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Review

Hazard and risk assessment of industrial chemicals in the occupational context in europe: some current issues☆

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Abstract

This paper is about industrial chemicals, the manner in which their toxicity is assessed and the use of such assessments in regulatory decision-making. It begins with general points concerning toxicological data availability and hazard identification, then moves on to risk assessment and occupational exposure limits, and finally looks briefly at three specific toxicological issues, asthma, chronic toxic encephalopathy, and "low toxicity" dust effects on the lung, where the science is far from resolved. The overall purpose of the paper is to raise, or perhaps to act as a reminder of a number of issues of particular relevance to industrial chemicals and the occupational setting, and hopefully to prompt further thinking and perhaps some new initiatives directed at the areas in question.

Keywords: EU classification system; EU chemicals policy; Occupational exposure limits; Asthma; Solvents; Dusts

Contents

☆ The views expressed in this paper are those of the author and do not necessarily represent the position of the UK Health and Safety Executive.

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1. Introduction

Genuine toxicity has occurred, and continues to occur, in people exposed to chemicals at work. In the UK, thousands of such cases are reported each year. Skin problems caused by irritation and/or sensitisation, and respiratory diseases including asthma and long-term problems of dust or fibre accumulation in the lungs are especially prominent (Keynes et al., 1996; Jones et al., 1998; Cherry et al., 2000). This is not intended to be an emotive introduction; however, it does indicate that in the workplace there is real-life toxicity occurring that needs to be addressed. In addition, there are many other instances of claims of, or conjecture about, potential adverse effects in workers exposed to chemicals, together with issues of data availability, sufficiency, interpretation and use in a regulatory context; all of which adds up to a substantial and challenging agenda.

This paper discusses a number of current issues surrounding the assessment of the toxicological hazards of industrial and general commercial chemicals and the risks to health that might be posed by exposure to them in an occupational environment. This perspective comes at a time when considerable change is being considered in Europe in relation to many elements of the established regulatory regime and procedures involved.

The intention of the paper is to focus more on the toxicological issues than on the detail of the regulatory system, which the reader can find in the references cited. Nevertheless, a brief outline of the regulatory principles involved is perhaps merited at the outset.

In the European Union (EU), the manner in which the toxicology of industrial chemicals is characterised and used in regulatory decision-making in the occupational context is based on the following concepts. Suppliers of chemicals should convey to the recipients of their chemicals information on toxicological hazards, accompanied by simple safety advice, via EU-standardised labelling and safety data sheets. Recipients and users of chemicals (and manufacturers/suppliers in relation to their own sites) are responsible for understanding their local situation. With reference to the hazard information supplied, they are responsible for assessing and appropriately managing the extent of worker exposure so as to eliminate, or at least minimise the risk of toxicity being expressed. Regulatory authorities across the EU have established this regulatory framework and also play more specific roles, such as defining how some substances should be labelled, or specifying occupational exposure limits for individual chemicals.

2. Data availability and hazard identification

Key to all of the above is toxicological knowledge. Very many chemicals were commercially manufactured, and supplied to others, in the UK, EU and across the world, before legislation was in place requiring any systematic approach to characterising their toxicological properties. About 20 years ago, when the European Economic Community, the EEC as it was then, was in the process of introducing such legislation for the first time, for what were to be "new" substances (see below), an inventory was drawn up of all industrial/commercial substances already deemed as being supplied into the European market as at September 1981. This EINECS (European Inventory of Existing Commercial Substances) has approximately 100,000 individual entities listed (EINECS, 1990).

The data available on these 100,000 "existing" substances are very variable in extent and quality. Some, such as the elements lead and mercury and their compounds, or benzene, have enormous and still growing toxicological databases, but for many the available toxicological data are very sparse (National Academy of Sciences, 1984; USEPA, 1998; Allanou et al., 2000). This situation has produced a prevailing sense within regulatory institutions of needing to catch up on data deficiency, with talk of "the burden of the past" (CEC, 2001). Several initiatives are underway aimed at addressing this issue; and a major development in EU chemicals legislation (REACH), being contemplated for the future, is discussed briefly at the end of this section.

In the meantime, there is a challenge for those involved in toxicological hazard and risk assessment, and risk management decision-making, in relation to industrial chemicals, to make maximum use of all potential means of bridging information gaps. Contributions to a toxicological hazard profile can come from considerations of chemical structure, physicochemical properties and what is known of the toxicology of analogous materials, from in vitro testing systems which now abound, from experimental animal studies, and from reliable human data, including epidemiology. The reliability of the information, as an indication of the potential consequences for human health of exposure to a chemical, generally increases as one moves through this list, but so also does the cost, time and difficulty involved in acquiring the information. Economics dictates that it is not viable to demand what might be considered "full" (extensive) toxicological datasets on all industrial chemicals. In the context of worker health protection, the ideal aim is to get the maximum correlation between what information is really needed (scope, type, predictive reliability) and what information is available. In a regulatory context, this has not yet been achieved.

2.1. Hazard classification in the EU

The EU has a comprehensive system of rules and criteria, by which it is intended that the toxicological

hazards of any supplied industrial/commercial substance are first elucidated and then indicated via classification listings, labels and Safety Data Sheets (SDS) (EEC, 1967, 1991, 1992a; EC, 1999). Hazard classification and its regulatory consequences have assumed enormous importance for industrial chemicals, particularly in relation to risk management decision-making.

The classification system has the scope to accommodate a wide range of potential manifestations of toxicity exhibited by any industrial/commercial chemical supplied on to the market. The system deals initially with individual substances and then leads on to a further set of rules by which the classification of preparations (mixtures) containing more than one substance should be determined (EEC, 1967, 1992a,b; EC, 1999; HSC, 2002a).

Classification now enjoys much more significance than merely information transfer. The act of classification represents a gateway beyond which there may be a large number of downstream consequences for a chemical. These are set out in legislation such as the Marketing and Use Directive, the Preparations Directive, the Carcinogens Directive, the Safety and Health at Work of Pregnant Workers Directive, the Chemical Agents Directive, and the "Seveso Directive" on control of major accidents (EEC, 1976, 1990, 1992b; EC, 1996, 1998, 1999). Thus, hazard classification can lead directly to risk management stipulations in several different spheres of chemical manufacture and use. For example, under the Marketing and Use Directive, substances classified as category 1 or 2 carcinogens, mutagens or reproductive toxicants are not allowed in consumer products, and category 1 and 2 carcinogens and mutagens are subject to the strict risk management specifications of the Carcinogens Directive (definitions of the categories used for classification for carcinogenicity within the EU are given below; similar principles apply in relation to germ cell mutagenicity and reproductive toxicity).

There are two routes through which classification may be done and, from the regulatory perspective, in each route two conflicting trends are operating. The two routes are:

1. self-classification by suppliers
2. adherence to EU-wide specified decisions imposed by regulators

2.1.1. Self-classification by suppliers

A supplier of a substance is directed to apply the EU rules to its knowledge of the toxicological properties of that substance and thereby derive the appropriate Classification and Labelling (C&L). All potential toxicological endpoints are covered by the classification system, but for very many substances no toxicological data have been generated and/or documented for several endpoints. Interestingly, this situation produces two different reactions.

One can be portrayed as "no news is good news", i.e. no data means no knowledge of a hazard which is taken to mean no classification. The other can be portrayed as a more precautionary approach in which the substance is classified and labelled in case it turns out to be toxic.

Neither approach is satisfactory from a toxicological standpoint. What is really needed is the development of a framework, agreed by all relevant parties, for the use of all available sources of potentially useful information, from chemical structure to human experience, in order to fill the gaps in the toxicology database. To take one aspect, within the EU C&L system there are three categories of classified carcinogen; there are detailed criteria and guidelines available to steer assessors towards the most appropriate position, within a framework in which the general meaning of the categories is as follows:

> category 1—confirmed (i.e. directly observed) carcinogen in humans;
> category 2—presumed human carcinogen, i.e. carcinogenic potential in humans judged to be likely, based on the available evidence; and
> category 3—possible human carcinogen, i.e. some evidence for carcinogenicity of potential relevance to humans, but surrounded by significant uncertainty

The example in Box 1 is illustrative of the type of confused situation that can arise.

2.1.2. EU-wide agreed C&L decisions

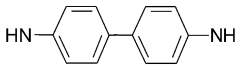
There are procedural arrangements within the EU for agreeing binding C&L positions on specified substances. The perceived need to generate agreed positions and the capacity of the procedures that facilitate this are such that only a small fraction ($<5\%$) of all EINECS-listed substances have passed through this process. In recent years the process has focused heavily on the so-called "CMR" endpoints of carcinogenicity, mutagenicity and reproductive toxicity.

Again, two competing themes apply here. One is the "no news is good news" attitude discussed above, when there are no data available. However, when data are available, there is a clear tendency to interpret the information in a cautious, some might even say overcautious manner. So, for example, the overall regulatory system does not respond to an absence of carcinogenicity data, but if any "positive" data are available, there is a great reluctance in some quarters to dismiss its relevance for human health, and hence strong pressure to classify in a "positive" manner, in one of carcinogenicity categories 1–3.

There is a pressing need for a more scientifically balanced approach. The case highlighted in Box 2 illustrates two problems. One is that the regulatory system must find room to give more acknowledgement, when merited by the balance of evidence, to those investing time,

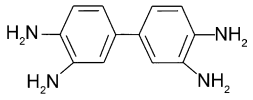
Box 1. 3,3′-diaminobenzidine—carcinogenic hazard

Benzidine



is an established human (bladder) carcinogen and, as such, has a formally agreed regulatory classification in the EU as a category 1 carcinogen.

3,3′-diaminobenzidine



does not have a formally agreed EU classification and hence the responsibility falls on the supplier to self-classify. It has a limited toxicological database. It is genotoxic in vitro; no in vivo genotoxicity studies have been identified. In relation to carcinogenicity, no studies have been performed to current internationally accepted protocols; the results of some rather old and non-standard studies in small groups of rats and mice do not yield a clear picture of its carcinogenic potential (DFG, 1992).

Safety Data Sheets available from a number of different suppliers indicate that 3,3′-diaminobenzidine is being marketed within the EU with self-classification verdicts for carcinogenicity of not classified, category 3 carcinogen, or category 2 carcinogen!

trouble and money in detailed, high quality mechanistic toxicology. Better toxicology serves everyone's interests. The alternative is that current attitudes exhibited by some regulatory agencies, putting up insurmountable hurdles that almost amount to demanding proof of a negative, will result in a reduction or even cessation of funding of such work, which would be to no-one's benefit.

On the other hand, if "no news is good news" prevails, there could be a nonsensical situation. That is, with the exceptions of "new substances " (see below) and some high production volume existing substances that have been prioritised for regulatory attention in the EU and worldwide, there would be a benefit to industry in not studying (aspects of) the toxicology of a substance, which again would ultimately be in no-one's interest.

In recent years there has been the development of a proposed Globally Harmonised System (GHS) by the United Nations for the classification and communication

Box 2. Dichloromethane and bromochloromethane—carcinogenic hazard

Dichloromethane, $[CH_2Cl_2]$, is metabolised primarily by an oxidative pathway to carbon monoxide and carbon dioxide. This pathway is saturable, with considerable interspecies variability, and a second pathway involving glutathione conjugation can become prominent (especially in the mouse) at relatively high exposure levels. A reactive metabolite, S-chloromethyl glutathione, lies on this second pathway (IPCS, 1996).

Rodent inhalation carcinogenicity studies published in the early 1980s showed that dichloromethane produced liver and lung tumours in mice exposed at 2000 and 4000 ppm. No significant tumour findings were noted in rats or hamsters (IPCS, 1996).

In 1987, on the basis of these results, dichloromethane was Classified in the EU as a category 3 carcinogen. Subsequently there has been a multimillion pound investment in research designed to understand the mode of action of dichloromethane in producing mouse liver and lung tumours and the relevance of this for human health.

There is now a much better understanding of the toxicokinetics and metabolic profile of dichloromethane in experimental rodent species and in humans. The reactive metabolite S-chloromethyl glutathione is implicated as the ultimate toxicant. While there remain (perhaps inevitably there always will be?) issues that could be explored further, it is reasonable to conclude that the balance of evidence is tipped heavily towards the mouse tumours not being of significance for human health (IPCS, 1996).

In 2003, dichloromethane is still classified in the EU as a category 3 carcinogen.

Bromochloromethane, CH_2BrCl, has been studied toxicokinetically only in the rat. On the basis of the results it appears to be metabolised in a very similar manner to dichloromethane (HSE, 2000). The toxicological database for bromochloromethane is small. Where studies are available allowing comparisons to be made, the toxicological profile for bromochloromethane is qualitatively similar to that for dichloromethane, with modest quantitative differences (HSE, 2000).

No carcinogenicity studies are available on bromochloromethane. A formal EU regulatory position on the Classification of bromochloromethane has not been developed; hence the duty is on suppliers to self-classify. Suppliers of bromochloromethane do not classify it as a carcinogen, on the basis that no carcinogenicity data are available.

of the hazards of substances and preparations (OECD, 2001). The model scheme has now been agreed at UN level (UN, 2003). It remains to be seen when and how this new system of classification rules and criteria will enter into regulatory use in the EU and in other parts of the world. However, the issues raised above will still apply; if anything they will become more pressing as the number of countries involved in the system grows greater.

2.2. Regulation of new substances in the EU

There is one class of industrial/commercial chemicals, the "new substances" for which the EU requires pre-marketing submission of standardised packages of toxicological (and other) information to the relevant regulatory authorities. This is via the 6th and 7th Amendments to the "EU Dangerous Substances Directive", implemented in UK by the Notification of New Substances (NONS) Regulations; the programme has been in place for more than 20 years (EEC, 1979, 1992a; NONS, 1993). In this period, there are very few cases known to the regulatory authorities of health effects having occurred in people exposed at work to a "new substance". How should this be interpreted? Does it mean that the regulations have been a great success, in that the pre-marketing testing has given all concerned prior warnings and the ability to prevent potential risk situations arising? Is it an argument for the principle being extended to all substances, new and existing?

There have been counter-arguments. The legislation on new substances is resource intensive for both industry and regulatory authorities, but where is the evidence of a real health threat or problem to justify the costs? There are also considerations about animal welfare as many of the tests require use of laboratory animals.

The most appropriate position lies somewhere between these extremes. The discipline of a chemical supplier having to consider and furnish information on the toxicological properties of the substance being supplied, in relation to a wide range of toxicological endpoints, seems undeniably sensible and beneficial. However, the need for toxicological information should not automatically invoke experimental testing. Commercial confidentiality precludes giving detailed examples, but in the UK we try hard to maximise the flexibility of the NONS Regulations. We welcome prospective notifiers to make contact with us, before embarking on any testing, to initiate a dialogue exploring the optimum means of generating the information required and incorporating approaches such as "read-across" from structural analogues and the use of in vitro screening tests.

2.3. The new European chemicals policy: REACH

In 2001, the European Commission published a "White Paper on the strategy for a future Chemicals Policy" (CEC, 2001). It set out proposals for a new regulatory system to be known by the acronym REACH (Registration, Evaluation and Authorisation of Chemicals). Essentially it is aimed at tackling two perceived problems. One is the lack of information, including data on toxicological hazards, for many industrial and commercial chemicals. The other is the view that current EU legislation, particularly that dealing with existing substances, has been ponderous and unresponsive to the wishes of some to see controls being applied to substances deemed to pose a threat to human health and/or the environment.

In the 2 years since the White Paper was issued there has been much debate about the nature and means of operation of such a REACH system and its socio-economic implications. In May 2003, the European Commission issued a proposal describing in considerable detail how it envisages that the REACH system might operate (EC, 2003). One issue of particular relevance to the toxicological community is the obvious tension that has been created between a desire to understand more about the toxicological properties of industrial and commercial chemicals and the strong policy position, particularly in the UK but also EU-wide, that testing of such substances in experimental animals should be "minimised".

These two goals, whilst not irreconcilable, clearly point in somewhat opposing directions. The challenge for the regulatory community is to find a way through the dilemma, by ensuring that additional information requirements are tailored to meet clear and valuable regulatory objectives while balancing the quality, precision and cost of any new information generated with the regulatory purpose to which it is put. This is giving fresh impetus to the thinking surrounding the use of approaches such as (quantitative) structure-activity relationships [(Q)SAR] and in vitro test methods that might not (yet) enjoy the status of full OECD validation and adoption. For instance, if at one stage an initial screening of a large number of substances is all that is required, it might be reasonable to use such approaches to achieve this.

Views on the details of this proposed new EU system are greatly influenced by what one accepts as an underlying philosophy. Should the system be aimed at securing total reliability and complete robustness and confidence in every step? Or is it sufficient to pursue the goal of a substantial improvement on the current situation? Most important is that the system should be workable.

3. Standard-setting and risk assessment

3.1. Assessment of risk and the setting of "health-protective" exposure standards

In many areas of regulatory toxicology, when assessing risk or setting recommended exposure limits or

standards, there is a strong tradition, stretching back about 50 years, of using so-called default uncertainty factors to allow for unknown but potential variabilities, based on an assumption of possible enhanced responsiveness in some exposed humans compared with the responses seen in the available animal and human toxicological data for a substance (IPCS, 1987; Lu 1988). A default uncertainty factor of 10 is conventionally applied to extrapolate from animals to humans and a further default uncertainty factor of 10 to take account of potential variability within the human population, making an overall factor of 100.

Toxicological risk assessment and exposure limit-setting for the occupational situation stands outside of this tradition. Several papers have explored current practice or have proposed approaches for the future, and in doing so have presented some explanation and justification for the workplace situation being different (Zielhuis and van der Kreek, 1979; Fairhurst, 1995). In truth, for many substances and industrial circumstances it would not be practically or economically viable to continue operating if a default uncertainty factor of 100 was applied. The problem is compounded when one considers that many industrial chemicals will have other weaknesses in the toxicological database, such that 100 could be multiplied by yet further uncertainty factors.

There is now some pressure on occupational risk assessment to rationalise (beyond "expert judgement") the approach used, with a clear framework for dealing with uncertainty. The thinking around some aspects of the issue is clearing. For example, in allowing for potential increased sensitivity of humans compared with experimental species, the issues are the same for workers as for any other section of the population and a recent workshop on "Variability and Susceptibility in Human Response to Occupational Exposure to Chemicals in the UK" reached a conclusion that variability and susceptibility in the working population is unlikely to be significantly different from that in the general adult population (IEH, 2002).

Behind considerations of these specific elements of uncertainty there is a basic question. The purpose of establishing any "health-protective" standard or desired margin of safety is to define what degree of control on occupational exposure is deemed necessary to secure health protection. However, in almost all cases there is uncertainty in the toxicological data available. The issue is whether are there valid socioeconomic reasons why it might be deemed that a lesser degree of reassurance about health protection is permissible in relation to adults at work compared with, say, children consuming a food additive. The goal is the same; the issue is whether or not the same level of confidence in having secured the goal should apply in each case. In the regulatory toxicology field this has yet to be worked through to a documented consensus position.

Also in this context, a great frustration is the poor recording of the exposures received by, and health experiences of people working with chemicals. In principle, the occupational environment should have been able to yield a wealth of data of value in exploring the uncertainty areas described above, for use in refining chemical risk assessment and standard-setting. In practice, with the exception of very few substances and situations, little has been compiled and documented in a manner robust enough to be useful for scientific and/or regulatory purposes. There is no real evidence that things are now changing and opportunities continue to be missed.

3.2. The benefit of occupational exposure limits

Occupational exposure limits (OELs) are specifications for the maximum airborne concentrations of substances, averaged over a reference time period (e.g. an 8-h shift) in workplace air. They have been the primary expression of workplace risk management expectations for the past 50 years. There are several well-established systems in different parts of the world that have a long and continuing tradition of developing and publishing lists of OELs, for example, in the USA (ACGIH, 2002), Germany (DFG, 2002), and the UK (HSE, 2002c).

The OELs for a good number of such listed substances were established many years ago, to weaker standards of regulatory toxicology than current expectations, a particular problem being the provenance and authentication of some of the supporting data. For any individual OEL-setting system or institution to attempt to bring all its existing OELs up-to-date, to a high quality standard, and also perhaps to extend its list to cover a larger number and wider range of substances, would be a task beyond the resources available.

From a UK perspective there are three current lines of thinking or activity. Firstly, the UK's OEL framework is under review (HSC, 2002b). As part of the transition from the current to the prospective new OEL system in the UK, it is proposed that many listed OELs be deleted, on the grounds of insufficient substantiating evidence (HSC, 2003). If this course of action is followed, the result will be a smaller but more consistently robust list of OEL values.

Secondly, for the UK and other EU Member States, the emerging EU OEL-setting system and the requirements this places on individual Member States is acquiring increasing significance (EC, 1998, 2000). The trend of regulatory policy thinking in the UK is towards national adoption of OEL values emerging from this EU system, and away from go-it-alone national limit-setting.

Thirdly, a more fundamental question is being asked in the UK about the benefits brought about by having an OEL value, when perhaps it is practical control

advice that is needed, if the goal is to secure effective management of the risk to health that might be posed by occupational exposure to a substance. Such considerations are reflected in the ongoing consultative process in the UK (HSC, 2003). The need for a clear understanding of the toxicology of a substance remains, but the end product of the regulatory process in which such an assessment is used is the point at issue.

4. Some practical examples of toxicological problems

4.1. Asthma

A current major concern in the field of occupational exposure to industrial chemicals is the reported incidence of occupationally-induced asthma. From data reported to the SWORD (Surveillance of Work Related and Occupational Respiratory Disease) scheme by chest and occupational physicians it is estimated that about 1000 new cases of substance-induced asthma are occurring each year in UK workplaces (McDonald et al., 2000). The most frequently identified causative agents are isocyanates, flour and grain dust, wood dust, laboratory animal dander, solder fume (colophony) and glutaraldehyde, but many other agents are implicated in different cases and sometimes the likely cause remains undetermined.

The most commonly cited mechanism for the induction of asthma, and probably the one operating in many cases, is one of immune-mediated sensitisation of the respiratory tract, although other mechanisms are also possible (Chan-Yeung and Lam, 1986; Kipen et al., 1994). A big problem in this area is the absence of a standard, internationally validated experimental animal test for the exploration of asthma-inducing (asthmagenic) potential. There have been several attempts to pursue this goal, so far without success (Karol et al., 1980; Botham et al., 1988; Kimber et al., 1996).

Thus regulatory programmes lack the means of experimentally testing substances for this property on a routine basis, as one would hope/expect to be able to do for other toxicological endpoints. The absence of such a test system also prevents exploration of other facets of asthmagenic potential, such as dose–response characteristics, potency, the possibility and location of a no-effect level (at least for induction), the mechanisms involved and interspecies variability, in the way one would for other endpoints.

Our understanding of the key toxicological features of chemical-induced asthma is almost exclusively dependent on human observational data. The species is the relevant one, but in every other respect the data (e.g. on exposure levels) are very limited. Much of the literature available concerns the characterisation/diagnosis of a prevailing problem, whereas what is needed is a test system that will predict potential problems.

4.2. Chronic toxic encephalopathy

Organic solvents are in widespread use in many sectors of industry. Due to their volatile and lipophilic properties, significant amounts of solvent can enter the body via inhalation of the vapour and/or absorption through the skin, particularly where workplace practices are poor. The effects of acute overexposure to solvents are well known. Typically, the primary action is central nervous system depression, producing effects ranging from dizziness and drowsiness to anaesthesia and even death, depending on the level of exposure.

However, for three decades since the mid-1970s there has been contention and controversy surrounding the suggestion that long-term occupational exposure to organic solvents in general can have a debilitating effect on the nervous system. A number of terms have been used to portray the condition, including "chronic toxic encephalopathy" (CTE), the term that will be used here (Axelson et al., 1976; Juntunen, 1993; Hogstedt, 1994). The condition has been described as:

> characterised by a global mental impairment including changes in; (i) cognitive functions, memory and concentration; (ii) personality; (iii) motivation, vigilance and energy. The clinical picture may be described as a psycho-organic syndrome or a mild degree of dementia, i.e. a clinical syndrome of premature ageing of higher cortical functions. (EC, 1997)

Where a diagnosis has been made, it has usually been based on subjective complaints by the patient and on the outcome of neuropsychological tests, together with a history of significant solvent exposure at work.

There has been much dispute surrounding the "CTE" condition (Grasso et al., 1984; Lees-Haley and Williams, 1997). Concerns about it have exerted strong pressure on regulatory and industry thinking in relation to organic solvent usage. However (and perhaps inevitably, given its description), the condition has not been modelled in experimental animals and lacks a clear mechanistic understanding at the biochemical or cellular level.

In the UK, very few descriptions of cases of clinical neurological problems associated with occupational exposure to organic solvents have appeared in the scientific literature (Dick et al., 2000). Over recent years, the UK advisory committees [the Advisory Committee on Toxic Substances and its scientific subcommittee WATCH (Working Group on the Assessment of Toxic Chemicals)] have been working with the Health and Safety Executive to address the various issues involved. One outcome of this work, a review of the evidence concerning occupational exposure to organic solvents and long-term nervous system damage detectable by

brain imaging, neurophysiology or histopathology, has just been published (Ridgway et al., 2003). The review concludes that there is a lack of clear evidence for effects detectable by such means. As regards the existence of the "CTE" condition, the position arrived at by the UK ACTS/WATCH process in 2001 was as follows:

> There is some evidence for a condition compatible with the current EU definition of "CTE" having occurred in individuals occupationally exposed to organic solvents. WATCH members differed in their views of the extent of, and range of different sources for, the supporting evidence. WATCH could not agree on any form of wording that captured any collective view as to the exposure conditions believed to be associated with the production of this condition. However, WATCH agreed unanimously that more work is needed to better characterise both the condition and the exposure conditions causing it.

This verdict suggests that there is still much work to do to properly characterise the toxicological picture (the condition, the dose–response characteristics and the underlying mechanism) and any necessary regulatory actions that should follow.

4.3. "Low Toxicity" dust effects on the lung

A major area of interest in occupational (regulatory) toxicology is that of the consequences of inhalation exposure to particulate material, a common occurrence in workplace environments. A substantial number of solid particulate (non-fibrous) materials possessing three characteristic properties—being of inhalable/respirable size, poorly water-soluble and of low cytotoxicity—have traditionally been grouped together as "low-toxicity dusts" in the occupational health and hygiene field.

Historically, specified airborne concentrations (as 8-h time-weighted averages) for the inhalable and respirable dust size fractions have acquired worldwide regulatory significance as one or more of the following:

- as generic dust standards;
- as specific occupational exposure limits allocated to a large number of individually listed substances in the absence of supporting data; and
- as a conceptual threshold, whereby lower levels of exposure to substances of this type are viewed as of no concern for health, but higher levels merit further examination.

In various systems throughout the world, the specified airborne concentrations range from 4 to 10 mg/m^3 for inhalable dust and 1.5–4 mg/m^3 for respirable dust (HSE, 2002c; DFG, 2002; ACGIH, 2002). However, given the broad applicability and significance of these numbers, the database underlying their derivation is rather weak. One central feature is that much of the experimental work in this area has been done in rats. There is an appreciable body of evidence that the rat expresses some responses in the lung to inhaled, respirable, "low toxicity" dusts that are not seen to anything like the same extent in mice or hamsters (IEH, 1999). The response in rats is generally characterised as an "overload" phenomenon—the retardation of macrophage clearance of particles and a range of effects that accompany this state—and there is considerable uncertainty as to whether or not it represents what might happen in the human lung, in both qualitative and quantitative terms. Is the rat a poor, invalid model for humans in relation to this area of toxicology?

Coming at this occupational area from the other direction has been the literature on epidemiological studies concerning exposure of the general population to atmospheric pollution in ambient air; these studies have shown a correlation between respiratory and cardiac morbidity and mortality and levels of respirable carbon-based particulate material (PM10) in the air (Dockery et al., 1993, Choudhury et al., 1997). It has been claimed that the correlation shows a linear relationship and an increase in health problems (particularly or exclusively among the already infirm?) is apparent even with measured PM10 levels of 50 μm/m^3 (EPAQS, 1998). What does this body of evidence mean, if anything, for those exposed to particulates occupationally?

A further complication is the area of "ultrafines"—particles with an aerodynamic diameter in the tens of nanometres. Experimental studies in rats show that exposure to such particles has a much more severe set of consequences in the lungs compared with the effects of micrometre-sized particles, at least when expressed in terms of mass/m^3, the units used in routine occupational exposure measurement (Oberdorster et al., 1990, 1996). If there were to be increasing use of, and therefore exposure to ultrafine particles in industry in the future we have not yet developed a robust regulatory position to accommodate this.

5. Conclusion

Toxicology remains very important and relevant to today's occupational environment; toxicity still occurs and there are ill-health problems still to be conquered (and also possibly new threats to be spotted in advance and headed off). There are numerous scientific issues that remain unresolved, where our knowledge and understanding are inadequate; a few examples have been discussed in this paper. There is also considerable agitation within the EU regulatory system, both in

terms of the characteristics of the regulatory framework and the way in which toxicology is (and should be) applied within that framework; there are many issues to discuss and considerable room for further improvements.

References

ACGIH, 2002. Threshold Limit Values for Chemical Substances and Physical Agents, and Biological Exposure Indices. ACGIH Worldwide, Cincinnati, USA.

Allanou, R., Hansen, B.J., van der Bilt, Y., 2000. Public availability of data on EU high production volume chemicals. EUR 18996. European Chemicals Bureau, Ispra, Italy.

Axelson, O., Hane, M., Hogstedt, C., 1976. A case referent study on neuropsychiatric disorders among workers exposed to solvents. Scandinavian Journal of Work and Environmental Health 2, 14–20.

Botham, P.A., Hext, P.M., Rattray, N.J., 1988. Sensitisation of guinea pigs by inhalation exposure to low molecular weight chemicals. Toxicology Letters 41, 159–173.

CEC, 2001. Commission of the European Communities: White Paper—strategy for a future chemicals policy. COM (2001) 88 final, Brussels.

Chan-Yeung, M., Lam, S., 1986. Occupational asthma—state of the art. American Review of Respiratory Diseases 133, 688–703.

Cherry, N.M., Meyer, J.D., Holt, D.L., Chen, Y., McDonald, J.C., 2000. Surveillance of work-related diseases by occupational physicians in the UK: OPRA 1996–99. Occupational Medicine 50, 496–503.

Choudhury, A.H., Gordian, M.E., Morris, S.S., 1997. Associations between respiratory illness and PM10 air pollution. Archives of Environmental Health 52, 113–117.

DFG, 1992. Occupational Toxicants—Critical Data Evaluation for MAK Values and Classification of Carcinogens, vol 3, pp. 131–135: 3,3′-diaminobenzidine and 3,3′-diaminobenzidine tetrahydrochloride. Deutsche Forschugsgemeinschaft, Commission for the Investigation of Health Hazards in the Work Area. VCH, Weinheim, Germany.

DFG, 2002. Maximum Concentrations at the Workplace and Biological Tolerance values for Working Materials. Report No. XX, Deutsche Forschungsgemeinschaft, Commission for the Investigation of Health Hazards in the Work Area. VCH, Weinheim, Germany.

Dick, F., Semple, S., Chen, R., Seaton, A., 2000. Neurological deficits in solvent-exposed painters: a syndrome including impaired colour vision, cognitive defects, tremor and loss of vibration sensation. Quarterly Journal of Medicine 93, 655–661.

Dockery, D.W., Pope, C.A., Xu, X., Spengler, J.D., Ware, J.H., Fay, M.E., Ferris, B.G., Speizer, F.E., 1993. An association between air pollution and mortality in six US cities. New England Journal of Medicine 329, 1753–1759.

EC, 1996. Commission Directive 96/82/EC of 9 December 1996 on the control of Major-Accident Hazards involving dangerous substances. Official Journal of the European Communities L010, 13–33.

EC, 1997. Information Notices on Diagnosis of Occupational Diseases. Report EUR 1468 EN. European Commission, Luxembourg.

EC, 1998. Council Directive 98/24/EC of 7 April 1998 on the protection of the health and safety of workers from the risks related to chemical agents at work (fourteenth individual Directive within the meaning of Article 16[1] of Directive 89/391/EEC). Official Journal of the European Communities L131, 11–23.

EC, 1999. Directive 1999/45/EC of the European Parliament and of the Council of 31 May 1999 concerning the approximation of the laws, regulations and administrative provisions of the Member states relating to the classification, packaging and labelling of dangerous preparations. Official Journal of the European Communities L200, 1–68.

EC, 2000. Commission Directive 2000/39/EC establishing a first list of indicative occupational exposure limit values in implementation of Council Directive 98/24/EC on the protection of the health and safety of workers from the risks related to chemical agents at work. Official Journal of the European Communities L142, 47–50.

EC, 2003. Proposal for a Regulation of the European Parliament and of the Council concerning the Registration, Evaluation, Authorisation and Restrictions of Chemicals (REACH Regulation). Available from http://europa.eu.int/comm/enterprise/chemicals/chempol/whitepaper/reach.htm.

EEC, 1967. Council Directive 67/548/EEC on the approximation of the laws, regulations and administrative provisions of the Member states relating to the classification, packaging and labelling of dangerous preparations. Official Journal of the European Communities P196, 1–98.

EEC, 1976. Directive 76/769/EEC of 27 July 1976 on the approximation of the laws, regulations and administrative provisions of the Member States relating to restrictions on the marketing and use of certain dangerous substances and preparations. Official Journal of the European Communities L262, 201–203.

EEC, 1979. Council Directive 79/831/EEC of 18 September 1979 amending for the sixth time Directive 67/548/EEC on the approximation of the laws, regulations and administrative provisions relating to the classification, packaging and labelling of dangerous substances. Official Journal of the European Communities L259, 10–28.

EEC, 1990. Council Directive 90/394/EEC of 28 June 1990 on the protection of workers from the risks related to exposure to carcinogens at work (sixth individual directive within the meaning of Article 16(1) of directive 89/391/EEC). Official Journal of the European Communities L196, 1–7.

EEC, 1991. Commission Directive 91/155/EEC of 5 March 1991 defining and laying down the detailed arrangements for the system of specific information relating to dangerous preparations in implementation of Article 10 of Directive 88/379/EEC. Official Journal of the European Communities L076, 35–41.

EEC, 1992a. Council Directive 92/32/EEC, amending for the seventh time Directive 67/548/EEC on the approximation of the laws, regulations and administrative provisions relating to the classification, packaging and labelling of dangerous substances. Official Journal of the European Communities L154, 1–29.

EEC, 1992b. Council Directive 92/85/EEC of 19 October 1992 on the introduction of measures to encourage improvements in the safety and health at work of pregnant workers and workers who have recently given birth or are breastfeeding (tenth individual Directive within the meaning of Article 16 (1) of Directive 89/391/EEC). Official Journal of the European Communities L348, 1–8.

EINECS (European Inventory of Existing Commercial Substances), 1990. Official Journal of the European Communities C146, 1.

EPAQS, 1998. DETR Expert Panel on Air Quality Standards: Particles. The Stationery Office, London, UK.

Fairhurst, S., 1995. The uncertainty factor in the setting of occupational exposure limits. Annals of Occupational Hygiene 39, 375–385.

Grasso, P., Sharratt, M., Davies, D.M., Irvine, D., 1984. Neuropsychological and psychological disorders and occupational exposure to organic solvents. Food and Chemical Toxicology 22, 819–852.

Hogstedt, C., 1994. Has the Scandinavian solvent syndrome controversy been solved? Scandinavian Journal of Work and Environmental Health 20, 59–64.

HSC, 2002a. Approved Classification and Labelling Guide. . , fifth ed. Chemicals (Hazard Information and Packaging for Supply Regulations 2002). HSE Books, Sudbury, UK.

HSC, 2002b. Discussion Document on Occupational Exposure Limits (OEL) Framework. HSE Books, Sudbury, UK.

HSC, 2003. A Consultative Document on Proposals to Introduce a New Occupational Exposure Limits (OEL) Framework. HSE Books, Sudbury, UK.

HSE (Health and Safety Executive), 2000. EH72/12 Bromochloromethane—Risk Assessment Document. HSE Books, Sudbury, UK.

HSE (Health and Safety Executive), 2002. EH40/2002: Occupational Exposure Limits 2002. HSE Books, Sudbury, UK.

IEH, 1999. Approaches to Predicting Toxicity from Occupational Exposure to Dusts. Medical Research Council Institute for Environment and Health (IEH), Leicester, UK.

IEH, 2002. Variability and Susceptibility in Human Response to Occupational Exposure to Chemicals. Medical Research Council Institute for Environment and Health (IEH), Leicester, UK.

IPCS (International Programme on Chemical Safety), 1987. Environmental Health Criteria 70. Principles for the Safety Assessment of Food Additives and Contaminants in Food. WHO, Geneva.

IPCS (International Programme on Chemical Safety), 1996. Environmental Health Criteria 164: Methylene Chloride. WHO, Geneva.

Jones, J., Hodgson, J., Clegg, T., Elliott, R., 1998. Self-reported Work-related Illness in 1995: Results from a Household Survey. HSE Books, Sudbury, UK.

Juntunen, J., 1993. Neurotoxic syndromes and occupational exposure to solvents. Environmental Research 60, 98–111.

Karol, M.H., Dixon, C., Brady, M., Alarie, Y., 1980. Immunologic sensitisation and pulmonary hypersensitivity by repeated inhalation of aromatic isocyanates. Toxicology and Applied Pharmacology 53, 260–270.

Keynes, H.L., Ross, D.J., McDonald, J.C., 1996. SWORD '95: surveillance of work-related and occupational respiratory disease in the UK. Occupational Medicine 46, 379–381.

Kimber, I., Hilton, J., Basketter, D.A., Dearman, R.J., 1996. Predictive testing for respiratory sensitisation in the mouse. Toxicology Letters 86, 193–198.

Kipen, H.M., Blume, R., Hutt, D.A., 1994. Asthma experience in an occupational and environmental medicine clinic. Journal of Occupational Medicine 36, 1133–1137.

Lees-Haley, P.R., Williams, C.W., 1997. Neurotoxicity of chronic low-dose exposure to organic solvents: a skeptical review. Journal of Clinical Psychology 53, 699–712.

Lu, F., 1988. Acceptable daily intake: inception, evolution and application. Regulatory Toxicology and Pharmacology 8, 45–60.

McDonald, J.C., Keynes, H.L., Meredith, S.K., 2000. Reported incidence of occupational asthma in the United Kingdom, 1989–97. Occupational and Environmental Medicine 57, 823–829.

National Academy of Sciences, 1984. Toxicity Testing: Strategies to Determine Needs and Priorities. National Academy of Sciences, Washington, DC.

NONS, 1993. The Notification of New Substances Regulations 1993. Statutory Instrument 1993 No. 3050. HMSO, London.

Oberdorster, G., Ferin, J., Finkelstein, G., Wade, P., Corson, N., 1990. Increased pulmonary toxicity of ultrafine particles? II Lung lavage studies. Journal of Aerosol Science 21, 384–391.

Oberdorster, G., Ferin, J., Soderholm, S., Gelein, R., Cox, C., Baggs, R., Morrow, P.E., 1996. Increased pulomonary toxicity of inhaled ultrafine particles: due to overload alone? Annals of Occupational Hygiene 1 (Suppl. 1), 295–302.

OECD, 2001. Harmonised integrated hazard classification system for chemical substances and mixtures. ENV/JM/MONO. OECD, Paris.

Ridgway, P., Nixon, T.E., Leach, J.-P., 2003. Occupational exposure to organic solvents and long-term nervous system damage detectable by brain imaging, neurophysiology or histopathology. Food and Chemical Toxicology 41, 153–187.

UN, 2003. The Globally Harmonised System for the Classification and Labelling of Chemicals. Available from www.unece.org/trans/danger/publi/ghs/officialtext.html.

USEPA (US Environmental Protection Agency)528, 1998. EPA Analysis of Test Data Availability for HPV Chemicals. USEPA, Washington DC.

Zielhuis, R.L., van der Kreek, F.W., 1979. The use of a safety factor in setting health based permissible levels for occupational exposure. International Archives of Occupational and Environmental Health 42, 191–201.