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Acute exposure to chemical substances and the occurrence of chronic health effects
A report of an RIVM workshop

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Samenvatting

Dit rapport geeft een samenvatting van de presentaties en de discussie van een interne RIVM-workshop met de titel ‘Acute blootstelling en chronische effecten’. Vanwege het optreden van een aantal chemische incidenten in Nederland en het feit dat acute blootstelling een belangrijkere plaats inneemt in enkele wettelijke kaders krijgt acute blootstelling aan chemische stoffen steeds meer aandacht.
Eénmalige blootstelling aan chemische stoffen kan in potentie chronische gezondheidsklachten induceren (bijv. ontwikkelingstoxiciteit, carcinogeniteit, immunotoxiciteit, allergie). Echter, wanneer de (vermeende) blootstelling aan chemische stoffen plaatsvindt tijdens een incident of ramp, kunnen er ook z.g. lichamelijk onverklaarde klachten ontstaan (bijv. hoofdpijn, geheugenproblemen, neus-, keel-, luchtwegklachten, vermoeidheid, etc.). Het doel van deze interne RIVM-workshop is om initiatieven en activiteiten op het gebied van chronische effecten en/of lichamelijk onverklaarbare klachten bij éénmalige blootstelling in kaart te brengen. De workshop-participanten hebben de volgende aanbevelingen geformuleerd: a) het zwaartepunt van de risicoschatting bij acute blootstelling moet (blijven) liggen bij de puur toxicologische risicoschatting, b) het RIVM hoeft niet het belangrijkste kenniscentrum in Nederland te worden op het gebied van Lichamelijk Onverklaarde Klachten, maar moet door strategische allianties wel toegang hebben tot state-of-the-art kennis en instrumenten om LOK te meten, c) het RIVM moet meer aandacht besteden aan het ontwikkelen van instrumenten voor specifieke elementen in de acute risicoschatting – zoals ontwikkelingstoxicologie, carcinogeniteit en de inductie van overgevoeligheid .

Summary

This report provides a summary of the presentations and the discussion at the internal RIVM workshop “Acute exposure and chronic effects”. Acute exposure to chemical substances has received increasing attention because of several chemical incidents in the Netherlands and because acute exposure becomes more and more important in regulatory frameworks.
A single exposure to chemical substances can potentially induce long lasting health effects (e.g. developmental toxicity, carcinogenicity, immunotoxicity, allergy). However, when (presumed) exposure to chemicals involves a severe incident or disaster, also medically unexplained symptoms may occur (headache, memory problems, upper respiratory tract complaints, fatigue etc…). The aim of the workshop is to identify ongoing activities and initiatives to deal with chronic and/or unexplained effects due to a single exposure to chemicals. The workshop participants made the following recommendations: a) focus risk assessment on toxicological aspects, b) RIVM does not need to be the focal point of expertise and specific knowledge on psycho-social induced health effects in The Netherlands, but it is advisable to strengthen any cooperation is in this area in order to gain full access to the available structures and knowledge within the Netherlands, c) further initiate research to develop tools for acute risk assessment on specific toxicological aspects like developmental toxicity, carcinogenicity, and induction of sensibilisation.

1. Introduction

Acute exposure to chemical substances and the risks associated with such a short term exposure have received increasing attention over the last decade. Especially since a number of major incidents have occurred within the Netherlands, in which exposure to chemical substances did – to some extent – occur. Examples of such incidents are: the crash of the El-Al airplane in Amsterdam, the explosion of a firework factory in Enschede, a fire in an incineration facility in Drachten, and a fire on a ship in the port of Vlaardingen releasing fumes over a part of the city of Schiedam. In addition to the occurrence of chemical incidents, acute exposure has become a major aspect of the toxicological evaluation of chemical substances in some regulatory frameworks. For example, derivation of the acute reference dose (ARfD) for pesticides has become a rather standard aspect of the regulatory toxicological assessment over the last couple of years. Furthermore, setting emergency response intervention values for hazardous substances (such as Acute Exposure Guideline Levels (AEGL's)) has become a routine task within RIVM. For human health risk assessment of certain consumer products (e.g. pest control products) – primarily those characterised by single use – acute exposures are the basis for their safety evaluation.
The risk assessment of acute or short term exposure to chemicals has repeatedly shown that some major knowledge or methodology gaps exist, specifically within regulatory frameworks. Within the project 'Acute toxicity and risk assessment' (RIVM project V/320003[†]) some of these gaps are being investigated in order to provide some solutions or at least some form of consistency in dealing with such aspects. Activities are set up on the issues of the ARfD, the use of developmental toxicity endpoints, and the risk assessment of carcinogenicity at single (peak) exposures.
In a fourth specific subproject, titled 'acute exposure and chronic effects', a first exploration is performed to describe activities, experiences and opinions in this subject within the RIVM. Based on this first exploration, possible lines of investigations could be proposed for future work on this specific issue.

[†] Former project number V/601900

2. Background Information

2.1 Problem definition

In every day life, people are exposed daily to a range of chemical substances mostly at low dosages. Such exposures normally do not pose a health risk to the population. However, over the past decades, short term exposure to toxic substances involving substantial amounts of people has received increasing attention. Such short term exposures may be encountered through contaminated food (e.g. the Minamata Disease in Japan, the Toxic Oil Syndrome in Spain, the 'dioxin-crises' in Belgium and The Netherlands, and more recently nitrofen contamination of corn in Germany) or through industrial or accidental releases (e.g. the Seveso incident, the Bhopal disaster, and the release of cadmium from a fire in Drachten (NL)). Among the industrial calamities, the Bhopal disaster is the worst chemical disaster ever [1].

People have been exposed to natural disasters from time immemorial. However, man's activities have created a new form of disasters, especially since the industrial revolution [1]. In his classical review, Bertazzi [1] pointed out that the first documented industrial disaster occurred probably in the 1600's. However, in the last century, various natural and industrial accidents and disasters have occurred and have been documented, and various comprehensive reviews on the health consequences of these incidents have been published [1,11].
After the Seveso incident chloracne was the most evident immediate health effect [2] although increased incidence of other effects (e.g. cardiovascular- and respiratory diseases; lymphatic- and hematopoietic neoplasms) have also been reported in later follow-up studies [3,4]. Many papers have reported delayed or prolonged health effects in victims exposed to methyl isocyanate in the Bhopal incident. Long lasting health effects were primarily chronic inflammatory damage to the eyes and lungs [5,6], lung function changes [6,7], immunologic and hematologic effects [7,8], and developmental toxicity [5,6,7,9]. A significant increase in fetal loss and neonatal death has been reported in the population exposed in Bhopal [9].
In these cases, a substantial exposure to a toxic substance has resulted in long lasting health effects.

When people are exposed to a chemical substance during a short time period (e.g. hours up to a few days), the primary concern is, of course, directed towards immediate health effects and necessary mitigation measures. Direct assessment of early effects is not only important from a health impact point of view, but is also useful in the definition of groups of people that need specific medical attention. In addition, early health effects can provide information on the extent of exposure and may identify groups of people that may require (medical) follow-up. However, attention for health effects has often been terminated when the incident (direct exposure) is over, and hence, epidemiological follow-up is often not performed to assess

delayed or persistent health effects, or the health care needs of the exposed (involved) population [10].
Nevertheless, it has been observed that a significant part of the people exposed in a ‘severe incident’ may have prolonged health complaints, sometimes even several years after the exposure [1,11, 12, 13]. An important question, however, remains whether the reported health effects are truely related to exposure to toxic substance per se or are due to a non-specific exposure to an ‘adverse event’. In the next section, these aspect are further described.

2.2 Exposure-related and Event-related effects

Acute or short term exposure to chemicals as a consequence of some type of accidental release or disaster has specific characteristics. Except for toxicological aspects related to the type of substance(s) released, (the amount of substance(s) released, the concentration of the substance(s) in air or – in some cases – water, and the duration of exposure) various other factors contribute to the appraisal of the event. These factors include non-voluntary exposure, loss of control, accidental or intentional exposure, uncertainty, unfamiliarity, unacceptability, loss of life or injury of family or relatives, loss of livelihood, loss of confidence and others [1,11,14,15]. Often chemical releases or disasters are experienced as a shocking event with a substantial psychological pressure which obviously is associated with some level of stress [11]. Thus, in many cases where people are exposed to chemicals as a consequence of an accidental release or a chemical disaster, the exposure of people can be viewed as a mixture of some form of stress and toxic substances. Each component of this ‘exposure-matrix’ has a certain potency to induce health effects [14,18]. In addition, both components may interact with each other to some extent [16,17] although for most cases such a level of interaction is not known at all. This was clearly described by Spurgeon who proposed a biopsychosocial model [18,19]. In this model both biological as well as psychological and social elements may contribute to the occurrence of symptoms after experiencing a hazardous situation.
In reality, people that have been exposed during a chemical release or a disaster may or may not show various symptoms and health effects. The majority of people with symptoms will tend to relate these symptoms or health effects to the chemical exposure that they may have perceived [19,20]. However, in actual risk assessment cases, the risk assessor will not always be able to relate the symptoms or health effects to the chemical(s) and exposure involved. An unresolved issue remains and toxicologically unexplained symptoms are identified, particularly if no formalized epidemiological investigation is undertaken to study the possible relation between chemical exposure and health effects. A valid question in these circumstances is whether the observed health effects are chemical-related, event-related, or a combination of both. In fact, event-related effects frequently occur and are often not related to any specific substance [11,12].

3. Purpose and outline of the Workshop

Within the RIVM, various groups are involved in the exposure assessment, health effects research, and risk assessment of accidental exposure to chemical substances. Among these are the National Poisons Information Centre (NVIC), The Expertise Centre for Substances (SEC) The Centre for Substances and Integrated Risk assessment (SIR), The Laboratory for Environmental-related Health Effects Research (MGO) including the Centre for Health Impact Assessment at Disasters (CGOR), The Inspectorate research and Environmental Incident Service (IMD), and the Laboratory for Toxicology (TOX).
Whether and how long lasting health effects and medically unexplained effects are dealt with in the normal risk assessment is variable depending on the nature of the incident, the severity of the incident, the time pressure, who is asking questions about the risk, and to whom the question is posed. The workshop is organised to identify similarities and differences in the risk assessment process on these aspects in various departments of the RIVM and to identify whether new initiatives for research are needed in this field.
The workshop was restricted to chemical incidents (biological- and nuclear incidents were not specifically subject of discussion). From various departments involved in risk assessment of chemical incidents, representatives were invited including SIR, SEC, NVIC, IMD, and MGO (see Appendix for a list of participants).

4. Presentations and opinions

4.1 The National Poisons Information Centre (NVIC)

The National Poisons Information Centre (NVIC) is specialized in acute risk assessments on the possible risks to humans as a consequence of exposure to chemical and biological agents, and radiation. One of the key tasks is the surveillance and monitoring of acute poisonings. The Centre provides a 24-hours information service for physicians, pharmacists, veterinarians, and members of local, regional and national authorities (first responders, Inspectorates and Ministries) who are confronted with possibly intoxicated patients. Information and advice is given with regard to health effects and treatment of individual patients as well as for groups in case of major disasters. At present, the NVIC receives over 35.000 information requests a year.
In addition to it's information and advisory task, the NVIC performs healthy volunteer and patient studies with emphasis on biokinetics and biodynamics of chemical agents. The results of these studies can be used to develop adequate physiologically based biokinetic or biodynamic models for human risk assessment, in order to fill in the gaps of knowledge which cannot be solved with in vitro or animal studies.

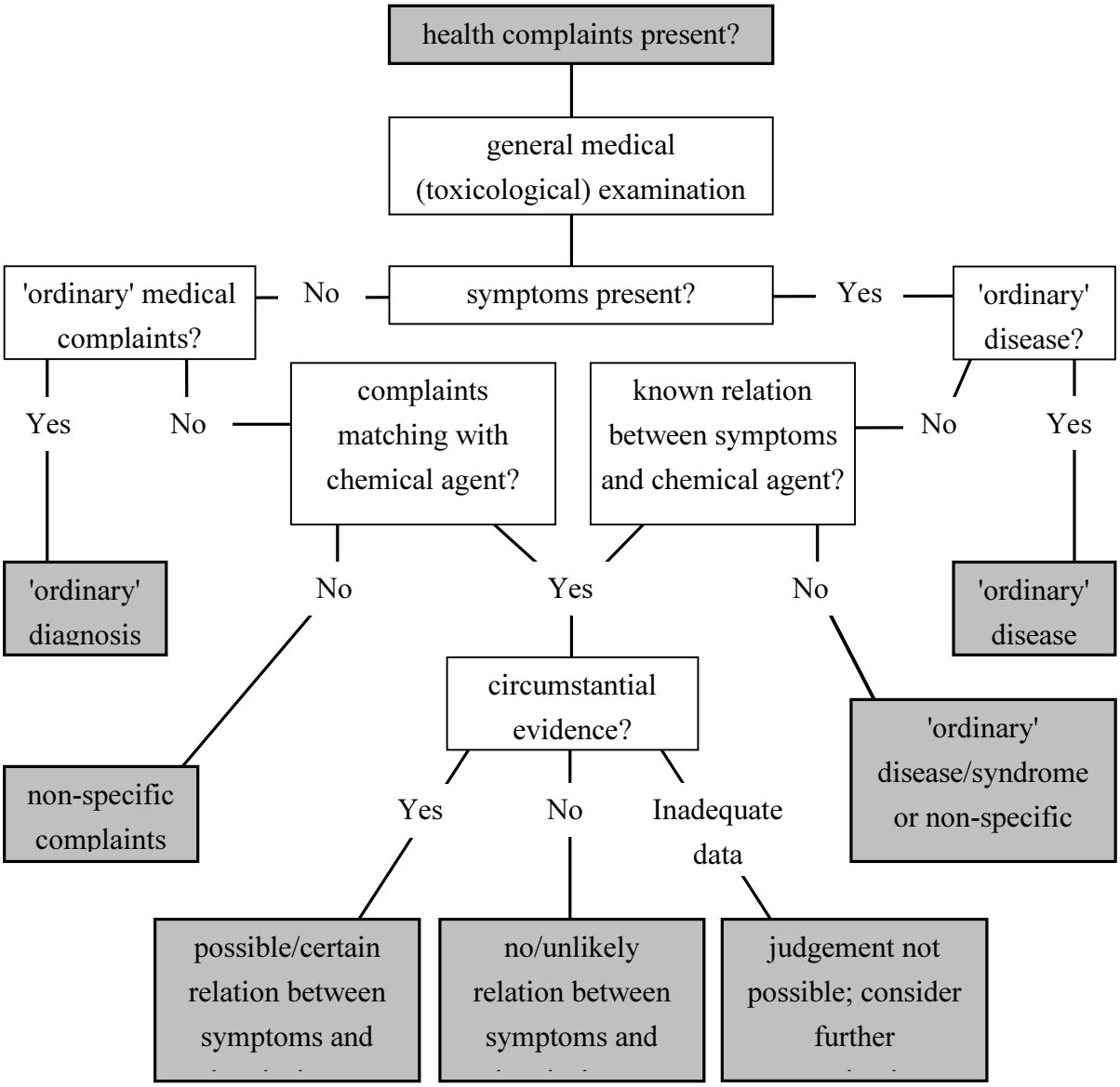
The risk assessment process as it is carried out with regard to acute poisonings consists of several steps, integrating the available scientific information on the toxicity of the chemical(s) involved, the exposure assessment and the effect assessment.
With regard to the issue of acute exposure and the question whether this exposure can lead to chronic health effects, the risk assessment process is the same. Special emphasis is put on the entire time span between exposure and health effects, and on the chronological order of appearance of health complaints and/or symptoms. The exposure assessment is aimed at estimating the level of exposure, expressed as mg/kg bodyweight or mg/m^3 air. The effect assessment provides information on the possible health effects that may occur after exposure to the chemical(s) involved, as well as information on the likelihood of such effects at the levels of exposure as estimated in the exposure assessment, and the time span as indicated by the patient. A comparison is then made between the actual health complaints and/or symptoms of the patient and the known clinical course of the intoxication by the specific chemical(s).

Adverse health effects can occur immediately during or after exposure. It is important to distinguish between primary health effects, as a direct consequence of exposure and the toxicity of the chemical(s) involved, and secondary health effects, due to the severe intoxication and general medical condition of the patient. For instance, coma and respiratory failure can be primary effects due to exposure to certain chemicals. If immediate and adequate treatment is not available, this can lead to severe hypoxia and irreversible brain damage with long lasting effects (secondary effects). Or, for instance, accidents occurring during severe ethanol poisoning, may result in bone fractures (secondary effect). One should therefore consider whether long lasting effects have a primary or secondary nature, as this may be of help in assessing the medical prognosis.

A different question is whether a specific exposure (or an assumed exposure) can lead to the occurrence of health effects after a certain lag time. Assessments of the risks of carcinogenic and reproductive effects are not carried out by the NVIC. For issues regarding mutagenesis and carcinogenesis NVIC refers to the Laboratory of Toxicology (TOX) and for develpmental toxicity to the Teratology Information Service (TIS).
Naturally, the more information on the (assumed) chemical(s) involved, the (assumed) exposure, and possibly occurring health effects is available, the easier the entire risk assessment process is carried out. On the other hand, the patient presenting himself with acute or chronic health complaints, without any information on chemicals or exposure, is a common medical situation. The approach to the patient with health complaints as a possible consequence of exposure to chemical agents, does not differ from the general approach to patients with health complaints. The NVIC frequently receives questions from physicians dealing with patients who attribute their health complaints to chemical exposure. These physicians are either adviced in writing, or patients consult the clinical toxicologists of the NVIC via the Medical Toxicology Outpatient Clinic of the Utrecht Medical Centre. The approach to these patients is as follows. First, a patient evaluation, including a history and general physical examination, is carried out. Much attention is devoted to possible exposures to chemical agents, for instance during work, recreational activities, accidents etcetera, in order to acquire clues to the identity of the chemical (if any). Then, based upon medical and clinical toxicological knowledge, a differential diagnosis is made. Both ‘ordinary’ medical conditions and intoxications are included in this differential diagnosis. Additional laboratory tests and other specific examinations can be carried out to establish a diagnosis. Based upon

years of experience with these patients an algorithm has been developed to make this risk assessment process transparant.

Algorithm for the medical decision whether or not it is likely that chronic health complaints and/or symptoms can be atrributed to exposure to chemical agents.



Long term experience from the NVIC, as well as from other clinical toxicology departments in the world, show that although often patients believe their chronic health complaints are caused by poisoning by chemicals, a thorough medical and toxicological examination, as well as biomonitoring rarely ever show an unusual exposure and burden of the accused chemical. If, after a lag time, chronic health complaints or symptoms are indeed caused by exposure to chemicals, this is mostly due to long term exposure to chemical agents, often in an occupational setting.
Chemical disasters have special features that require specific consideration. The principles of risk assessment are the same, however, the impact of the disaster plays it's own role. The reporting of physical symptoms in the aftermath of a disaster is the result of a complex combination of cultural, psychological, social, and physiological factors.

The role of the NVIC is mostly restricted to the acute phase of an intoxication and to the necessary medical treatment. Structured, organized follow-up of patients is uncommon. Therefore, little information is available on the occurrence of chronic effects due to acute intoxication except for information already available in the TIK[‡]-database.

4.2 The Environmental Health Service (MMK)

Mark van Bruggen (RIVM/IEM) is the national coordinator for the Environmental Health Specialists ('Medisch Milieukundigen') in The Netherlands. Part of his assignment involves handling ad-hoc risk assessments such as those described in section 4.3. For this workshop, he has requested the environmental health experts within the various municipal health services across the country to report on the occurrence of chronic effects due to single or short term exposures to chemicals.
However, most of the cases handled by environmental health experts involve long term exposures. So, there are no data recorded on experiences from the municipal health services with respect to acute exposures. According to this information, there is no evidence that chronic effects due to a single exposure occurs frequently, nor to the contrary. However, follow-up investigation to monitor any long lasting effects is not routinely performed. Therefore, if any effects occurre after some lag-time is almost impossible to relate them to a certain chemical exposure.
Most of the incidental exposures at the municipal level deal with inhalation exposure with fires. It is a rather standard procedure to state that people who were close to the fire, inhaling

[‡] TIK: Toxicologisch Informatie en Kennis systeem.

fumes, could experience some health effects but that no other risk for public health is anticipated. Recently, RIVM published a report on the release of specific chemical substances during fires [21].
An important role of environmental health experts at the municipal level concerns risk communication. In this respect it needs to be decided whether uncertainties in the risk assessment need or do not need to be communicated to the public. In addition, one should take into account the expected perception of the advice.

4.3 The Centre for Substances and Integrated Risk Assessment (SIR)

The Centre for Substances and Integrated Risk Assessment (SIR) is involved in the hazard and risk assessment of all types of chemicals (except for human drugs) with respect to human health. Frequently, SIR is consulted for actual risk assessments in the case of incidental / accidental exposures. Examples are fires, chemical releases, and exceeding of toxicological limits in environmental compartments or food. As an illustration, Paul Janssen (Project leader Ad-Hoc Risk Assessments) presented some examples of actual cases to describe the experiences within SIR.

Case 1 – Emission of catalysator substance

Single emission of 30-60 tons of white powder containing 1100 mg nickel per kg powder. The exposure to nickel was estimated to occur over 1 hour and was calculated using models: 0.0005 mg/m^3 for a few hours due to inhalation, oral 0.01 mg due to ingestion of dust particles and dermal contact with the undiluted material.
Risk assessment:
oral limit value: 0.1 mg/day; exposure 0.01 mg $\Rightarrow$ no risk
inhalation NOAEL: 0.02 mg/m^3, exposure 0.0005 mg/m3 $\Rightarrow$ no risk
dermal LOAEL (for hypersuceptible humans): 5 mg/kg bw; exposure 1100 mg/kg $\Rightarrow$ risk
However, additional cancer risk is < 1 : 10^{-6}.

Case 2 – Bijlmer Disaster (El Al Plane Crash in Amsterdam)

As a consequence of a crash of a transport plane on a crowded living area in Amsterdam, a severe fire with chemical releases occurred. Below, for some compounds monitored, a brief

risk assessment is presented. All exposure levels as presented below represent mean values for 1 hour periods [22].

Chromium (VI)

Critical effects: cancer and respiratory sensitisation

Exposure: 0.086 mg/m^3

Additional cancer risk 1 : 10,000 (as calculated by approach of the Dutch Health Council (using Dose-Rate-Correction-Factor of 10)

LOAEL for sensititsation = 0.002 mg/m^3 (for workers) $\Rightarrow$ risk cannot be excluded

Hydrogen fluoride

Critical effect: irritation

Exposure 0.04 mg/m^3

1h limit value for severe irritation (WHO): 1.6 mg/m^3 $\Rightarrow$ no risk

Carbon monoxyde

Critical effect: COHb formation

Exposure 64 mg/m^3

1h limit value 30 mg/m^3 (Based on a maximal 2.5 % COHb level in blood).

Health effects in humans with cardiac problems is possible but substantial effects in human population (dizziness, nausea, vomiting) are not expected.

Antimony

Critial effect: cancer and respiratory sensitization

Exposure 0.5 mg/m^3

Additional cancer risk 1 : 100.000

LOAEL for respiratory sensitisation 0.40 mg/m^3 $\Rightarrow$ probably no risk.

As illustrated in the cases above, the normal procedure for these types of risk assessments is to compare the estimated or measured exposure levels with available limit values. The most easily (or only) available limit values are chronic limit values such as the ADI, RfC, or TLV (for occupational exposure). If needed, limit values are used as systemic values or are subject to route-to-route extrapolation. When the exposure level during a short term incident does not exceed a chronic limit value, no risk is expected. When the exposure exceeds the chronic limit value, a refinement of the risk assessment is necessary using other types of limit values (e.g. acute or short-term MRL's from ATSDR, or emergency response intervention values such as ERPG's or AEGL's) or using NOAEL's or LOAEL's directly from toxicity studies.

Irreversible, long lasting, toxic effects which may be relevant after an acute exposure are:

- Cancer
- Immune effects (allergy, sensitisation)
- Teratogenicity
- Endocrine disruption (complex issue, many potential windows of vulnerability)
- Neurotoxicity in children (?)

The occurrence of long lasting effects due to a single exposure is almost never investigated. So, actually it is not known whether these types of effects do occur. Only with respect to carcinogenicity some information is available. When the toxicological mechanism of action and the target site are known, PBPK-modeling may be an approach to determine the effect of a single exposure. However, this condition does not occur for many chemicals.

4.4 The Centre for Health Impact Assessment of Disasters (CGOR)

At the RIVM, a centre for (epidemiological) health impact assessment of disasters was initiated in 2001; the center was formally opened in February 2003 and is part of the Laboratory of Environmental Health Research (MGO). The project director of this centre, Marc Ruijten, gave a presentation on the thoughts and needs from his point of view.
As a starting point, the need of clear definitions was emphasized. With respect to *acute exposure*, a maximal duration should be defined with the remark that the exposure should be incidental or intentional. So, repeated intermittent peak exposures should not be covered in this definition. Examples of acute exposures to chemicals are those due to explosions or fires. Important determinants for the appraisal of such an event is the need or possibility to escape and the fact whether the event is accidental or intentional.
In addition to this basic question, it was pointed out that disasters are not confined to chemicals. Also nuclear and (micro)biological risks fall within the scope of the centre. In general, an incident can generally be qualified as a shocking event with high psychological pressure.
The qualification *chronic effects* after acute exposure has at least two aspects: latency and reversibility. Relevant questions are: what latency time should be taken into account (more

than 1 week ?), and what criteria should be used for reversibility ? The most important examples of chronic effects are carcinogenicity, reproduction toxicity, and neurotoxicity. In addition to these frank toxicity endpoints, people involved in a disaster often have psychological problems related to facing such a stressfull event. Furthermore, the involved population may show various types of health effects which cannot be explained by exposure to chemicals identified (Medically Unexplained Physical Symptoms, MUPS). In Dutch, such effects are abbreviated LOK (lichamelijk onverklaarde klachten). It is important to further research the etiology of such health effects : are the effects 'chemical – related', 'event – related' or 'individual – related'?

CGOR is a consumer of risk assessment information (hazard as well as exposure). This information is needed for:

1. Input on the decision of initiating an epidemiological health investigation
2. Determination of the most relevant type of investigation
    - Goal of the investigation
    - Single investigation / follow-up needed
    - Selection of relevant substances for exposure monitoring
    - Selection of relevant health effects for monitoring
    - Toxicokinetic information
    - Reference values (for both exposure and physiological endpoints)
    - The formulation of additional information
3. Establishing the safety of rescue workers (policemen, firemen, first-aid workers).

On the other hand, CGOR is also a producer of risk assessment information because the centre contributes to:

1. Knowledge on concentration-time-effect-relations of chemicals
2. Knowledge on 'event-related' health effects
3. Knowledge that can be used for reducing public concern, the psychological handling of the event and an assessment of the required (medical / psychological) health care.

5. Discussion

After the presentations described in chapter 4, an exploratory discussion was initiated based on the questions below. It was not the intention of the workshop to provide definitive answers to all of these individual questions. However, the questions provided merely served as a general framework for discussion.

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a. What is meant by 'chronic effects after acute exposure' ? Long-lasting effects after a single exposure ? Which effects are included ?
b. Is the answer to question a. similar for all RIVM – stakeholders in this area ?
c. Is the available expertise within the RIVM sufficient in this area ?
d. If not, which type of knowledge or expertise is lacking ?
e. Is this knowledge or expertise available within other Dutch organisations or institutes ?
f. Is it necessary for the RIVM to obtain this type of knowledge within its own organisation? If so, in what way should that type of knowledge / expertise be developed ?
g. Is the knowledge / expertise available sufficiently applied in cases of acute exposure to chemicals ?
h. Is it possible to separate 'chemical-related' and 'event-related' effects ?
i. If so, is it possible to develop a general guideline focused on the identification and assessment of 'event-related' effects ?
j. Risk communication: Impact of the incident, do we need to use comparisons in risk communication (e.g. the risk is equivalent to smoking 2 cigarettes) ?

In the sections below the discussion on the subject of 'Acute exposure and chronic effects' is summarised in a number of subheadings. The information and opinions described below only reflect the discussion of the participants of the workshop and do not necessarily imply that these are official opinions or strategic decisions by RIVM.

Definitions

Acute exposure and chemical agents

Within the context of this workshop, the concept of 'acute exposure' was discussed. . The participants agreed on the following definition: *'a single exposure within a time-frame of one or a few consecutive days'*. In every day life, this definition covers most chemical incidents or intoxications and a major part of the cases in which toxicological limits are exceeded in the

environment or in food. The risk assessment of intermittent exposures, e.g. repeated peak exposures to the same substance(s), is a problematic issue and is not further discussed within this workshop although this scenario may be a relevant issue also for chemical incidents (e.g. repeated intermittent exposure of firemen or police officers performing perimeter control). Although the participants of the workshop acknowledged that many aspects of the discussion are relevant to exposure to various agents, including biological agents and radiation, the discussion will be confined to exposure to chemical agents.

Chronic Effects

After some deliberations, the participants agreed to the following definition of chronic effects within the context of this workshop: *'Health effects that will remain present for a considerable period of time after exposure, which may appear immediately or after a substantial latency time of at least days to weeks'.*

The severity of the effect (e.g. carcinogenicity or teratogenicity) is not a restrictive criterion for inclusion or exclusion. Therefore, in principle every type of effect that can be covered by this definition is relevant for the discussion. However, various participants indicated, based on their experience, a number of toxicological endpoints that may be important to consider after a single exposure to chemicals. These effects are actually reported to occur after a single exposure to chemicals or, based on their severity, always require specific attention. These effects include:

- Carcinogenicity
- Developmental toxicity (especially teratogenicity)
- Induction of allergic reactions (hypersensitivity) or an increase in effects of already existing hypersensitivities.

However, also long lasting effects on any other organ or system should be regarded.

Risk assessment for chemicals

The risk assessment of a single exposure to a chemical substance is often a straightforward procedure. The measured or the estimated exposure level is compared to available toxicological limit values (ADI, RfC, TLV, other values such as the ATSDR MRL's, AEGLs, or ERPGs, or recommendation values from clinical toxicology). When such limits are not available, exposure is related to NOAELs or LOAELs from toxicity studies. When the exposure does not exceed the limit value, the health outcome can be predicted with

reasonable accuracy. When the exposure level and duration are above the limit value, effects cannot be excluded and a further refinement of the risk assessment is performed. The most likely health effects are those that can be deduced from the toxicological profile of the substance (e.g. liver weight or neurotoxicity). This approach is substance-driven. In other words, the risk assessment procedure proceeds from substance to possible or likely effects. This approach has been performed for a long time and is well-known within the RIVM and is standardised within certain (regulatory) framworks. The approach is used by both SEC/SIR and NVIC.

There is less experience within the RIVM with risk assessments in the opposite direction, i.e. starting with symptoms or health effects and assessing a potential previous exposure. However, the basic approach, such as employed by clinical toxicologists of the NVIC, is to try to match the pattern of symptoms and health effects with toxicological profiles of potential substances. Such cases occur when people report health effects and ascribe them to a previous exposure to known or unknown chemicals.

Examples:

- a woman showing hematological abnormalities which, according to this individual, are related to an accident with benzene release some years before. However, upon medical toxicological examination there appeared to be no relation.
- General health complaints observed in people involved in the Bijlmer-disaster (Plane crash) have been ascribed to potential exposure to unknown chemicals of the cargo which would have been released at the crash of the airplane.

Part of the symptoms and health effects observed in people (potentially) exposed to chemicals during an incident or chemical release for a short period of time, may be explained by exposure to a specific chemical. However, another part of such symptoms and health effects cannot be related in a reasonable way to any chemical exposure (see e.g. the ‘Sheep Dipping Story’[19]). When establishing the probability of such health effects due to a specific chemical exposure, the following criteria can be used:

- The number of different symptoms or health effects
- The coupling of symptoms: is it possible to link various symptoms or health effects to a single pathophysiological process ?
- The history of the individual case: which types of exposure could have occurred and at what time, what are confounding factors (occupational conditions, smoking etc…) ?

- Which reasonable match can be found with the toxicological profiles of substances potential exposed to ?
- What is the degree of certainty that the current toxicological profile of the chemicals involved is complete, and not missing important endpoints?

Although similar approaches are used by SEC/SIR, NVIC and within the field of Environmental Health Experts (MMK), there is also a difference. The work of MMK and NVIC is mostly retrospectively organised, i.e. risk assessment is performed for a situation that has actually occurred. Although SEC/SIR is also involved in retrospective risk assessment, a large part of SEC/SIR activities also deals with prospective risk assessment, for example in the case of regulatory assessments.
Another difference is the level of risk estimation. Where NVIC is often focused on the individual (advising on the toxicological risks of a certain patient and on its treatment), the work of MMK and SEC/SIR mostly deals with population risks or differences in subpopulations.

Stress, event-related phenomena, and associated expertise
In addition to health effects that can be more or less directly attributed to toxicity, sometimes a risk manager has to deal with a number of symptoms or health effects which cannot be reasonably explained by any potential exposure to chemicals. Such Medically Unexplained Symptoms (Lichamelijk Onverklaarde Klachten, LOK) may not be ‘chemical-related’ but ‘event-related’, possibly as a consequence of psychosocial stress exposure associated with other aspects of the incident or even the personality of the victims. In this respect it was emphasized that also for psychosocial stress, people probably need a certain ‘exposure’ above a threshold in order to develop health effects. In addition, it was stated that much could be learned from non-chemical incidents, since also in cases of e.g. natural disasters people may show ‘event-related’ symptoms or health effects.
RIVM toxicological risk assessors have limited knowledge and experience with the assessment of such psycho-social related health complaints. It was generally agreed by the participants of the workshop, that the chemical risk assessors at the RIVM should focus on the chemical-related risk assessment. However, it would be a step forward if risk assessors will realise that beside chemical-related effects, also other health effects can be anticipated. However, no conclusions or opinions should be formulated on psycho-social induced effects by chemical risk assessors (SEC/SIR, NVIC). Because Medically Unexplained Symptoms

appear to occur so frequently after disasters, it is crucial that the Centre for Health Impact Assessment of Disasters (CGOR) develops a reasonable knowledge of the determinants of such symptoms, and prepare for their actual assessment. This Centre should build strong relationships with other Dutch expert centers and institutes which cover this area sufficiently, such as Impact (National Expert Centre for Psychosocial Care after Disasters) and the Institute for Psychotrauma.
It was concluded that RIVM does not need to be the focal point of expertise and specific knowledge on psychosocial induced health effects in The Netherlands, but it was advised to strengthen any cooperation is in this area in order to have full access to the available structures and knowledge within The Netherlands.

Risk communication

Acute exposure to chemical substances mostly relates to chemical incidents. In these conditions large attention from the public and media is involved. Therefore, risk communication is a very important issue under these conditions [10,23]. Although not being a major subject for the present workshop, the participants discussed various aspects of risk communication. Here we only stipulate the aspects covered in the discussion. For a detailed discussion on risk communication, other sources need to be consulted [23,24].
In case of a chemical incident, both risk evaluation of exposure to chemical susbtances as well as risk communication are important activities. The participants discussed which of these two aspect should require more attention: a thorough assessment of the exposure and human health risks or a sound communication with the people and media. Because often uncertainty and anxiety are present within the population, risk communication directed towards reducing these feelings is important. However, it is also important that risk communication is transparent and should be open and fair. In this respect, a rapid but well-performed risk assessment is a prerequisite for a successful transparent risk communication. In addition, it was discussed whether risk assessors in these cases need to communicate their uncertainties concerning their risk assessment. Although uncertainties need to be considered to some extent, in cases of chemical incidents, people need simple and unidirectional information in order to provide clarity in the severity and/or the possible consequences of the incident. If uncertainty in the risk assessment is substantial and is communicated, it is important to be clear how to handle such uncertainty (e.g. provide directions to resolve the uncertainty, provide a time frame to provide additional information, take necessary actions to provide maximal health protection (see e.g. ref 23).

Furthermore, in risk communication it should be considered how a certain risk assessment outcome is perceived by risk managers and other policy makers and/or the general public. This does not mean that the outcome itself should be different, but the form of the presentation is relevant (see also ref. 23).

Other points

In addition to the general themes presented above, some points were discussed or became apparent during the meeting that are interesting to note. Below a short summary is given of these points.

Exposure

When chemical incidents occur, the public interest to know whether health effects can be expected is logical. However, an adequate estimation of the type, frequency and severity of health effects can only be given when the exposure characteristics and the composition of the exposed population are known. This is a major problem for risk assessment during / after chemical incidents because exposure is normally poorly characterised. Both the type of chemical exposures (identification of substances or mix of substances) are well as the concentration and time of exposure are mostly unknown or estimated at best. Therefore, it is of great importance to perform as many measurements as possible to obtain a general knowledge about human exposure during chemical incidents. From these data we can learn how to estimate or model a potential exposure during chemical incidents. Recently, RIVM started a new project on integrated monitoring and modelling of chemical substances released during chemical incidents (titled ‘Risk assessment for populations during inhalation exposure as a consequence of calamities by means of integral monitoring en modelling – RISPIEK’). Projectleaders are H. Bloemen (RIVM/LVM) and F. Cassee (RIVM/MGO).

Coordination

Various departments within the RIVM are involved in the risk assessment during chemical incidents (SEC/SIR, NVIC, CGOR, MMK, and recently also the Centre for External Safety (CEV) of the RIVM). Sometimes the same question is posed to different departments at the same time, sometimes also by different people (authorities as well as public) or organisations. There is a risk that different departments may provide different opinions about the health risks of a certain chemical incident. Although this might be scientifically justifiable or explainable, the outside world (ministries, organisations, media, general public) will consider

the RIVM as a single entity. Therefore, it is recommendable that – certainly in cases of major chemical incidents – the RIVM provides a single or integrated opinion. This subject will be further handled within project V/630940 (Centre for Health Impact Assessment of Disasters).

6. Conclusions and recommendations

Based on the presentations and the subsequent discussion, the following conclusions or recommendations from this workshop can be proposed.

- Risk assessment during acute exposures to chemical substances by NVIC, SEC/SIR, and MMK should be focused on the toxicological consequences.
- Besides the effects anticipated on the basis of the toxicological profiles of chemical substances involved in any acute exposure, risk assessors within NVIC, SEC/SIR, and MMK should recognise that other or more effects might occur (such as event-related non-specific health effects). It is not their task to make any assessment about the likelihood of their occurence and no conclusions should be drawn. However, they could in some cases inform CGOR about specific situations.
- According to the workshop particpants, RIVM does not need to be the focal point of expertise and specific knowledge on psycho-social induced health effects in The Netherlands, but it was advised to strengthen any cooperation is in this area in order to gain full access to the available structures and knowledge within the Netherlands. Because Medically Unexplained Symptoms appear to occur so frequently after disasters, it is crucial that the Centre for Health Impact Assessment of Disasters (CGOR) develop a reasonable knowledge of the determinants of such symptoms, and prepare for their actual assessment.
- It is concluded that for various health endpoints relevant to acute exposure risk assessment to chemical substances, substantial lacks of knowledge exist. For such endpoints it is recommended that RIVM initiates further research to develop tools for actual risk assessment of acute exposures. These endpoints include:
  - developmental toxicity (teratogenicity)[§]
  - carcinogenicity §
  - (delayed) neurotoxicity (other than transient and reversible CNS depression)
  - Induction of sensibilisation

[§] This aspect is further investigated in project V/601900 (new project no. V/320003 in 2003).

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Appendix: Members of the discussion panel

- Peter Bos (RIVM/SIR)
- Marc Ruijten (RIVM/MGO - CGOR)
- Irma de Vries (NVIC)
- Bert-Jan Baars (RIVM/SIR)
- Flemming Cassee (RIVM/MGO)
- Theo Vermeire (RIVM/SEC)
- Mark van Bruggen (RIVM/IEM, National coordinator Environmental Medical Services)
- Marcel van Raaij (RIVM/SIR)