for acute exposure scenarios
For substances produced or imported at more than 1 tonne per year, the registrant should submit a registration dossier, which includes a hazard characterization of the substance.

The extent of the information requirements for hazard characterization depends on the tonnage, following Annexes VII to X. In addition, for hazardous chemicals produced or imported at a tonnage of more than 10 tonnes/year, a risk assessment is required for specific uses, target populations and durations of exposure.

Guidance has been developed over the past few years for industry and the authorities to encourage a smooth implementation of REACH. The Guidance Documents, sometimes referred to as REACH Implementation Projects (RIPs), were drafted and discussed within projects led by the EC services, involving stakeholders from industry, member states and non-governmental organizations. Finalized Guidance Documents may be found at the following website: http://guidance.echa.europa.eu/guidance_en.htm#GD_PROCC_I.

The REACH Regulation and Guidance Documents and/or exposure scenarios do not specifically address emergency situations; the primary objective of the REACH regime is designed to address 'normal uses' of the chemicals and not accidental or deliberate exposures.

However, REACH guidance on how to establish the "Derived No Effect Level" (DNEL), used for the risk assessment and management, presents some similarities with existing methodologies for the setting of acute thresholds like the AEGL or the AETL methodologies. This guidance is described in chapter R.8 'Characterisation of dose [concentration]-response for human health' with a focus on acute toxicity on chapter R8.2.1. and R8.8. (http://guidance.echa.europa.eu/docs/guidance_document/information_requirements_r8_en.pdf?vers=20_08_08.)

The general concept of DNEL derivation is illustrated in Figure 4.1.

The guidance proposes general concepts of the dose-response characterization, including selection of the dose descriptor and uncertainty factors, which could be used even for short-term exposure duration. Nevertheless a, specific paragraph is dedicated to the dose descriptor for acute toxicity (R8.2.1). Here, it is stated that the selection of dose descriptor for acute exposure/toxicity may be difficult.

It is proposed to take as the ideal starting point for the derivation of the acute toxicity DNELs, and NOAELs or LOAELs for sublethal effects, such as local respiratory irritation caused by cytotoxicity or CNS depression, although it is recognized that frequently only data from LD_{50} studies are available.

For some of those dose-descriptors, such as in emergency situations, rescuers need action levels based on observed effects at levels of toxicological concern and therefore NOAELs are not the most suitable PoD. In addition, in case of the same PoD for both DNELs and an AERV, the final thresholds differ due to the application of different uncertainty factors. The choice of descriptor is summarized in Table 4.1.

If no dose descriptor is available for acute toxicity, then a qualitative risk characterization is recommended.

In appendix R8.8 on acute toxicity, one can find more detailed guidance for this kind of exposure. Guidance is provided on the identification of a typical dose descriptor, the use of alternative data, modification of the dose descriptor and application of AFs (pp. 106–114 of the guidance).

Need for AERVs
Guidance on derivation of DNELs is similar in principle to guidance documents for acute exposure thresholds developed by NAC-AEGL, ACUTEX TGD for accidental exposures. There are, however, fundamental differences. DNELs are derived to provide **safety** levels, below which effects are not expected to occur, whereas AERVs are **predictive** threshold levels above which effects are expected to occur in susceptible subpopulations.

Guidance is also provided on other endpoints that may appear during single exposures, such as corrosion and irritation of the skin and eyes, and sensitization (both skin and inhalation routes).

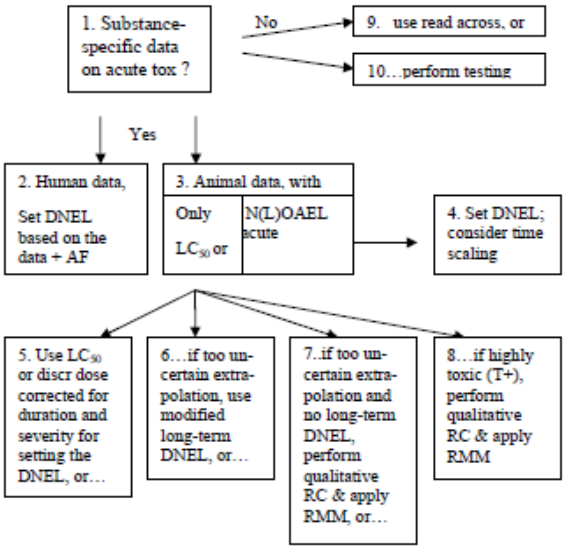

Figure 4.1. Decision tree for setting an acute inhalation toxicity DNEL. (RMM: risk management measures.)

Table 4.1. Summary of dose descriptor within REACH.

Dose descriptor	**Modification of the dose descriptor (over and above that described in the general guidance)**	**Selection of assessment factors (over and above those described in the general guidance)**
N(L)OAEL from animal acute toxicity studies	Consider time scaling by applying the modified Haber's Law	Consider additional factor to account for the inherent deficiencies of acute toxicity studies
N(L)OAEL from animal repeated dose toxicity studies	Time scaling might be inappropriate	
$LD(C)_{50}$ or discriminating	Consider time scaling by applying the modified Haber's Law	Apply additional severity factor; determine its magnitude by considering the whole tox database
N(L)OAEL from human data	Consider time scaling by applying the modified Haber's Law	
N(L)OAEL for local cytotoxic effects on the respiratory tract	Consider time scaling by applying the modified Haber's Law	

No specific guidance is provided on the endpoints described in Chapter 3 for single exposures. The guidance document deals with the reproductive endpoint, neurotoxicity and carcinogenicity only for chronic exposures. Sensory awareness is too specific to emergency situations to be taken into account by the REACH requirements.

An important point is that the REACH regime encourages the limitation of animal experimentation due to animal welfare considerations. Such a requirement introduces the development and the use of data provided by non-animal means like *in silico* (QSARs) and *in vitro* methods, and read-across approaches.

Until now, even if the AEGL SOP does not describe this issue. The AEGL Committee used to apply the read-across approach when there was a lack of toxicological data in the context of the category/family of chemicals or when the stability of a chemical in the atmosphere is so brief that it is more relevant to use the thresholds for its products of decomposition. Read-across is not described by the other methodologies. The use of QSARs is also a challenge for acute threshold setting, in particular for poor-data substances. This point should be further explored in detail by scientists. Furthermore, the new publication of updated OECD TG 403 and new TG 436 implies the availability of new data for the inhalation route, like the $C \times t$ approach.

Emerging threats
As the purpose of the REACH framework is to assess the toxicity of newly developed compounds, it therefore provides a mechanism for assessing emerging threats.

In addition, if regulators plan to extend the field of REACH to single exposures, one should explore the relevance of the DNEL concept to acute exposure situations. Currently, it is clear that the DNEL methodology is too generic to answer the specificities of single exposures. This last point supports the need for AERVs and supporting documentation.

Finally, REACH also introduces a new task for toxicologists and AERV setting with the promotion of alternative methods and non-animal testing: namely, how to interpret *in silico* and *in vitro* results when establishing acute exposure values. This will pose a considerable challenge.

Conclusions and recommendations
REACH is primarily concerned with long-term exposures as opposed to acute. However, the revision of the Regulation is scheduled for every two years and the issue of single exposures may rear its head, in particular in the context of workers' exposures and the revised Seveso II Directive. Single exposures of chemicals are not clearly dealt with in the Guidance Documents or Requirements; it is of real significance when considering the life cycle of a chemical.

With regulators extending REACH's responsibility to single exposures, one should explore the relevance of the DNEL concept to acute exposure situations. Currently, it is clear that the DNEL methodology is too generic to answer the specificities of single exposures. There is therefore a need to develop AERVs, with supporting documentation.

REACH introduces a new challenge for toxicologists and AERV setting with promoting alternative methods and non-animal testing, in particular interpreting *in silico* and *in vitro* results when establishing acute exposure values. This will pose a considerable challenge.

4.4 GHS / CLP

History and background
The CLP Regulation 1272/2008 (for 'Classification, Labelling and Packaging') is an EU Regulation that aligns the EU system of classification, labelling and packaging chemical substances and mixtures to the GHS (Globally Harmonised System of Classification and Labelling of Chemicals). The GHS was developed to minimize global differences between systems of different jurisdictions for classification and labelling. It is expected to facilitate global trade and the harmonized communication of chemical hazard information, to promote regulatory efficiency and of course to provide protection from the hazardous effects of chemicals.

Legislation
The CLP Regulation complements the REACH Regulation (EC No 1907/2006) and from 1 June 2015 will replace the current system contained in the Dangerous Substances Directive 67/548/EEC (DSD) and the Dangerous Preparations Directive 1999/45/EC (DPD).

The Regulation incorporates the classification criteria and labelling rules agreed at UN level, the GHS. The GHS introduces new classification criteria, hazard symbols (pictograms) and labelling phrases, taking into account existing systems, such as the EU Supply and Use System, the Canadian pesticide

systems, the Group of Experts on the Scientific Aspects of Marine Environmental Protection (GESAMP) hazard procedure, the International Maritime Organization (IMO) Scheme for Marine Pollutants, the European Road and Rail Transport Scheme (RID/ADR), and the US Land Transport Scheme (for transport, see section 4.7).

The CLP Regulation requires companies to appropriately classify, label and package their substances and mixtures before placing them on the market. It aims to protect workers, consumers and the environment by means of labelling that reflects the possible hazardous effects of a particular chemical. It also takes over provisions of the REACH Regulation regarding the notification of classifications, the establishment of a list of harmonized classifications and the creation of a classification and labelling inventory.

The classification of chemicals is to reflect the type and severity of the intrinsic hazards of a substance or a mixture. It should not be confused with risk assessment, which relates a given hazard to the actual exposure of humans or the environment to the substance or mixture featuring this hazard. Nevertheless, the common denominator for both classification and risk assessment is hazard identification and hazard assessment.

Guidance on hazard and risk assessment for acute exposure scenarios
The CLP Regulation and GHS are more practical systems than, for example, the REACH Regulations. Nevertheless, Guidance Documents have been developed to help industry to classify their substances and mixtures. These documents have been discussed in the framework of the REACH Regulation and are available on the REACH navigator website.
Two Guidance Documents are available, one on the general principles and the other on the application of the CLP criteria:
http://guidance.echa.europa.eu/docs/guidance_document/clp_introductory_en.pdf and http://guidance.echa.europa.eu/docs/guidance_document/clp_en.pdf

The Guidance Document on the application of the CLP criteria has been developed to assist primarily manufacturers or importers applying classification and labelling criteria; it also includes practical examples. Guidance is available for generic points as read-across, specific limit concentrations but also for different subjects, e.g. physical and chemical, human health and environmental endpoints.

Chapter 3.1 (pp.192–221) focuses on acute toxicity criteria and how to classify for this endpoint. It provides guidance on information identification in human and non-human data, evaluation of hazard data and classification. Inhalation route exposure is taken into account and specific guidance is given. For example, considerations regarding corrosive substances, aerosols or bioavailability by the inhalation route may help the reader to identify critical aspects.

Need for AERVs
No specific methodology is provided for the determination of AERVs, but the data required by REACH and submitted to ECHA may be relevant for AERV derivation. In other words, classification depends on the value (calculated or estimated) of the lethal dose or lethal concentration (associated with 50 per cent mortality). In some cases, the same studies could be used for setting AERVs, in particular for the tier 3 level (mortality or life threatening). Classification of a substance for endpoints that are relevant for AERV derivation, such as irritation

of the eyes and the upper respiratory tract, reproductive toxicity, carcinogenicity and neurotoxicity, provide important information on toxicity hazards.

These endpoints are mentioned in the chapter on specific target organ toxicity – single exposure (STOT-SE). The data used for the classification as STOT-SE may be a relevant source for the determination of AERVs.

The CLP Regulation is aimed primarily at Classification and Labelling (C&L) and focused on predefined distinct concentration cut-off points for C&L as an intrinsic property of a substance. The resulting symbols/values are not fit for use in the context of emergency response. In addition, as the requirements are only a categorization of the acute toxicity according to set cut-off points, the underlying studies may have different requirements, resulting in acute inhalation toxicity studies that are less fit for use as PoD for emergency values (example: TG 436 versus TG 403 data). For emergency use, the aspects irritation of the eyes (and skin) are also interesting and to be taken into account as these toxic effects could lead to escape impairment.

Emerging threats
The Regulations do not specifically address emerging threats.

Conclusions and recommendations
The GHS / CLP Regulations focus on existing substances and provide common language elements for hazard classification and labelling. This common framework helps the storage and the safe transportation of chemicals through provision of hazard information.

The implementation of the CLP Regulation within the Seveso III draft European Directive brings the CLP to cooperate with AERVs but the CLP Regulation and its associated guidance do not provide sufficient framework for developing AERVs.

4.5 OECD Guidelines: Acute inhalation toxicity testing

History and background
Acute inhalation toxicity can be defined as the total of adverse health effects caused by exposure to a characterized concentration of a mixture of chemical substance(s) over a single exposure period of less than 24 hours. The airborne concentration may represent vapours, gases and/or small particles. At present, acute toxicity testing predominantly utilizes mortality as the toxicity endpoint; non-lethal effects are only scored and reported to a limited extent. For use within regulatory frameworks, these inhalation studies have to meet specific criteria with regard to design of the study, GLP (Good Laboratory Practice) and outcome of the study (either point values – LC_x, ranking concentrations, concentration versus time relationships etc.), which were laid down in the original OECD Guideline 403. The first version of this guideline dates back to 1981.

Legislation
In the context of the regular reviewing programme of the OECD test guidelines, a renewal of the OECD TG 403 and the development of OECD TG 436 were initiated. OECD Guidance Document 39 (OECD GD39) on acute inhalation toxicity testing (April 2009) was written to 'assist the regulated community and regulator in selecting the most appropriate acute inhalation TG, so that particular data requirements can be met while reducing animal usage and suffering'.

The OECD TG 403 describes the traditional acute inhalation (LC_{50}) toxicity study in which animals are exposed to one concentration (limit test) or at least three concentrations of the test substance, using five males and five females (or five animals of the most susceptible sex, if known) for a fixed period of time (usually 4 hours). The revised version comprises both this traditional approach as well as a new approach, the concentration versus time approach (the so-called $C \times t$ protocol). This makes it possible to derive a concentration-response relationship over a range of exposure durations, i.e. to determine the relationship $C^n \times t = LC_x$, thus making it possible to calculate the concentration for a range of exposure durations that will result in a mortality of x per cent. The $C \times t$ protocol is recommended to be used whenever there is a specific regulatory or scientific need that calls for the testing of animals over multiple exposure durations, such as for purposes of emergency response planning (e.g. AEGL values) or land-use planning. A statistical simulation analysis has demonstrated that using two animals per $C \times t$ combination (one per sex using both sexes or two of the most susceptible sex) may generally be adequate when testing four or five concentrations for multiple exposure durations and as such has as good a statistical basis as the other approaches with the same total number of animals. A $C \times t$ study with four or five exposure concentrations and five durations will yield 20 or 25 data points, respectively. With these data points, the $C \times t$ relationship can be calculated using statistical (probit) analyses (see section 3.4.2).

The alternative Test Guideline OECD TG 436 is a new guideline on 'Acute inhalation toxicity – acute Toxic Class Method-ATC' and is purely designed to rank toxicity of chemical substances for classification and labelling purposes (i.e. to estimate whether the LC_{50} ≤100 ppm, or >100-500 ppm, or >500-2500 ppm etc.) according to GHS. This design uses fewer animals than both the original and the new OECD TG 403 and suffices for classification and labelling, but does not provide robust LC_x values.

According to Guidance Document OECD GD39 acute inhalation should be tested as a rule, unless there is compelling reason not to: humane, scientific or practical. For instance, testing of substances with GHS category 5 toxicity is discouraged. In addition, the physical form of a substance may preclude human inhalation, waiving the need for an acute inhalation toxicity study. These considerations already minimize the number of acute inhalation studies performed in general. As a second rule, in view of animal welfare considerations in all legal frameworks, the use of laboratory animals must be kept as low as possible.

Guidance on hazard and risk assessment for acute exposure scenarios
From the above, the type of study design chosen by a company will usually fit the minimal requirements for classification and labelling, at the same time using the minimum number of laboratory animals, depending on the registration requirements of the regulatory framework. OECD GD 39 (OECD GD 39) clearly indicates that OECD TG 436 is usually the preferred method of choice. Only if there is a regulatory or scientific requirement for an assessment of the concentration-response relationship, with or without a detailed analysis of the $C \times t$ relationship, is OECD TG 403 preferred. Since in most regulatory frameworks (pesticides, biocides, REACH etc.), the basic requirement of an acute inhalation study is the Classification and Labelling in agreement with GHS, and there will be a shift from determination of a concentration-response relation (OECD 403) to ranking concentrations (OECD 436).

Need for AERVs
The derivation of AERVs, toxicity information of different levels of severity and over a range of exposure concentrations and durations, is needed because incidental chemical releases and accompanying human exposures also vary greatly in concentration and time. As such, determination of the concentration-time relationships at effect levels of varying severity is very important. For the purpose of AERV derivation, studies performed in accordance with the $C \times t$ approach as taken up in the new OECD 403 are suited perfectly as point of departure. Performance of the OECD 436 does not provide relevant quantitative information for emergency response planning or land-use planning purposes.

In the absence of a legal framework for deriving AERVs, there is no regulatory framework that has defined data requirement for the performance of specifically designed acute inhalation toxicity studies. The acute inhalation toxicity studies available now for the purpose of deriving AERVs are generally performed within the data requirement package of other regulatory frameworks, such as new and existing chemical substances (now under REACH), biocides, pesticides, veterinary, pharmaceutical or otherwise. Within these frameworks, the choice of study design is driven by OECD GD 39, leading to lethality data that are unsuitable for the derivation of AERVs. Furthermore, because the focus of the acute (inhalation) toxicity studies is on classification and labelling for lethality, the studies usually do not provide information on sublethal or even less severe acute (local or systemic) effects, which are also relevant effect levels for AERV derivation.

The new OECD Guideline 403 provides guidance on the toxicological data requirements that are also of importance for risk assessment purposes, deriving AERVs as described in the methodology section in Chapter 3. However, in the absence of a general regulatory framework dictating the need for deriving AERVs, the regulatory and scientific provisions to perform an acute inhalation toxicity study according to OECD 403 are not met in practice. For the derivation of adequate AERVs this study design is highly recommended. Although different regulatory frameworks provide a statutory obligation to submit acute inhalation toxicity data, the purpose of this demand differs significantly, thereby influencing the study design.

Emerging threats
The new OECD 403 ($C \times t$) addresses the relevance of this new approach for emergency response planning and, as such, AERVs. The OECD GD 39 does not address this issue explicitly, but only refers to specific regulatory or scientific needs.

Conclusions and recommendations
The newly developed $C \times t$ approach, as included in the revised OECD 403, is an improvement for acute inhalation toxicity testing in the context of deriving AERVs. This relevance is also clearly stated in the test guideline. However, the accompanying OECD GD 39 clearly steers its reader in the direction of the performance of acute inhalation studies using the acute toxic class method (OECD TG 436). The $C \times t$ approach is only recommended in case of specific regulatory demands, which will not often occur within the existing frameworks. Weighing the data needs for the purpose of deriving a quantitative concentration-response relationship over a range of exposure durations in the decision-making process for acute toxicity testing is no common practice. Existing regulatory frameworks do not require the assessment of acute chemical incident scenarios when defining data requirements for purposes of registration

or notification. Consequently, it is expected that, in future, more and more acute inhalation toxicity studies will be performed in accordance with the newly proposed test guideline OECD 436. This will generally provide acute inhalation toxicity data that are not suitable as point of departure for the derivation of AERVs. Therefore, this will make it more difficult, if not impossible, in the future to adequately assess and manage health risks of single chemical exposures through incidental or deliberate release of chemicals. It is therefore recommended to pay attention to the issue of acute chemical incident scenarios in the various international regulatory frameworks, also on the level of basic toxicological data requirements for registration.

4.6 International Health Regulations

History and background

The International Health Regulations' (IHR) origins lie with the International Sanitary Regulations adapted at the International Sanitary Conference held in Paris in 1851. This reflected the recognition of a need for international cooperation following the European cholera epidemics of 1830 and 1847. Following the establishment of the WHO constitution in 1948, the International Sanitary Regulations were revised and subsequently became the International Health Regulations. The original regulations required notification of only a very small range of communicable diseases, such as cholera, plague and yellow fever, and did not recognize other environmental threats, such as chemical and radiation events.

Legislation

In 1995, the IHR were amended and required 194 countries across the globe to report both disease outbreaks and other Public Health Emergencies of International Concern (PHEICs), and thus include, in addition to communicable disease, chemical and radiation events also. The objective is to limit disease spread whilst minimizing international public health impact. The IHR also stipulate that each country must strengthen public health capacity and resilience for detection, alerting and subsequent response to PHEICs. As such, public health professionals need to be competent with respect to planning and preparedness for, and subsequent response to, chemical incidents.

According to the IHR (2005) a PHEIC refers to an extraordinary public health event that:

a) constitutes a public health risk to other states through the international spread of disease (or disease precursors such as chemicals in air, water, food or articles); and
b) potentially requires a coordinated international (health) response.

To meet the requirements of IHR (2005), countries are required to establish a set of core capacities, including an acute chemical risk assessment (Annex 1 of the Regulations).[10]

Guidance on hazard and risk assessment for acute exposure scenarios

The IHR do not specifically refer to hazard and risk assessment, merely to the need to alert and notify with regard to PHEIC, including chemical events.

[10] http:/www.who.int/csr/ihr/en/

Need for AERVs
The requirement to be able to respond in a timely and effective manner implies a need to be aware of chemical hazards and to ensure that risk is assessed, prioritized and mitigated, with subsequent emergency planning and preparedness for major industrial accidents and deliberate release alike. Therefore, the IHR lend themselves to enhancing planning and preparedness, an important component of which is quantifiable risk assessment, including tools such as AERVs.

Emerging threats
The Regulations give no specific guidance regarding emerging threats and are not designed to address this issue.

Conclusions and recommendations
The IHR provide a tool for international alerting regarding major incidents of public health concern and thus facilitate international communication, which may in turn lead to cooperation, collaboration and mutual aid. Therefore, the IHR are not a basis for development of AERVs, but rather an enhancement of but one aspect of preparedness, namely detection and alerting. Be that as it may, enhanced international collaboration as a consequence of mandatory notification may provide a vehicle for enhanced preparedness in other areas, including the development of AERVs.

4.7 Storage and transport of chemicals

History and background
International harmonization is based on recommendations at UN level. These are provided in the so-called 'Orange Book' (*United Nations Recommendations on the Transport of Dangerous Goods*), which are derived from the recommendations of the UN Committee of Experts. These recommendations form the basis for a series of codes covering classification, packaging and labelling of dangerous goods for transport by road, rail, sea or air.

The UN classification system for chemicals for transport differs from that for supply principally due to historical legislative actions of countries placing separate requirements for production and transport. However, following the UN agreement on the Globally Harmonised system for classification and labelling of chemicals (GHS), steps are being taken to harmonize both systems on the GHS recommendations. Recently, the European Parliament and Council adopted a new Regulation on the classification, labelling and packaging of substances and mixtures, which will incorporate the classification criteria rules agreed at UN level (EC 1272/2008).

The UN recommendations are implemented worldwide through various international protocols, conventions or model agreements.

Legislation –Transport
In outline, the following regulations apply in the EU to implement the UN recommendations for transport. These are based on the Model Regulations for Transport of Dangerous Goods developed by the UN Economic Commissions for Europe (www.unece.org/trans/danger/publi/unrec/rev13/13nature_e.html).

These regulations provide a classification system for categorization of hazardous chemicals based upon specific characteristics. Chemicals are classified according to whether they are Explosive, Flammable, Toxic, Oxidizing, Peroxides, Corrosive, Infectious, Radioactive or Miscellaneous chemicals. The classification allocates codes in the form of UN numbers to the aforementioned types of chemicals and thus provides a standardized means of recognition.

Legislation for inland transport of dangerous goods is enacted by Council Directive 2008/68/EC (see http://ec.europa.eu/transport/index en.htm). This incorporates earlier Directives for specific transport types (as detailed below), together with additional requirements for inland waterways.

Transport – Road
Road transportation is covered by Council Directive 94/55/EC as the approximation of the laws of member states with regard to the transport of dangerous goods by road: 'European agreement concerning the international carriage of dangerous goods by road (ADR)'. (ADR sets out the requirement for classification, labelling and packaging dangerous goods transported by road; it is updated every 2 years). Transported goods are legally classified as dangerous if they are included in the list drawn up by the UN transport recommendations, and consequently appear in Annex A to the ADR. The UN list covers over 3,000 different substances, which have been catalogued by the International Chemical Safety Cards system (ICSC). These substances are classified by means of a four-digit UN code, termed the UN Number, as described earlier.

Transport – Rail
The international carriage of dangerous goods by rail within Europe is governed by Annex I of the Convention Concerning International Carriage by Rail *(COTIF*, Convention de l'Organisation Intergouvernmentale pour les Transports Internationaux Ferroviaires*).* Annex I refers to the Regulations Concerning the International Carriage of Dangerous Goods by Rail*.* It is more commonly known as 'RID' (Règlement Concernant le Transport International Ferroviaire des Marchandises Dangereuses*)* and is enacted by European Council Directive 96/49/EC.

RID controls the conditions under which transit is undertaken and establishes a uniform system to facilitate the continuing development of international rail traffic. Regulations include dangerous goods lists, special provisions and exemptions related to limited and excepted quantities, use of packaging, consignment procedures and provisions concerning the conditions of carriage, loading, unloading and handling. The procedures and classifications apply the UN model requirements.

Transport – Sea
Transportation by sea is by far the most effective means for carriage of large volumes of dangerous goods. Estimates indicate some 2,000 hazardous and noxious substances (HNS) carried regularly by sea with bulk trade of 165 million tonnes per year worldwide (www.itopf.com/informationservices/publications/papers/HNSPapers.html).

European legislation is based upon international conventions developed by the International Maritime Organisation (IMO) and incorporated within the European Third Maritime Safety Package. This includes directives on all aspects of maritime transport.

Adopted conventions from IMO include Safety of Life at Sea (SOLAS) and the International Convention on the Prevention of Pollution from Ships (MARPOL) (http://www.imo.org/). MARPOL provides details on oil, liquids and packaged goods, and classifications based upon harmful effects to human health and the marine environment. The conventions have developed labelling and classification systems, including the International Maritime Dangerous Goods (IMGD, 2008) packaged goods code based upon the UNECE system, as well as codes for bulk liquids (liquid intermediate bulk containers; IBC numbers), gases (liquefied gases in bulk; ICG code) and solids (bulk containers; BC).

Recent developments have included the implementation of the Protocol on Preparedness, Response and Co-ordination to Pollution Incidents from Hazardous and Noxious Substances (OPRC-HNS Protocol 2000), which places requirements for provision of resources and expertise to respond to incidents involving HNS, as well as procedures for compensation. HNS exclude oil and are defined according to studies of chemical effects on human health and environmental damage developed from studies by the Joint Group of Experts on the Scientific Assessment of Marine Environmental Protection (GESAMP). Acute health effects using LC_{50} and LD_{50} data for inhalation, oral and dermal exposure are incorporated into the assessment.

Transport – Air
International Civil Aviation Organisation (ICAO) technical instructions form the basis for legislation and control in Europe and internationally. The principles employed are analogous to provisions required for packaged goods carried by other forms of transport. Airlines generally work to IATA (International Air Transport Association) rules, which are based on these ICAO technical instructions.

Legislation – Storage
Most countries have a requirement that chemicals and dangerous substances are stored and handled in such a way that minimizes risks posed by the substances and limits exposure e.g. in the UK under the Control of Substances Hazardous to Health (COSHH). COSHH Regulations serve to protect employees from hazards posed by substances used in the workplace. This involves a risk assessment, control of exposure, health surveillance and planning for incidents. Such activities are also considered within planning policy in order to mitigate risks in respect to the environment air quality and statutory nuisance such as those associated with odours and noise.

There does not appear to be any EC Regulation/Directive that specifically covers storage of dangerous chemicals, excepting those with certain hazardous characteristics such as flammable and explosive properties. However, the Directives relating to major hazards from chemical accidents place requirements on thousands of industrial sites where dangerous substances are used and stored in quantities exceeding specified thresholds. These are contained within the Seveso II Directive, which has been discussed in detail previously in this report (see section 4.2).

Whilst the above do not prescribe exposure limits in respect of operations, they require appropriate risk assessments to be undertaken, including exposure assessment both to workers and the wider public.

European Framework Directive 89/391/EEC places requirements on member states to assess and control chemical risks in the workplace, while Directive 98/24/EC covers risks in the workplace from chemical agents, both of which include requirements to assess and control risks from chemicals stored in the workplace (see section 4.10).

Issues associated with wider public health are generally addressed by national quality standards, which provide health based exposure limits. These are typically protective of susceptible groups in respect of chronic risk and single exposure but are limited to a very small number of key pollutants as covered by European Directive 1999/30/EC and its implementation in member states.

In addition to the above, EC Directive 96/61/EC (now 2008/1/EC) sets requirements for industrial pollution prevention for specified industrial operations, known as integrated pollution prevention and control (IPPC). In essence, the IPPC Directive is about minimising pollution from various industrial sources throughout the EU. Operators of industrial installations' activities covered by Annex I of the IPPC Directive are required to obtain an environmental permit from the authorities in the EU countries. About 52.000 installations are covered by the IPPC Directive (http://ec.europa.eu/environment/air/pollutants/stationary/ippc/summary.htm). The Directive requires suitable control of process emissions, including controls for chemicals stored on sites.

Further development of exposure limits is now being undertaken as part of the REACH programme, which is discussed further below (see section 4.3).

Guidance on hazard and risk assessment for acute exposure scenarios
Human health risk from acute exposure is determined from animal LC_{50} and LD_{50} data, with subsequent utilization of uncertainty factors to account for inter- and intraspecies differences. Substances are arbitrarily divided according to respective LC_{50} and LD_{50} values. Accordingly, substances with an LC_{50} (inhalation) of less than 5,000 ppm based upon rats exposed for 1 hour, are considered acutely toxic, while an LC_{50} (inhalation) of less than 200 ppm is the threshold for very toxic substances. As well as inhalation, acute toxicity assessment may also consider dermal LD_{50} data, based upon 24-hour contact tests and mortality within 14 days and on oral LD_{50} data, single dose with mortality within 14 days.

Need for AERVs
The legislation for transport or storage does not specifically require risk assessment, but the comprehensive information on volumes of hazards transported lends itself to risk prioritization and subsequent implementation of AERVs.

Emerging threats
The legislation does not specifically cover emerging threats.

Conclusions and recommendations
There is extensive and rigorous national and international legislation and regulation for the storage and transport of chemicals by sea, rail, road and by air. Regulation demands that the physico-chemical and toxicological properties of such chemicals are appropriately labelled and displayed, together with information on incident management. There is therefore extensive information on the volumes and characteristics of chemicals stored and transported that

could form the basis for risk prioritization and a subsequent basis for development of AERVs.

4.8 Waste Directive

History and background

Hazardous waste can, as a consequence of either accidental or deliberate release, result in significant environmental contamination, exposure and subsequent public health impact. Communities so exposed may experience both acute and chronic health effects, requiring extensive and prolonged coordinated emergency response. The EU Directive of 12 December 1991 (Council Directive 91/689/EEC) defined hazardous waste in article 1:4. Three annexes restrict hazardous waste to named substances and substance categories.

Hazardous waste generation is still increasing. It grew 13 per cent between 1998 and 2002 to 58.4 million tonnes, with a strong link between economic activity and hazardous waste generation (commission staff working document, 21.12.2005). This indicates a strong need for reduction policies.

Legislation

The Waste Framework Directive (2006/12/EC) has been designed to stimulate reduction of waste in several ways. The Directive is primarily aimed to protect human health and the environment against harmful effects caused by the collection, transport, treatment, storage and tipping of waste, by laying down general principles on waste disposal and recovery. In line with this the Waste Directive encourages member states to take measures to restrict the production of waste by:

- stimulating the development of clean technologies more sparing in their use of natural resources;
- developing and marketing cleaner products (manufacture, use or disposal contribute less to amount or harmfulness of waste and pollution hazards);
- developing techniques for final disposal of dangerous substance contained in waste destined for recovery.

A further objective of the Directive is that the Community as a whole has to become self-sufficient in waste disposal and it is also desirable for member states individually to aim at self-sufficiency. The Directive is also in addition aimed at removing the discrepancies between Member States' legislation with regard to waste disposal and recovery by urging them to draw up waste management plans. In this way, movement and concentration of waste should be reduced.

The revised Waste Framework Directive 2008/98/EC sets out the basic concepts and definitions related to waste management and lays down waste management principles such as 'the polluter pays' or the 'waste hierarchy'. However, the following are excluded from this Directive according to its Article 2: gases to atmosphere, land in situ, natural soil, radioactive waste, decommissioned explosives, faecal matter, and also, if covered by other legislation, wastewaters, mining wastes.

Guidance on hazard and risk assessment for acute exposure scenarios

Hazardous wastes are listed in accordance with the procedure laid down in Article 18 of Directive 75/442/EEC, on the basis of Annexes I and II. These wastes must have one or more of the properties listed as hazard codes (H1-15) in Annex III, properties such as explosive, oxidizing, flammable, irritant,

harmful, toxic, carcinogenic, corrosive, infectious, teratogenic, mutagenic, toxic gases, toxic leachate, ecotoxic, toxic leachate. It is commonly a mixture of several chemical substances, which may alter the environmental behaviour of individual chemical components, the toxicological exposure, and the toxicological behaviour of individual chemical components. Historical chemical incidents often concern only one selected toxicant of very high toxicity.

The list takes into account the origin and composition of the waste and, where necessary, also the limit values of concentration. This list is periodically reviewed, if necessary by the same procedure and may add any other waste that is considered by a Member State to display any of the properties listed in Annex III. Such cases shall be notified to the Commission and reviewed in accordance with the procedure laid down in Article 18 of Directive 75/442/EEC, with a view to adaptation of the list.

The properties of waste listed in the Annex III (Council Directive 91/689/EEC) may provide guidance on the behaviour and fate of individual chemical substances as part of hazardous waste.

There is no direct obligation to submit risk scenarios for hazardous waste. However, there are regulations for the storage (Seveso II Directive), and transportation (Council Directive 2008/68/EC), as indicated elsewhere in the present report. At the national level there are regulations concerning occupational exposures.

Need for AERVs
The Waste Directive does not specifically require risk assessment, but the comprehensive information on volumes of hazards materials lends itself to risk prioritization and subsequent implementation of AERVs. Hazardous waste most often comprises an ill-defined mixture of more or less dangerous substances (chemical, biological, radiological). Only in cases when a clearly dominating agent can be defined is an AERV for this single agent a relevant tool for risk reduction.

Emerging threats
The Directive provides measures for the recovery of waste by means of recycling, re-use or reclamation, and the use of waste as energy source. This can introduce new chemical exposure risks in the sense of the transporting and storage of large quantities of chemical wastes for newly designed uses. On the other hand, it may stimulate centralization of plants, thereby confining the exposure area and the potential number of people at risk.

Conclusions and recommendations
The properties of waste listed in the Annex III (Council Directive 91/689/EEC) may provide guidance on the behaviour and fate of individual chemical substances as part of hazardous waste. This list should be scrutinized for substances suitable for the toxicological assessment with reference to single exposure through air.

As a whole it can be concluded that it is unclear what the extent of impact of the (new) Waste Directive is on the development of new or emerging acute chemical exposure risks.

4.9 Terrorism

History and background
The European Council states that the CBRN threat from terrorism remains 'significant'. Known terrorist groups and other groups without organizational connections have shown interest in developing CBRN as well as 'E' capabilities. Chemical agents and explosive chemicals (E) can be extremely hazardous agents for the mass destruction of material, ecosystems and human populations.

To keep Europe protected against a mass casualty chemical attack, there is a need for a range of effective counter measures. Cooperation between partners in international organizations on transport security and non-proliferation of CBRN materials, as well as providing technical assistance on protective security to priority countries as a component of our wider technical assistance programmes, are needed.

Legislation
Two documents are central for further development. A key priority involving 'C terrorism' was adopted by Council on 1 December 2005, and the 'EU Strategy against proliferation of weapons of mass destruction and their means of delivery (WMD)' was adopted by the European Council on 12 December 2003. The EU JHA Council (Justice and Home Affairs) adopted specific conclusions in 2007 that called for further EU-level work on CBRN security.

The key priorities have to be met and each member state is responsible for carrying out the stated tasks. All EU countries have to consider:
- manufacturing, possession, acquisition, transport, supply or use of weapons, explosives or of nuclear, biological or chemical weapons, as well as research into and development of new biological and chemical weapons;
- release of dangerous substances, or causing fires, floods or explosions, the effect of which is to endanger human life.

In terrorism legislation, there are no discussions regarding the need of toxicological data to inform the risk assessment of different agents. However, the EU commission adopted an EU CBRN Action Plan (CBRN, 2009) The overall goal in that plan is to reduce the threat as well as the damage from CBRN incidents. The actions included in the CBRN Action Plan will be financial, supported by different programmes in EU (*Prevention, Preparedness and Consequence, Management of Terrorism and other Security Related Risks*; *Prevention of and Fight against Crime*; *Civil Protection Financial Instrument*; and the *Seventh Framework Programme for research, technological development and demonstration activities (in particular the Security Research theme).* The Health Programme (DG Sanco) supports the Health Security work, which is not discussed in the CBRN Action Plan.

The CBRN Action Plan is divided into areas of prevention, detection, preparedness and response. This will lead to establishment of risk scenarios.

Any new EU measures in this field should be based on risk and threat assessments as well as a cost-benefit assessment.

Guidance on hazard and risk assessment for acute exposure scenarios
Currently, the risk assessment pertaining to terrorist threats does not take account of toxicological data. The overall goal of the above policy package is an all-hazard approach to reduce the threat of and damage from CBRN incidents of

accidental, natural or intentional origin, including acts of terrorism. This implies a wider approach than only chemical weapons and thus includes Toxic Industrial Chemicals (TICs).

Chemical weapons (C and E) show an extremely high acute toxicity and are at the very top of all known dangerous chemical substances lists. This implies a big difference in risk when comparing C- and E-associated warfare agents to less toxic, but still dangerous, and perhaps more available, substances, such as TICs. The risk assessment of C- and E-warfare agents requires laboratories and test ranges of very high security.

Need for AERVs
At the moment, the framework is under construction and the elements needed for AERVs are partly unknown and partly scattered among certain national institutes within Europe and elsewhere. Furthermore, no referrals to new and emerging risks are given in the plan. However, the use in terrorism of known C-warfare agents is a central issue in the CBRN security strategy.

Emerging threats
Council Conclusions of 27 November 2008 on the creation of a CBRN database invited EUROPOL to create a European CBRN database in which to gather and centralize technical information on CBRN terrorism-related events and CBRN products and materials, which may be used with malicious intent.

The CBRN Task Force launched a report in February 2008, with a view to preparing a list of measures that could be undertaken at EU level and in the Member States in order to lower the risks of terrorist acts using CBRN materials.

The Member States are encouraged to undertake the implementation of the EU CBRN Action Plan in order to enhance the preventive, detection and response measures in the field of CBRN threats and risks. The goal is to promote an enhanced security culture inter alia by focusing on the enhancement of knowledge in Member States in the field of CBRN security by way of improved risk assessments and research, as well as the exchange of best practices. Joint training and exercises will contribute to an adequate perception of the risks associated with CBRN materials by disseminating experience and knowledge to relevant stakeholders such as public authorities, first responders, researchers, the general public, security managers and staff.

Only indirectly new and emerging risks are mentioned. However, a terrorist activity often implies new, surprising inventions and methods, e.g. improvised explosive devices (IED).

Conclusions and recommendation
The CBRN threat from terrorism remains constant. The primary goal of the legislation is to reduce the likelihood of a CBRNe event by updating a list of high-risk chemical agents as indicated by scientific and security experts. Currently, such lists take account of volumes utilized and transported, and chemical availability. The list, however, should be based on a risk assessment analysis and therefore should take account of toxicological parameters. In the current CBRN Action Plan Health Security questions are not addressed. This question should be addressed.

Agreement is required on the criteria and method to be used for establishing and applying such lists. Once established, this will lead to enhanced hazard security, encourage control improvement of information and a strengthened import/export regime.

For detection of a scenario-based/modelling approach to identify work priorities in the detection field, it is also important to establish and improve the methods and good practices for detection. The public health community may have a role to play in ensuring that health becomes a central component of the CBRN plan.

4.10 Occupational Exposure Limits

History and background

Occupational Exposure Limit values (OELs) have been a feature of the industrialized world for the last fifty years or so. They were first introduced at a time when the benefits of preventing occupational ill-health were beginning to be appreciated, and analytical methodology had advanced to a state in which it was possible to measure the levels of contaminating substances in the workplace air. OELs began to be established in order to provide criteria for the basis of decisions as to whether the airborne concentrations of given substances were sufficiently low to prevent adverse health effects.

OELs are set by competent national authorities or other relevant national institutions as limits for concentrations of hazardous compounds in workplace air. OELs for hazardous substances represent an important tool for risk assessment and management and valuable information for occupational safety and health activities concerning hazardous substances.

The most widely known OELs are the threshold limit values (TLVs) (ACGIH, 2010). Strictly speaking, TLV is a reserved term of ACGIH. It is, however, sometimes loosely used to refer to other analogous concepts in occupational health and toxicology. The historical importance of the ACGIH list lies in the fact that, although there had been limit values prior to the TLVs, industrial hygienists adopted the list in many countries as such, or with modifications. Later on, several countries developed their own lists of OELs and own procedures and criteria in their setting. Most widely known background documentations have been those of Germany, UK, the Netherlands and the Nordic Countries.

Legislation

In the EU, a system of Indicative Occupational Exposure Limit Values (IOELVs) was first introduced in 1980 by Directive 80/1107/EEC and the first list of 27 substances in Directive 91/322/EC in 1991. The Member States had to implement national limits before 31 December 1993. The list was amended by Directive 2006/15/EC in 2006, which transferred 10 of the 27 substances to a different regulatory regime. A second list was defined in Directive 96/94/EEC but this was repealed by Directive 2000/39/EC.

In 1998, Directive 80/1107/EEC was repealed and replaced by a new regime under the chemical agents' Directive 98/24/EC. An occupational exposure limit value was defined as ‘the limit of the time-weighted average of the concentration of a chemical agent in the air within the breathing zone of a worker over a specified reference period’. The Directive led to the establishment of the Scientific Committee on Occupational Exposure Limit Values (SCOEL) to advise the European Commission. Two Directives have established further lists

of IOELVs: 2000/39/EC and 2006/15/EC. As of 2008, the IOELVs under Directive 91/322/EC remain in force but under review. A third list of IOELVs, now under Directive 98/24/EC, is under preparation.

The REACH Regulation introduced the concept of derived no-effect levels (DNELs), and the guidance for the implementation of REACH also introduced derived minimum-effect levels (DMELs). The difference between these values can be simplified: DNELs are derived for substances with toxicological threshold levels and DMELs for substances with non-threshold endpoints like cancer. The setting of DNELs/DMELs for occupational exposure scenarios closely resembles the methodology in the setting of occupational exposure levels. So far it is not clear how the possible conflicts between the DNELs/DMELs and OELs will be handled in the EU and at the member state levels.

It is probable that some substances will even receive multiple different DNELs from the different registrants.

The definitions, and to some extent also the background criteria and the legal status, of the OELs differ in various countries. The methodology of setting the European limits has been documented by SCOEL (SCOEL, 2009). Many EU Member States have their own methodologies to set national limit values, but the methodology of SCOEL is principally similar to the other European national committees, such as the German MAK Commission, the German Ausschuss für Gefahrstoffe (AGS), the Dutch Expert Committee on Occupational Standards (DECOS) and the Nordic Expert Group. The public data on the OELs and the lists of OELs in various countries have been compiled by EU-OSHA (European Agency of Safety and Health at Work; http://osha.europa.eu/en/topics/ds/oel) and the German IFA (Institut für Arbeitschutz der Deutschen Gesetzlichen Unfallversicherung; http://www.dguv.de/ifa/en/gestis/limit_values/index.jsp).

The IOELVs are not binding for the member states but they must be taken into consideration in setting national exposure limits. Some member states have pre-existing national limits lower than the IOELVs and are not required to revise these upwards. In practice, most member states adopt the IOELVs but there are some variances upwards and downwards.

Guidance on hazard and risk assessment for acute exposure scenarios
It is necessary to decide whether a short-term exposure limit (STEL) is required in addition to an 8-hour time weighted average (TWA) limit, with the prerequisite that the 8-hour TWA is not exceeded. The 8-hour limits are the 'standard' limits in occupational hygiene but do not provide sufficient protection from all occupational exposures and it is possible that a short-term limit is needed. This is likely when a brief exposure may produce a critical effect. The examples of these effects are nuisance (bad smell, etc.), irritation of respiratory tract and eyes, central nervous system depression and cardiac sensitization. The 8-hour limit may be much lower than the exposure at a level where there is a risk of short-term effects.

The STEL is also a value above which exposure should not occur and most often, it relates to a reference period of 15 minutes. Instead of a 15-minute STEL, some exposing agents may have a 'ceiling value', which refers to a limit without any specific exposure period, and implies that this value should not be exceeded at any time during the work shift. ACGIH states that the STEL 'is the concentration to which it is believed that workers can be exposed continuously for a short period of time without suffering from 1) irritation, 2) chronic or

irreversible tissue damage, 3) dose-rate dependent toxic effects, or 4) narcosis of sufficient degree to increase the likelihood of accidental injury, impaired self-rescue, or materially reduced work efficiency'. The TLV–STEL will not necessarily protect against these effects if the daily TLV–TWA is exceeded. The TLV–STEL usually supplements the TLV–TWA where there are recognized acute effects from a substance whose toxic effects are primarily of a chronic nature; however, the TLV–STEL may be a separate, independent exposure guideline.'
When setting a STEL, the short-term effects to be considered include:

- systemic effects, among them specific organ effects, CNS effects, and cardiac arrhythmia;
- corrosivity, irritancy, odour;
- effects on special risk groups;
- effects of exposure frequency/duration, also cumulative effects of the repeated exposure.

The target population of OELs are workers, who are supposed to be healthy and in general, in better physiological shape than the general population, which is the target population of the acute exposure response values (AERVs). The safety margins (or AFs in REACH parlance) are lower, sometimes very much lower in the setting of OELs than when setting values for the general population. When the socio-economic aspects are taken into account, these often decrease the AFs. The general population is more heterogeneous and includes sensitive subpopulations that have to be taken into account when deriving AERVs. The confounding exposures to other chemical, physical, physiological, etc. agents are probably more common in the general population.

Need for AERVs

Occupational standards, by definition, refer to occupational exposure and thus prioritize short-term exposures of the workforce, thereby excluding sensitive subpopulations, such as children, the elderly and the frail. They are therefore not directly transferable to environmental exposure post chemical incident.

AERVs are derived to protect an exposed population from the consequences of a single incidental exposure. Therefore, in case of a chemical incident within an occupational setting AERVs are by definition not meant to protect the worker in these situations since the incidental exposure is in addition to the everyday occupational exposure. In these cases, STELs might be more appropriate risk assessment and management tools than AERVs.

However, a special case might be first responders who are by profession involved in the repression phase following a chemical incident (e.g. firefighters). They will be irregularly exposed for an undetermined number of occasions to specific chemicals, to one chemical more than to another. There are no specific guidance values to assess the health risk of these first responders. Application of OELs may be too rigid both from a health point of view (OELs are meant for daily exposures 5 days per week for approximately 40 years) but also from a practical point of view (it might prevent first responders from doing their job in minimizing risks for the exposed population, thereby leading to unnecessary health risks). AERVs might represent too high concentrations for irregular repeated exposures. Thus, there might be a need for AERVs that are tailored to the irregular repeated exposure situations of first responders.

Emerging threats
The derivation of occupational exposure limits specifically refer to hazards currently found in the workplace and therefore do not address future threats.

Conclusions and recommendations
The scenarios and the adverse effect endpoints relevant for occupational exposure levels differ in many aspects from those of AERVs. OELs are generally set to protect 'healthy', adult workers for their whole working life (defaulting to 40 or 45 years) with 8 hours per day exposures. Although STELs (often for 15-min exposures) are also derived in addition to 8-hour values, they are infrequently based on critical effects like incapacitation or death, which are often the important key endpoints for AERV-2 and AERV-3.

To summarize, while the data used to set the OELs/STELs is a valuable contribution to the background database of acute exposure values for the heterogeneous general population, the OELs are not appropriate and must not be used for emergency response planning. A specific need may be guidance to deriving AERVs for first responders who are repeatedly but irregularly exposed to specific chemicals.

4.11 Conclusions

The European Union has an extensive chemical industry to support societal need and is composed of major (and minor) chemical installations and an elaborate transportation system across open borders. Many of the chemicals synthesized and transported are high production volume chemicals (HPVs), a proportion of which are Toxic Industrial Chemicals (TICs). Chemical incidents may occur during different stages of the life cycle of a chemical, including manufacture, storage or transportation, providing an almost infinite number of scenarios, the potential for extensive exposure and thus catastrophic public health impact. Such incidents may occur either as a consequence of accidents or following acts of deliberate release, including terrorism.

Legislation pertaining to chemical safety is extensive in the EU, covering the principal facets of development and marketing of new chemicals, storage of hazardous chemicals at major industrial installations, occupational exposure and transportation of chemicals by road, rail, sea and air, application and subsequent waste disposal. The regulatory frameworks reviewed in the present chapter collectively address the various components of chemicals from synthesis to disposal ('cradle to grave') and thus aim at one or more stages of the chemical's life cycle.

No overarching legal framework exists within the EU that addresses quantitative human health risk assessment from single exposures. Chapter 4 reviewed a selection of existing regulatory frameworks to verify whether these regulations provide a vehicle for the subsequent derivation of AERVs, in particular whether regulations provide guidance for health risk assessment from single exposures or whether there is a demand for data on health effects from single exposures.

It is concluded that little (or no) guidance on chemical risk assessment from single exposures was present in any of the reviewed regulatory frameworks, except for acute DNELs as specified in REACH. However, REACH is primarily concerned with *chronic* exposures as opposed to *acute* (*single*) exposures to chemicals. To extrapolate the REACH framework to single exposures, the

applicability of the derivation of the DNELs to single exposure situations should be further explored. The current DNEL methodology is too generic to answer the specificities of single exposures. There is therefore a need to develop AERVs, with supporting documentation.
Although within the occupational environment Short-Term Exposure Limits (STELs) are derived and well established. The scenarios and the adverse effect endpoints relevant for occupational exposure levels differ in many aspects from those for AERVs. OELs are generally set to protect 'healthy' adult workers for their entire working life. STELs (often for 15-min exposures) are also derived for more than one exposure per day for multiple days. Further, they are infrequently based on critical effects like incapacitation or death, which are often the important key endpoints for AERV-2 and AERV-3. One issue, however, needs further elaboration. First responders, who are by profession involved in the repression phase following a chemical incident, will be irregularly exposed for an undetermined number of occasions to specific chemicals. There are no specific guidance values to assess the health risk of these first responders. Neither OELs nor AERVs are directly applicable to the exposure situations of these workers. There is also a need for guidance to derive AERVs for first responders who are repeatedly but irregularly exposed to specific chemicals in extreme exposure scenarios.

In other frameworks, acute toxicity data are merely used for Classification and Labelling purposes and the data demanded are not suitable for AERV derivation. A chemical may have different applications and thereby can be regulated within different regulatory frameworks. Also, depending on the life stage of the chemical (production, storage, application, consumer product, waste), risks from exposure will be regulated through different pieces of legislation. In each stage of the life cycle of a chemical, there is a potential release and subsequent exposure, which may result in a large-scale incident. There is no regulatory obligation, however, in most instances to address human health risks from single exposures in a quantitative way, let alone through the consideration of incident scenarios. Acute reference concentrations and acute DNELs are expected to be of only limited value since they do not address topics essential for AERVs (such as time scaling) and aim at derivation of a no-effect concentration which is of limited value in chemical incidents.

The GHS/CLP Regulation focus on existing substances and provide common elements of language for hazard classification and labelling. The implementation of the CLP Regulation within the Seveso III draft European Directive brings together the CLP with the need for AERVs but the CLP Regulation and its associated guidance do not provide sufficient framework for developing AERVs.

The newly developed $C \times t$ approach that is now part of the revised OECD 403 is an important tool to provide data in agreement with the needs for deriving AERVs. It provides insight in the concentration-time relationship and an estimation of the value for the exponent n. However, the legal or scientific framework obliging industry or government to take this issue into account is lacking. Existing regulatory frameworks do not require the assessment of chemical incident scenarios. This may in future result in even less suitable acute inhalation toxicity studies becoming available for deriving AERVs. The focus of the acute toxicity guidelines is now on Classification and Labelling with as few animals as possible within a specific regulatory framework, and not on a quantitative risk assessment. It is expected that the OECD TG 436 will be the choice of preference for testing acute inhalation toxicity. OECD TG 436 will not provide data suitable for AERV derivation.

The European Commission has recognized the importance of planning and preparedness for chemical incidents, whether accidental or deliberate, and has recognized the need to plan for such eventualities, including recognition of emerging threats and prioritising chemicals of concern in the CBRNe arena. The extensive utilization of chemicals and their potential public health impact necessitates extensive planning and preparedness prior to subsequent response. Current legislation in this arena recognizes the potential impact of chemicals, but does not specifically address toxicity. It may provide a platform for highlighting chemicals of concern in all phases of utilization and thus subsequently allow the development of AERVs. Incidental release of chemicals into the air, both accidental and intentional, might happen during every stage of their life cycle and via such a platform, health risks from possible incident scenarios during different stages might be assessed in a quantitative way.

AERVs are an important aspect of chemical incident risk assessment and thus a harmonized approach would facilitate international cooperation and collaboration following chemical incidents of international concern. The IHR might provide a tool for enhancing international planning and preparedness in this area.

It is recommended that the potential for community exposure to chemicals due to incidental emergency exposure situations during the life cycle (as highlighted by the international regulatory framework) is explored and that a number of these scenarios are developed with a view to highlighting toxicological data input requirements.

5 Conclusions and recommendations

5.1 Present situation

Chemical incidents occur frequently and clearly have the potential to expose up to thousands of individuals simultaneously. Prevention or mitigation of human health effects is often the major determinant underlying accident prevention policy and emergency response decisions. Public health management, aiming to reduce the burden of disease caused by chemical incidents is virtually impossible without health risk information. Human health risks are assessed by the integration of chemical-specific information on the relationship between exposure and health effects with exposure information relating to the specific situation, so that the actual risk can be characterized.

The risk assessment of industrial chemicals, pesticides and biocides for their intended use is a common European exercise that is mainly focused on the calculation of 'safe' exposure levels for repeated exposures over periods of up to a lifetime. At present, no European guidance is available for the risk assessment of single exposure scenarios following chemical incidents, accidental or intentional. Health risk assessment in chemical incidents deviates from what is common practice for exposures up to a lifetime. For chemical incidents the emphasis should be to predict concentration thresholds for different levels of severity of expected health impact, taking into account potentially susceptible subpopulations. Such concentration thresholds are required for a range of severities of health effects and exposure periods in order to ensure a quick and adequate response to actual exposure scenarios.

Conclusion
The ability to perform a human health risk assessment is a prerequisite for effective chemical incident prevention, preparedness and response. The availability of a validated methodology specifically tuned to such risk assessments is therefore of high importance.

5.2 AERVs are cornerstones for incident management purposes

An accurate and precise prediction of human health risks resulting from chemical incidents is a cornerstone of strategy and policy (implementation) for all stages of a chemical incident's life-cycle (prevention, preparedness, detection and alert, response and recovery). Activities in all these stages (including crisis communication) would benefit from standardized human health risk information using validated information, tools and guidance tailored to the needs of each stage, rather than reliance on information compiled ad hoc. In particular during the response phase, the decision-making process on appropriate risk mitigation measures and/or actions occurs under significant time pressure. AERVs represent the most feasible way to provide timely, standardized and easily comprehensible exposure-response (-effect) information for health impact assessment and the management of chemical incidents. The adequacy of mitigation decisions heavily depends on the predictive accuracy of the AERVs. Over-protective AERVs might lead to risk mitigation measures that are inappropriate and do not balance the health risks from exposure with the health risks caused by the measures. For example, additional public health risks may be introduced due to the mitigation measures (such as unnecessary evacuation) or because such actions may unnecessarily increase public concern. On the

other hand, insufficiently protective AERVs will result in an underestimation of the health risk for the exposed population. Neither situation is desirable. Therefore the focus for AERVs should be on as precise a prediction as possible of concentration thresholds for different levels of severity of expected health impacts. AERVs are required for a range of severities of health effects and exposure periods to allow a quick and adequate response to all actual exposure scenarios.

Conclusion
A validated methodology with broad European consensus to derive AERVs is a prerequisite for the rapid human health risk assessment of chemical incidents and therefore most urgently needed. An important feature of such a methodology should be the prediction of concentration thresholds for different health severity levels for a range of relevant exposure durations.

5.3 Inconsistencies exist between present frameworks

Chapter 3 describes a comparison between a number of methodologies for AERV derivation (frameworks) that are active or under development. Despite the many obvious similarities between the frameworks at first glance, significant differences were observed in the basic philosophy underlying the AERVs such as the target population to be protected. One obvious commonality was the use of three AERV tiers as thresholds for discomfort (AERV-1), disability (AERV-2) and mortality (AERV-3) in most frameworks.

Differences also existed in the use of specific toxicological endpoints as the point of departure for AERV tiers including endpoints with a high societal impact and importance (such as carcinogenicity and reproductive toxicity). In addition, the use of different modelling tools contributed to different AERVs for the same chemical.

A numerical comparison between these AERV methodologies (section 3.5) illustrated that the aggregated methodological differences can lead to significant discrepancies in AERV values and the health risk assessment based on them, in terms of the number of people exposed and injured, the expected severity of health effects and the ability of chemical incidents to cross administrative boundaries.

Conclusion
The existing AERV methodologies serve different purposes, the methodologies for deriving AERVs differ and the AERVs produced by them are not interchangeable, even though they are often used in practice as if they are. This may lead to inconsistencies and inaccuracies in the chemical incident risk assessment.

5.4 Adequacy of present risk assessment methodologies

AERVs are important tools for an accurate prediction of human health effects, and therefore a starting point for possible risk management decisions that have to be taken under intense time pressure in the acute phase of a chemical incident. There is no common framework or guidance within the EU for the risk assessment of chemical incidents or the derivation of AERVs. Present risk assessment paradigms mainly aim at long-term (up to lifetime) exposures for specific populations (such as operators, workers, consumers and bystanders)

and do not provide an adequate basis for AERV derivation. Furthermore, these more generally accepted risk assessment paradigms are aimed at protecting the described (sub-) population against all adverse health effects, whereas the AERV approaches have a predictive character and describe the different adverse health effect levels that are expected to occur at specific concentration and time points. Although AERVs have been derived for many chemicals (mainly AEGLs and ERPGs), large numerical differences exist between the AERVs derived within these frameworks. Öberg et al. (2010) compared AEGLs and ERPGs and concluded that the values differed by a factor of three or more for almost 40 per cent of the substances. Section 3.5 demonstrated that this is a universal finding across all existing AERV frameworks.
Consequently, the risk assessments based on AERVs derived by the different methodologies predict widely different health impacts. Our survey revealed that end-users may not recognize these differences and considered that AERVs derived within the different frameworks are interchangeable (Heinälä et al. 2013), while in fact they are not. These circumstances introduce the additional risk of inaccurate health impact assessments and the mitigation measures based on them, and may affect the communication and trust between diverse parties engaged in risk assessment and management.

Conclusion
The present risk assessment paradigm does not provide transparent and consistent information, tools and guidance to support end-users in making risk assessments for chemical incident prevention, preparedness and response. Harmonization of the present risk assessment paradigm aiming at single exposures from chemical incidents is therefore urgently needed.

5.5 Existing legislation does not provide adequate handles or guidance

Chapter 4 describer whether selected existing regulatory frameworks such as Seveso II, REACH, CLP, OECD and IHR provide incentives and/or a common basis for laying down a framework (e.g. concerning data requirements, obligation and/or guidance for risk assessment for single or short-term exposure) for the derivation of AERVs. The domains of these regulatory frameworks include several stages of a chemical's life-cycle but possible incident scenarios and the consequences thereof are not always considered. In most of the legislative frameworks reviewed, data on the health risks of acute or single exposure situations appeared to be required, but guidelines for such risk assessment are hardly addressed or only qualitatively used (for instance for Classification and Labelling purposes). If guidance for the risk assessment of single exposures is provided (e.g. acute DNEL or Acute Reference Concentrations), it focuses on a safe exposure level at which no health effects are to be expected, i.e. only at or below the AERV-1 level, and does not address technical tools and guidance essential for AERVs (such as for time scaling and derivation of different tiers). Occupational STELs that have been derived for many substances are also not suitable for AERV purposes.

The revised OECD 403 contains the newly developed $C \times t$ acute inhalation toxicity test protocol, which has been developed to provide the exact type of lethality data required for deriving AERVs. It provides insight into the complex relationship between exposure duration, concentration and response. However, there is no legal or scientific obligation for industry or government to produce data in accordance with this specific protocol.

Conclusion
Even though the Seveso Directive, the CBRNe action plan and the International Health Regulations are all more or less aimed at diminishing and handling human health risks due to chemical exposures, the present regulatory frameworks do not provide incentives (e.g. in terms of data requirements and guidance) for the derivation of AERVs. A review of legislation presently under revision or development suggest that such a basis for AERV derivation is not to be expected in the short term.

5.6 New and emerging risks are identified

From the present evaluation (mainly Chapter 2) and from the results of the accompanying survey (Heinälä et al. 2013) it appears that European academics, policy makers and emergency responders involved in the risk assessment of chemical incidents are most concerned with current risks, and less focused on new and emerging risks. Nevertheless, this study identified the following new and emerging risks:

- Continuous marketing of new chemicals with only a limited toxicological database; the present concerns include nanoparticles and biofuels.
- LNG regasification: induces an increased risk of exposure to combustion gases (exposure to mixtures).
- Natural gas production from manure and waste: induces an increasing demand on the skills and knowledge of involved farmers, thereby increasing the potential for chemical incidents involving the release of toxic chemicals (e.g. hydrogen sulphide).
- Increasing land use pressure, resulting in:
    - high concentration of chemicals in a limited area due to, for example, advanced storage technologies (such as CCS and liquid or solid fuel);
    - increasing risk of occurrence and consequences of natural-technological accidents (NaTechs);
    - underground constructions (e.g. for public transportation) resulting in prolonged exposure durations because of longer escape routes.

The survey (Heinälä et al. 2013) identified several developments causing an increasing likelihood of chemical incidents is likely, including the influence of industry work practices, productivity and efficiency demands, changes in companies' working practices and globalization. In addition, there is concern over possible future chemical terrorism or sabotage. A high level of uncertainty was expressed regarding the impact of climate change on potential future chemical incident risks (Heinälä et al. 2013). However, it is difficult to assess whether these topics can be classified as real emerging risks on account of a lack of adequate data. It is noted that it is still not common practice to consider possible chemical incident scenarios in new developments, whether technological developments or the development of new chemicals to be marketed.

Conclusion
Emerging chemical incident risk scenarios and risk drivers have been identified, many of them with a high level of uncertainty. It is therefore recommended to monitor more frequently for new trends in chemicals, scenarios and risks from chemical incidents at an early stage.

A harmonized system for AERV derivation and guidance for AERV application will most likely be adequate to deal with new chemicals and chemical incident scenarios. If new incident scenarios are more regularly monitored at an early

stage of developments it can be evaluated whether situation-specific adaptations or additions of risk assessment information, tools and guidance are required.

5.7 Additional topics of concern

Two additional issues, namely chemical mixtures and first responder protection, which are expected to be of increasing importance in the future but have not been addressed in any present methodology for AERV derivation, need further development. The development of AERVs for mixtures such as combustion gases was considered to be important on account of the potential increase in incidents where the release of chemical mixtures (e.g. in the event of fires) is likely. Therefore, there is an increasing need to derive AERVs for the most common mixtures or to standardize a default approach to adequately deal with such mixtures. From the accompanying questionnaire it was concluded that the AERVs presently available for single chemicals are already considered difficult to use (Heinälä et al. 2013). This finding underlines the need for clear tools and guidance on how to deal with single exposure to chemical mixtures. The possibility of deriving AERVs for the most common mixtures should be explored.

In terms of first responder protection, with a potential increase in chemical incidents professional first responders will experience more frequent exposures. At present, there are no tools that adequately protect these first responders. AERVs are meant for single exposures of the (general) population on a chemical incident site. Occupational exposure levels (OELs) are derived for lifetime exposure (eight hours per day for five days per week) and as such also do not properly address the appropriate (intermittent) exposure and health issues involved in the risk assessment of chemical incidents by first responders.

Conclusion
A specific need for an approach to deal with exposure to mixtures in chemical incidents is identified. It is preferred to derive AERVs for the chemical mixtures that are most common in chemical incidents. In addition, a methodology for the derivation of (A)ERVs for professional first responders needs to be developed.

5.8 Recommendations

The increasing need for adequate AERVs within the EU is demonstrated by the fact that several individual EU Member States are developing their own systems because a follow-up of the EU 5th Framework project ACUTEX remains forthcoming. These initiatives vary from adopting existing AERVs (e.g. the adoption of AEGLs by the UK) to the development of a national methodology (e.g. in France and The Netherlands). Joint European development and the convergence of methods, tools and guidance for the derivation and application of AERVs would be beneficial to (see also Chapter 1):

- strengthen the capacity of EU Member States to deal with chemical incidents;
- improve the authority and credibility of AERVs as a critical element in rapid risk assessment and of the risk assessments based on them;
- ensure a level playing field and an equal level of protection for all European citizens;
- strengthen and improve the consistency of risk and crisis communication in case of chemical incidents by different stakeholders such as authorities, industry and transport companies;
- facilitate a harmonized response to incidents with trans-boundary effects, where administrative boundaries may be within and between Member States;

- improve European consistency in the parameters used in performing risk assessments;
- ensure consistency of the risk assessment methodology underlying the AERVs with other European risk assessment frameworks;
- avoid challenges from the public, policy- and decision-makers, and industry as well as accident investigators resulting from caused by differences in AERVs and by differences in the consequence analyses based on such values;
- assist multinational companies and competent authorities in making consistent risk assessments Europe-wide, thus avoiding duplication of effort.

For these reasons the harmonization of methodologies and procedures for the derivation of AERVs is recommended. Harmonization is needed at different levels, including:

- the level of basic philosophy;
- the level of methodology (preparation of a Guidance Document); including guidance on:
  - how to deal with specific endpoints;
  - susceptible subpopulations;
  - use of time-scaling and dose-response modelling tools.
- the level of the AERV derivation process, including formalization and dissemination of AERVs.

A recurring area of concern is the lack of toxicological data to adequately deal with these topics. The possibility of demanding a minimum data set for AERV derivation should be explored. It is noted that some of the topics mentioned need further development; these are described into more detail in Section 3.7.2. It was concluded in Section 3.7 that, in addition to a harmonized methodology, an overarching international committee responsible for the final AERV values is needed to ensure harmonized AERVs. Furthermore, to ensure the successful implementation and adoption within Europe of these harmonized AERVs (and the methodology to derive them), support from a broad European policy platform should be secured.

Moreover, the accompanying survey (Heinälä et al. 2013) revealed that the use and application of AERVs are considered to be difficult by end-users. Therefore, guidance is needed on the application of AERVs in chemical emergency situations and risk assessment of chemical incidents in general. In addition, more training/education is needed for personnel involved at all levels, especially regarding information gathering, the use of AERVs and the use of appropriate modelling tools.

Regarding emerging risks (either new or increasing) it is recommended to consider possible incident scenarios at an early development stage of new chemicals/technologies. This might include a procedure for the identification and evaluation of chemical incident scenarios during the life-cycle of a chemical as a regulatory requirement.

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7 References

ACGIH (2010) TLV®s and BEI®s. American Conference of Governmental Industrial Hygienists, Cincinnati

ACUTEX (2006) Methodology to develop AETLs. www.circa.europa.eu/Public/irc/jrc/acutex/library

AIHA (2010) American Industrial Hygiene Association Guideline Foundation. Administrative Operating Procedures. www.aiha.org/insideaiha/GuidelineDevelopment/weel/Documents/AIHA%20GF%20AOP%202010.pdf

Anandan C, Nurmatov U, Van Schayck OCP, Sheikh A (2010) Is the prevalence of asthma declining? Systematic review of epidemiological studies. Allergy, 65:152–167

ART (2010) The Advanced REACH Tool. http://www.advancedreachtool.com/ (accessed 20th August 2010)

Ausen D (2010) Foresight biomedical sensors. http://www.sintef.no/fobis (accessed 7th September 2010)

Barton HA, Chiu WA, Woodrow Setzer R, Andersen ME, Bailer AJ, Bois FY, Dewoskin RS, Hays S, Johanson G, Jones N, Loizou G, Macphail RC, Portier CJ, Spendiff M, Tan YM (2007) Characterizing uncertainty and variability in physiologically based pharmacokinetic models: state of the science and needs for research and implementation. Toxicol. Sci., 99:395–402

Bois FY, Jamei M, Clewell HJ (2010) PBPK modelling of inter-individual variability in the pharmacokinetics of environmental chemicals. Toxicology, 278:256–267

Borysiewicz MJ, Borysiewicz MA (2010) Atmospheric dispersion modelling for emergency management, in MANHAZ monograph models and techniques for health and environmental hazard assessment and management, Center of Excellence MANHAZ, Institute of Atomic Energy, Poland. http://manhaz.cyf.gov.pl/manhaz/ind.php (accessed 20th August 2010)

Bos PMJ, Baars BJ, Van Raaij MTM (2004) Risk assessment of peak exposure to genotoxic carcinogens: a pragmatic approach. Toxicol. Lett., 151:43–50

Bos PMJ, Zeilmaker MJ, Van Eijkeren JCH (2006) Application of physiologically based pharmacokinetic modeling in setting acute exposure guideline levels for methylene chloride. Toxicol. Sci., 91:576–585

Bosgra S, Van Eijkeren J, Bos P, Zeilmaker MJ, Slob W (2012) An improved model to predict physiologically based model parameters and their inter-individual variability from anthropometry. Crit. Rev. Toxicol., 42:751–767

Boyes WK, Evans MV, Eklund C, Janssen P, Simmons JE (2005) Duration adjustment of acute exposure guideline level values for trichloroethylene using a physiologically-based pharmacokinetic model. Risk Anal., 25:677–686

Bruckner JV, Keys DA, Fisher JW (2004) The Acute Exposure Guideline Level (AEGL) program: applications of physiologically based pharmacokinetic modeling. J. Toxicol. Environ. Health, A67:621–634

CBRN (2009) Council conclusions on strengthening chemical, biological, radiological and nuclear security in European Union – an EU CBRN action plan. 15505/1/09, Rev 1

COT (1986) Committee on Toxicology, National Research Council. Emergency and Continuous Exposure Levels for Selected Airborne Substances. Volume 6: Benzene and Ethylene Oxide. Washington, D.C.: National Academy Press

Dekkers S, De Heer C, Rennen MAJ (2001) Critical effect sizes in toxicological risk assessment: a comprehensive and critical evaluation. Environ. Toxicol. Pharmacol., 10:33–62

Dekkers S, Telman J, Rennen MAJ, Appel MJ, De Heer C (2006) Within-animal variation as an indication of the minimal magnitude of the Critical Effect Size for continuous toxicological parameters applicable in the Benchmark Dose approach. Risk Anal., 26:867–880

Diack C, Bois FY (2005) Pharmacokinetic-pharmacodynamic models for categorical toxicity data. Regul. Toxicol. Pharmacol., 41:55–65

ECETOC (1991) Emergency exposure indices for industrial chemicals. Technical Report no. 43. Brussels

ECETOC (2003) Derivation of assessment factors for human health risk assessment. Technical report no. 86. European Centre for Ecotoxicology and Toxicology of Chemicals. Brussels

EIONET (2010) Model Documentation System. http://air-climate.eionet.europa.eu/databases/MDS/index_html (accessed 2010-08-20)

ENRHES (2009) Engineered Nanoparticles: Review of Health and Environmental Safety.
http://ihcp.jrc.ec.europa.eu/whats-new/enhres-final-report

PHMSA (2012) Pipeline and Hazardous Materials Safety Administration, US Department of Transport. 2012 Emergency Response Guidebook.
http://www.phmsa.dot.gov/hazmat/library/erg

ERP Committee (2006) Procedures and responsibilities.
http://www.aiha.org/insideaiha/GuidelineDevelopment/ERPG/Documents/ERP-SOPs2006.pdf

EU (2010a) Draft 'GHSified' annex I of the SEVESO II directive 96/82/EC, draft working document, art. 2.3 and annex I, April.
http://ec.europa.eu/environment/seveso/pdf/ghs_annex1.pdf

EU (2010b) Impact assessment study into possible options for adapting annex I of the SEVESO II directive into the GHS, DG Environment, February.
http://ec.europa.eu/environment/seveso/pdf/ghs_impact%20assessment.pdf

Felter SP, Conolly RB, Bercu JP, Bolger PM, Boobis AR, Bos PMJ, Carthew P, Doerrer NG, Goodman JI, Harrouk WA, Kirkland DJ, Lau SS, Llewellyn GC, Preston RJ, Schoeny R, Schnatter AR, Tritscher A, Van Velsen F, Williams GM (2011) A proposed framework for assessing risk from less-than-lifetime exposures to carcinogens. Crit. Rev. Toxicol., 41:507–544

Foster PMD, Harris MW (2005) Changes in androgen-mediated reproductive development in male rat offspring following exposure to a single oral dose of flutamide at different gestational ages. Toxicol. Sci., 85:1024–1032

Fransman W, Cherrie J, Van Tongeren M, Schneider T, Tischer M, Schinkel J, Marquart H, Warren ND, Kromhout H, Tielemans E (2009) Development of a mechanistic model for the Advanced REACH Tool (ART), TNO report V8667, September

Gale P, Brouwer A, Ramnial V, Kelly L, Kosmider R, Fooks AR, Snary EL (2010) Assessing the impact of climate change on vector-borne viruses in the EU through the elicitation of expert opinion. Epidemiol. Infect., 138:214–225

Göransson Nyberg A, Bucht A, Sandström B, Wigenstam E, Cassel G, Joussineau S, Lewensohn R, Stenke L (2010) Mass casualties and health care following the release of toxic chemicals or radioactive material (EU Project 2007/209) WP 7 – Scientific Report Contribution of modern biotechnology (Deliverable D6)

Haber F (ed) (1924) Zur Geschichte des Gaskrieges. In: Fünf Vorträge aus den Fahren 1920–1923. Berlin: Verlag von Fulius Springer, 23–29

Harrus S, Baneth G (2005) Drivers for the emergence and re-emergence of vector-borne protozoal and bacterial diseases. Int. J. Parasitol., 35:1309–1318

Heezen PAM, Mahesh S (2010) Veiligheid grootschalige productie van biogas, verkennend onderzoek risico's externe veiligheid. RIVM report no. 620201001/2010. Bilthoven: RIVM

Heinälä M, Gundert-Remy U, Wood M, Bos PMJ, Ruijten MWAM, Zitting A, Bull S, Russell D, Nielsen E, Cassel G, Leffler P, Tissot SM, Vincent J-M, Santonen T (2013) Survey on European methodologies in the risk assessment of chemical exposures in emergency response situations. RIVM report 320300002. Bilthoven: RIVM

HPA (2007) Chemical incidents in England and Wales 2005. ISBN 0 85951 584 2. Didcot

HPA (2010a)
http://www.hpa.org.uk/web/HPAwebFile/HPAweb_C/1259152298305

HPA (2010b)
http://www.hpa.org.uk/web/HPAwebFile/HPAweb_C/1284475648621

IHR (2005) International Health Regulations. WHO (World Health Organization), published in 2008. http://www.who.int/csr/ihr/en/

IMGD (2008) International Maritime Dangerous Goods code under the auspices of the International Maritime Organisation (IMO), edition 2008, including Amendement 34-08. http://www.imo.org/safety/mainframe.asp?topic_id=158

IPCC (2007) Climate Change 2007: synthesis report. Contribution of Working Groups I, II and III to the Fourth Assessment Report of the Intergovernmental Panel on Climate Change [Pachauri RK, Reisinger A (eds)]. IPCC, Geneva

Jones KE, Patel NG, Levy MA, Storeygard A, Balk D, Gittleman JL, Daszak P (2008) Global trends in emerging infectious diseases. Nature, 451:990–993

JRC (2006) Land use planning guidelines in the context of article 12 of the Seveso II directive 96/82/EC as amended by directive 105/2003/EC. Ispra: Joint Research Center

Kalnicky DJ, Singhvi R (2001) Field portable XRF analysis of environmental samples. J. Hazard. Mater., 83:93–122

Lindhout P, Ale BJM (2009) Language issues, an underestimated danger in major hazard control? J. Hazard. Mater., 172:247–255

Loizou G, Spendiff M, Barton HA, Bessems J, Bois FY, d'Yvoire MB, Buist H, Clewell HJ 3rd, Meek B, Gundert-Remy U, Goerlitz G, Schmitt W (2008) Development of good modelling practice for physiologically based pharmacokinetic models for use in risk assessment: the first steps. Regul. Toxicol. Pharmacol., 50:400–411

Mielke H, Gundert A, Abraham K, Gundert-Remy U (2005) Acute inhalative exposure assessment: derivation of guideline levels with special regard to sensitive subpopulations and time scaling. Toxicology, 214:256–267

Miller FJ, Schlosser PM, Janszen DB (2000) Haber's Rule: a special case in a family of curves relating concentration and duration of exposure to a fixed level of response for a given endpoint. Toxicology, 149:21–34

NAS/COT (2009) Subcommittee for AEGLs.
www.epa.gov/oppt/aegl/pubs/chemlist.htm

Nielsen E (1998) Emergency Planning Exposure Guideline Values (EPEGVs). Unpublished report prepared for the Danish Environmental Protection Agency

Noblis (2009) Defining the potential public health impacts associated with a catastrophic chemical release: protocol for the derivation of predictive toxicity measures for selected injury severity categories. Version 1.2

NRC (1993) National Research Council. Guidelines for developing community emergency response levels for hazardous substances. Washington, D.C.: National Academy Press

NRC (1996) National Research Council. Understanding Risk: Informing Decisions in a Democratic Society. Stern PC, Fineberg HV (eds). Washington, D.C.: National Academy Press

NRC (2001) National Research Council. Standard operating procedures for developing acute exposure guideline levels for hazardous chemicals. Subcommittee on acute exposure guideline levels. Committee on Toxicology. Washington, D.C.: National Academy Press

Öberg M, Palmen N, Johanson G (2010) Discrepancy among acute guideline levels for emergency response. J. Hazard. Mater., 184:439–447

OECD GD 39 (2009) Environmental Directorate: Guidance Document 39 on acute inhalation toxicity testing, OECD Environment, Health and Safety Publication, Series on Testing and Assessment, no. 39

OECD TG 403 (2009) OECD Guideline for the Testing of Chemicals. Acute Inhalation Toxicity

OECD TG 436 (2009) OECD Guideline for the Testing of Chemicals. Acute Inhalation Toxicity – Acute Toxic Class Method

OECD (2001) Report of the OECD Experts meeting on acute exposure guideline levels (AEGLS), 7–8 June, 1999, Paris, France. ENV/JM/MONO(2001)2. Retrieved via
http://www.oecd.org/findDocument/0,3354,en_2649_34369_1_119681_1_1_1,00.html

OECD (2006) Report of the OECD-EC Workshop on Risk Assessment Practices for Hazardous Substances Involved in Accidental Releases, 16–18 October, Varese, Italy.
ENV/JM/MONO(2007)29 SERIES ON CHEMICAL ACCIDENTS no. 16. Retrieved via
http://www.oecd.org/findDocument/0,3354,en_2649_34369_1_119681_1_1_1,00.html

Pearce N, Aït-Khaled N, Beasley R, Mallol J, Keil U, Mitchell E, Robertson C and the ISAAC Phase three study group (2007) Worldwide trends in the prevalence of asthma symptoms: phase III of the International Study of Asthma and Allergies in Childhood (ISAAC). Thorax, 62:758–766

Pesatori AC, Consonni D, Bachetti S, Zocchetti C, Bonzini M, Baccarelli A, Bertazzi PA (2003) Short- and long-term morbidity and mortality in the population exposed to dioxin after the 'Seveso accident'. Ind. Health, 41:127–138

Pichard A, Tissot S (2003) Acute toxicity thresholds – methodology for determining thresholds of lethal effect, irreversible effects, reversible effects and sensory awareness. Institut National de l'Environnement Industriel et des Risques (INERIS)

Post ACUTEX Workshop (2006) Summary of conclusions and recommendations from the post-acutex follow-up seminar, 10–12 May, final version. European Commission Joint Research Centre, Ispra, Italy

Prem KP, Ng D, Mannan MS (2010) Harnessing database resources for understanding the profile of chemical process industry incidents. J. Loss Prevention in the Process Industries, 23:549–560

Pronk MEJ, Wijnhoven SWP, Bleeker EAJ, Heugens EHW, Peijnenburg WJGM, Luttik R, Hakkert BC (2009) Nanomaterials under REACH. Nanosilver as a case study. RIVM Report 601780003/2009

Prüss-Üstün A, Corvalán C (2006) Preventing diseases through healthy environments. Towards an estimate of the environmental burden of disease. Geneva: WHO

Ruijten MWAM, Van Doorn R (2006) Handreiking voor de afleiding van interventiewaarden voor rampenbestrijding. GGD: RIVM

Ruijten MWAM, Van Doorn R, Van Harreveld APh (2009) Assessment of odour annoyance in chemical emergency assessment. National Institute for Public Health and Environmental. RIVM Report 609200001/2009

Scheepers PTJ, Bos PMJ, Konings J, Janssen NAH, Grievink L (2011) Application of biological monitoring for exposure assessment following chemical incidents: a procedure for decision making. J. Expo. Sci. Environ. Epidemiol., 21:247–261

Schwaiger K, Bauer J (2009) Epidemiologie neuer und wiederkehrender Vektor-assoziierter Krankheiten [emerging and resurging vector-borne diseases] unter besonderer Berücksichtigung von Klimaveränderungen in Deutschland (Review). Berl. Münch. Tierärztl. Wochenschr., 122:141–160

SCOEL (2009) Scientific Committee on Occupational Exposure Limits. Methodology for the derivation of occupational exposure limits: key documentation (version 6), December. Available at http://ec.europa.eu/social/BlobServlet?docId=4526&langId=en> (accessed 2nd June 2010)

Sferopoulos R (2010) A review of Chemical Warfare Agent (CWA) detector technologies and commercial off-the-shelf items. Report no. DSTO-DG-0570, DSTO, Australia. Available from http://hdl.handle.net/1947/9902 (accessed 20th August 2010)

Shine C, Kettunen M, Ten Brink P, Genovesi P, Gollasch S (2009) Technical support to EU strategy in invasive alien species (IAS). Recommendations on policy options to minimize the negative impacts of invasive alien species on biodiversity in Europe and the EU. Final report for the European Commission. Brussels: Institute for European Environmental Policy (IEEP)

Slob W, Pieters MN (1998) A probabilistic approach for deriving acceptable human intake limits and human health risks from toxicological studies: general framework. Risk Anal., 18:787–798

Slob W (2002) Dose-response modeling of continuous endpoints. Toxicol. Sci., 66:298–312

Starck LN, Jeuland M, Braun-Unkhoff M, Lecerq P, Bogers P, Salvi O (2010) ALFA-BIRD – Alternative Fuels and Biofuels for Aircraft Development. IASH newsletter no. 42, 17–23

Stevenson H, Bos PMJ, De Raat WK (1995) Review of applied factors to derive health based recommended exposure levels, TNO Report No V95.092, TNO Nutrition and Food Research, The Netherlands

Trainor MT, Ridgway O, Macbeth RW, Wilday AJ, Balmforth HF (2006) Substance prioritisation for the development of EU Acute Exposure Toxicity Thresholds (AETLs). J. Hazard. Mater., 133:16–23

Van Loveren H, Cockshott AGT, Gundert-Remy U, de Jong WH, Matheson J, McGarry H, Musset L, Selgrade MK and Vickers C (2008) Skin sensitization in chemical risk assessment: report of a WHO/IPCS international workshop focusing on dose–response assessment. Reg. Toxicol. Pharmacol., 50:155–199

Van Raaij MTM, Janssen PAH, Piersma AH (2003) The relevance of developmental toxicity endpoints for acute limit setting. RIVM Report 601900004/2003

Von Mutius E (1998) The rising trends in asthma and allergic disease. Clinical Experimental Allergy, 28:45–49

Upton MN, McConnachie A, McSharry C, Hart CL, Smith GD, Gillis CR, Watt GCM (2000) Intergenerational 20-year trends in the prevalence of asthma and hay fever in adults: the Midspan family study surveys of parents and offspring. BMJ, 321:88–92

US EPA (1986) U.S. Environmental Protection Agency. Guidelines for carcinogen risk assessment. Fed. Reg., 51:33992–34003

US EPA (1991) U.S. Environmental Protection Agency. Guidelines for developmental toxicity risk assessment. Fed. Reg., 56:63798–63826

US EPA (1996) U.S. Environmental Protection Agency. Proposed guidelines for carcinogen risk assessment. Washington, D.C. EPA/600/P-92/003C

US EPA (2005a). Guidelines for carcinogen risk assessment. Washington, D.C. EPA/630/P-03/001F

US EPA (2005b) Supplemental guidance for assessing susceptibility from early-life exposure to carcinogens. Washington, D.C. EPA/630/R-03/003F

Verhagen H, Feron VJ, Van Vliet PW (1994) Risk Assessment of Peak Exposure to Genotoxic Carcinogens (Publication no. A94/04). The Hague: Health Council of The Netherlands

Welsh M, Saunders PTK, Fisken M, Scott HM, Hutchison GR, Smith LB, Sharpe RM (2008) Identification in rats of a programming window for reproductive tract masculinization, disruption of which leads to hypospadias and cryptorchidism. J. Clin. Invest., 118:1479–1490

WHO (1993) IPCS. Biomarkers and Risk Assessment: Concepts and Principles. Environmental Health Criteria 155. Geneva: WHO

WHO (1999) Principles for the Assessment of Risks to Human Health from Exposure to Chemicals. Environmental Health Criteria 210. Geneva: WHO

WHO (2005) Chemical-specific adjustment factors for interspecies differences and human variability: Guidance document for use of data in dose/concentration-response assessment. IPCS Harmonisation Project Document no. 2. Geneva: WHO

WHO (2009) WHO Manual: Public Health Management of Chemical Incidents. Geneva: WHO

Wijnant S, Meulenbrugge JJ (2010) Externe veiligheidsrisico's van nieuwe stoffen. TNO Bouw en Ondergrond, Apeldoorn: TNO report 034.84295.

Wingfors H, Edlund C, Hägglund L, Waleij A, Sjöström J, Karlsson R, Leffler P, Qvarfort U, Ahlberg M, Thiboutot S, Ampleman G, Martel R, Duvalois W, Creemers A, Van Ham N (2005) Evaluation of the contamination by explosives and metals in soils at the Älvdalen Shooting Range. FOI-report, FOI-R--1877—SE

Wood M, Duffield S (2001) Proceedings from the Workshop on Acute Exposure Guideline Levels (AEGLs), 28–30 May, Major Accident Hazards Bureau, Joint Research Centre, European Commission, Ispra, Italy

Wood M, Pichard A, Gundert-Remy U, De Rooij C, Tissot S (2006) The AETL methodology as a potential solution to current challenges associated with the development and use of acute exposure levels in Seveso II applications. J. Hazard. Mater., A133:8–15

Zijverden van M, Sips AJAM (2009) Nanotechnology in perspective. Risks to man and the environment. RIVM Report 601785003/2009

8 Appendix

Methodological characteristics of current acute exposure guideline methods.

Subject	AEGL	AETL	DIV	EPEGV	ERPG	VSTAF
Sensory awareness	Level of distinct Odour Awareness (LOA)	Level of Distinct Sensory Awareness (LDSA)	Level of distinct Odour Awareness (LOA)	Odour in EPEGV-1	Odour in ERPG-1	SP: threshold of sensory awareness
Tier 1	AEGL-1	AETL-1	VRW	EPEGV-1	ERPG-1	SER: threshold of reversible effect
Tier 2	AEGL-2	AETL-2	AGW	EPEGV-2	ERPG-2	SEI: threshold of irreversible effects
Tier 3	AEGL-3	AETL-3	LBW	EPEGV-3	ERPG-3	SPEL: threshold of lethal effect (1%)
Tier 4	-	-	-	-	-	SELS: significant lethal effect (5%)
Determined exposure duration	10 and 30 minutes, 1, 4 and 8 hours	10 and 30 minutes, 1, 2, 4 and 8 hours	10 and 30 minutes, 1, 2, 4 and 8 hours	1 hour	1 hour	1, 10, 20 and 30 minutes, 1, 2, 4 and 8 hours
Basis of the derivation of PoD	Predominantly single study	Single study (clear criteria adopted)	Weight of evidence	Predominantly single (acute exposure) study	Weight of evidence	Weight of evidence: predominantly acute effects; immediate or delayed death, systemic effects, skin, eye and respiratory effects
Unit	ppm	ppm	mg/m^3	ppm and/or mg/m^3	ppm	ppm and mg/m^3
Target population	Sensitive, but not hypersensitive (e.g. persons with breathing impairment)	Healthy middle-aged population	Sensitive, but not hypersensitive	Sensitive, but not hypersensitive	Sensitive, but not hypersensitive	Sensitive subjects are not considered

Subject	AEGL	AETL	DIV	EPEGV	ERPG	VSTAF
Assessment factors:						
- Interspecies	1-10	1-3	Not specifically defined; current revision similar to AEGL	Not applied, as EPEGVs are intended to be predictive rather than protective	Not transparently defined; WOE	Usually not applied, but may be taken into account
- Interspecies	1-10	1-3*				
Time scaling	Based on probit analyses; otherwise default values (1,3)	Based on probit analyses; otherwise default values (1,3)	Based on probit analyses; otherwise default values (1,3)	Only 1-hour value determined	Not transparently applied	Based on data probit analyses
Sensory awareness	Separate level: Level of distinct Odour Awareness (LOA)	Separate level: Level of Distinct Sensory Awareness (LDSA) including sensory stimuli (taste, colour vision, atmospheric haze)	Accounted for in VRW. Methodology under revision: Level of distinct Odour Awareness (LOA)	Accounted for in EPEGV-1	Accounted for in ERPG-1	Separate level: SP: threshold of sensory awareness. Effects are of sensorial nature and mainly translate into visual and/or olfactory detection of the chemical substance
Carcinogenicity						
- Type of carcinogen	Genotoxic	Genotoxic	All carcinogens	All carcinogens	Genotoxic	One-shot carcinogens

Subject	AEGL	AETL	DIV	EPEGV	ERPG	VSTAF
- Considered at tier	Not incorporated in any tier, but discussed separately in an annex	AETL-2 or AETL-3	AGW (non-genotoxic carcinogens with a known threshold) For other carcinogens carcinogenicity is not incorporated in any threshold, but carcinogenic risk potential (CRP) is mentioned as a separate value	EPEGV-2	ERPG-2	Not addressed specifically, but might be addressed case by case for the derivation of an additional threshold for irreversible effects
- Point of departure	Human virtually safe dose (VSD) or unit risk	Animal tumour risk	Unit risk estimate	Human or animal tumour risk	Human unit risk	
- Dose rate correction factor	6	10	2.8	unknown	2.8	
- Considered risk	10^{-4}, 10^{-5}, 10^{-6}	10^{-4}, 10^{-5}	10^{-4}	10^{-6}	10^{-4}	
Reproduction toxicity						
- Considered at	AEGL-2	AETL-2 (male fertility)	AGW (tier 2)	EPEGV-2	ERPG-2	Not considered. An update of the methodology is expected to address this issue

Subject	AEGL	AETL	DIV	EPEGV	ERPG	VSTAF
- Point of departure	Resorptions and foetal malformations/ variants Foetal body weight case by case	The unborn child does not belong to the target population of AETLs but is addressed by additional factors to be applied by the end user	Resorptions and foetal malformations/ variants Foetal body weight case by case	Effects on reproduction and developmental toxicity	Teratogenicity and foetotoxicity, reproductive effects	
Sensitization	not specifically addressed	Not specifically addressed	Not specifically addressed	Mentioned without further guidance	Not specifically addressed	Not specifically addressed
Neurotoxicity	not specifically addressed, but sufficient case studies	Is addressed but no specific guidance	Not specifically addressed, conformity with AEGL approach is searched for	EPEGV-2, without further guidance	Not specifically addressed	Mentioned in the thresholds for irreversible effects
References	NRC 2001; NAS/COT, 2009; van Raaij, 2003	ACUTEX, 2006	Ruijten and van Doorn, 2006, currently under revision	Nielsen, 1998	AIHA Guideline Foundation, Administrative Operating Procedures, 2010; ERP Committee, 2006	Pichard and Tissot, 2003. An update is scheduled.

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