THE ASSESSMENT OF TOXIC HAZARDS.

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Toxicity may be expressed in a variety of forms depending on the chemical which is involved, the nature of the population exposed, and the conditions of exposure. It is therefore more difficult to predict toxic hazard than fire or explosion hazard. None-the-less it is possible to define the major criteria which require consideration and the form of information required. The nature of the criteria is discussed and a scheme proposed for their application to the assessment of possible toxic hazard to man and to the environment from major incidents.

INTRODUCTION

The recent catastrophe in Bhopal, India, in which a rapid release of large quantities of methylisocyanate caused the death of over two thousand people and severely injured many tens of thousands more, has been a tragic reminder of the potential toxic hazards which are associated with the manufacture, storage, transport and disposal of many chemicals.

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As acknowledged in the Advisory Committee on Major Hazards Third Report (1), the problems of ranking chemicals according to their potential for toxicity are far greater than ranking them for their fire and explosion potential. There are three principle reasons for this: firstly, the models available for assessing toxicity have rather poor reproducibility and typically provide only indirect information on hazard to man and/or to environmental species; secondly, chemicals often differ markedly in the nature of the toxic effects they produce and thirdly the scientific basis of toxicity is not sufficiently well established to permit reasonable prediction of toxic properties from knowledge of physicochemical properties alone.

Assessment of the potential toxic hazard of a chemical requires both information on the adverse effects of that chemical to an organism (intrinsic toxicity) and on the likely nature, level and duration of exposure of the organism to the chemical (exposure considerations).

Exposure Considerations

On release a chemical will normally be diluted to a considerable extent via the air or other dispersal systems before biological organisms including man are exposed. For most types of lesion there is a direct relationship between the exposure levels and the persistance and the magnitude of the toxic response. Hence knowledge of the likely and 'worst case' levels which a chemical may attain in an incident is important to the anticipation of effects on the population. Physical and chemical reactions may take place on release of a chemical which may modify its presentation form to biological organisms. Namely:

i) Non volatile chemicals may form aersols (i.e. dusts, fumes, smoke, mists or fog). The size and shape of the aersol particles may have a major influence on uptake by an organism and therefore toxicity. For example inhaled particles of 5μm or larger are normally deposited in the nasopharyngeal region, particles of 2-5 μm tend to be deposited in the tracheobronchial region, while particles of 1μm and below usually penetrate to the alveolar region of the lung (Doull et al)(2). The is an important consideration because maximal absorption of chemicals normally occurs from the alveolus.

ii) Concentration on airborne particulates which may be inhaled or onto solid surfaces which may facilitate skin contact.

iii) Degradation to other products which may be more or less

toxic than the original chemical. Combustion products in a fire may be many and varied. Aldehydes, carbon monoxide and carbon dioxide are common breakdown products of hydrocarbons; organonitrogen compounds may yield cyanide, free amines, azides, ammonia or oxides of nitrogen, while organohalocompounds may give rise to hydrogen halides and on occasion free halogen, phosgene, dioxins and dibenzofurans.

iv) Reaction with other chemicals present to form new chemical species. For example nitrite may combine with amines to form carcinogenic nitrosamines.

v) Concentration in food chains, members of which may ultimately be ingested by man or other economically important species.

v) Some products undergo changes if stored improperly. For example, malathion is classified by the World Health Organisation, quite properly, as "Class III - slightly hazardous". Improperly stored malathion can be converted to the much more acutely toxic iso-malathion and this has had tragic consequences. Problems involving storage of chemicals are often not adequately considered in identifying potentially hazardous situations.

Intrinsic Toxicity Considerations

Toxic effects produced by brief exposure to a chemical may be encountered at the site of primary exposure, for example irritation to the respiratory system, eyes and skin were very common in the Bhopal Disaster, or at other body sites (termed systemic toxicity) e.g. nervous system effects such as euphoria and narcosis are often experienced when release of organic solvents occurs. It should be noted that certain toxic lesions are reversible when exposure to an offending chemical is removed while other effects may be irreversible. In establishing the relative hazard of chemicals which have differing toxic effects the likely immediate and longer term consequences of each lesion on each organ of importance must be assessed.

Since for most chemicals there is little or no data available on their direct toxic effects in man, an estimate must be made from experimental findings in animal models. Commonly both the magnitude and the nature of the toxicity is influenced markedly by both exposure factors (as described above) and the genetic make-up, physiological and pathological features of those exposed. This must be borne in mind in relating toxicity findings in animal models to the likely situation in a major incident. For example, in terms of potential toxic hazard usually exposure via inhalation>ingestion>the skin this reflects the typical relative rates of absorption by these three routes (Doull et al (2)).

HAZARD SITUATIONS REQUIRING ASSESSMENT

In identifying the potential toxic hazard from a major incident it is necessary to consider:

a) the likely immediate (acute) adverse effects on the human population from exposure to the chemical and/or its combustion and other degradation products;

b) the probable delayed (subacute or chronic) direct adverse effects on the human population;

c) the immediate environmental impact;

d) any long term consequences to the environment arising from the incident.

a) Assessment of Likely Immediate (Acute) Effects on the Human Population

It is most important to identify both the intrinsic lethality of a chemical to man and its ability to produce effects which may severely impair the capacity of individuals to escape safely from an incident or take other defensive actions.

i) Lethal effects

To define the lethal effects of a chemical, statistical inferences, based on results in a small group of animals, are frequently employed. For the oral and topical routes the percentage of animals affected is most commonly expressed by a subscript, hence LD_{50} is the Lethal Dose (usually expressed in mg of chemical/kg animal body weight) to 50% of the animals at that dose level. For exposure by inhalation, the effect levels are often expressed in terms of LC (Lethal Concentration often after a 4hr exposure). The dose causing 50% of deaths is used for historic reasons and because it can be determined with the greatest accuracy. However there are several serious criticisms to the use of LC_{50} or LD_{50} results for identifying and comparing toxicity arising from acute exposure:

- It could be reasoned that the minimum dose which causes any lethality should be the index employed in identifying hazard rather than the dose which kills 50% of a population. However, it is difficult to calculate from LD_{50} or LC_{50} a minimum lethal dose, e.g. LD_1 because there is no fixed relationship between an LC_{50} an LD_{50} value and say an LC_1 or an LD_1 value. This is because the slope of the graph expressing the relationship between dose and lethal effect varies from chemical to chemical. For example it has been shown that for a number of pesticides the ratio of LD_{50} to LD_1 can vary by over seventy-fold (Dr. K.N. Woodward, unpublished data). If only LD_{50} or LC_{50} is available then

a "worst case" calculation of LD_{50} (or LC_{50} x 0.02 should be used to identify an LD_1 (or LC_1).

- In a major incident, exposure by inhalation or through the skin is far more likely than oral route exposure, yet most lethality data are determined after oral administration. Because of the relative paucity of lethality data for inhalation and dermal exposure, extrapolation of lethality data from the oral route to the relevent exposure situations using "worst case" calculations may be required. For this purpose to calculate LC_1 the oral LD_1 data should be multiplied by 0.1, whereas to calculate LD_1 dermal from LD_1 oral a suitable multiplying factor is probably 3-5.

  A further problem arises because where LC_{50} data do exist they are usually determined after a 4 hour exposure to a chemical. In a major incident many individuals will be exposed for much shorter periods than 4 hours. Since for many chemicals toxicity (including lethality) is a function of dose level and duration of exposure, findings from a 4 hour exposure may considerably overestimate the toxic hazard. The means of extrapolating to shorter exposure times is however controversial.

- Assessment of the lethal effects of chemicals is usually conducted only in rodents yet findings in a rodent may be a poor indicator of toxic hazard to man. Large interspecies differences are also common. Since the Seveso Directive is based on an incident in which Dioxin (2,3,7,8-tetrachlorodibenzo-p-dioxin - TCDD) was released into the atmosphere it is appropriate to use this as an illustration. Ingested Dioxin is about 100 times less acutely toxic to mice than to guinea pigs, and the Syrian hamster is about 600 times less susceptible than the guinea pig. Differences of this magnitude between three species make extrapolation from animals to man somewhat problematical. In an attempt to identify whether one species is more predictive of lethal properties of chemicals in man than another, Krasovskii (3) analysed the scientific literature on the acute toxicity of some 260 chemicals in man and other mammals. Krasovskii concluded that man was usually more sensitive than the commonly used test species to the acute toxic effects of chemicals.

  If no data exists to identify, for a particular chemical, which species is likely to be the most appropriate representitive of the human response the findings from the most sensitive species must be adopted for hazard assessment purposes.

- Differences in LC_{50} and LD_{50} also commonly occur between animals of different ages, sex, and between strains of animals of the same species. Other factors include timing of observation, housing conditions and diet may also contribute to variability of results. As a consequence

repeat LD_{50} tests under apparently very similar conditions often produce variations of >40% (Brown, (4)).

- Chemicals with a high LD_{50} (i.e. a low lethality) may none-the-less have highly undesirable acute effects at lower doses (see below).

Lethality findings such as LC_{50} and LD_{50} are best regarded as an approximate indicator of lethal potency, rather than as an absolute figure. It should be emphasised that for ranking purposes it is in any case quite unnecessary to obtain an accurate LC_{50} or LD_{50} rather what is required is a simple division into one of a small number of categories (see section on application of toxicity data).

The ranking systems used by various authorities are given in Table 1. The situation is clearly unsatisfactory. As can be seen, there are considerable discrepancies both in the action levels and in the terminology used. Furthermore it should be noted that the basis for ranking is oral LD_{50} data regardless of likely exposure route.

ii) Non-Lethal Effects

For the direct effects on man of fire and explosion it has been claimed that there is a fairly reproducible relationship between the number of dead and the number of injured. However the available evidence would suggest that this is not the case for release of toxic chemicals; consequently for each chemical the non-lethal as well as the lethal effects need to be assessed. Immediate non-lethal effects of particular concern are those of mutagenicity, irritancy and narcosis.

Mutagenicity

Chemicals may induce damage to the DNA of either germ cells or somatic cells. Damage to germ cell DNA is of particular concern because it could be passed on to successive generations. It could also lead to increased congenital malformations and still births. DNA changes in somatic cells have been implicated as the initiating stage in the induction of cancer by many chemicals. A wide range of short term in vivo and in vitro tests have been devised to identify the mutagenic potential of a chemical (Dean (5)). Although some caution is needed in extrapolating the findings from these tests to the human situation there is little doubt that mutagenic potential ought to receive attention in assessing the acute hazard that could arise from a major incident.

Irritancy and Narcosis

Certain adverse effects to the physiological system, although not necessarily intrinsically very serious may none-the-less be very important in a major incident by restricting a

subject's ability to adopt appropriate safety procedures. These include:

i) Irritancy. Severe irritant effects on the respiratory system may impose great limits on the physical capacity of an individual to move quickly to another location; irritation to the eyes may obscure the identification of a safe route while irritation to the skin may restrict the ability to obtain tactile information which if vision is obscured may be vital for escape.

ii) Narcotic effects. Clouding of mental altertness may result in inappropriate action or even unconsciousness (see various publications from the Fire Research Station, U.K.). (NB: These problems may be exacerbated in a fire by the thermal effects on the eyes, skin and respiratory system and visual obscuration by solid and liquid particles).

It is therefore apparent that although consideration of direct lethal effects are undoubtedly of major importance, severe irritant and/or narcotic effects may have lethal consequences. Irritants may through engendering tissue damage render affected individuals vulnerable to pathological organisms. Eye and lung infections are very common following severe irritation of the respiratory tract. This may be of major concern if an incident occurs in a country with relatively poor public hygiene and medical services.

b) Assessment of the Probable Delayed Adverse Effects in Man

Acute exposure may result in a delayed response rather than an immediate effect (see Doull et al (2)). Teratogenic, carcinogenic and sensitisation effects are of particular concern. Directly pertinent information regarding the potential of a chemical to produce these effects is normally not available because the standard tests for carcinogenicity, teratogenicity and sensitisation involve repeated exposure to the test chemical usually by the oral route. It is often difficult to identify the relevence of positive findings in such tests to the brief exposure situation which is most likely in a major incident. However, in the absence of additional information potent teratogens, carcinogens and sensitisers must be regarded as likely to produce these adverse effects following high level, albeit brief exposure.

c) Immediate and Longer Term Environmental Impact

Individual environmental species may vary in their acute and delayed response to particular chemicals. Assessment of environmental impact is more concerned with effects on populations rather than effects on individuals. Effects on the environment may include:

- damage to animals or crops of economic importance. This may be of concern either due to the loss of these species

and/or because residues of the chemical may accumulate in them and be ingested by man:

- contamination of drinking water supplies:

- loss of amenities such as damage to important wild life species, contamination of recreation areas, etc.

Each must be considered in assessing potential hazard (Kates (6)). It is notable that in major incidents such as those at Sevaso and Bhopal a major impact on these environmental components occurred in addition to the much more highly publisised direct impact on man. Of particular concern are likely to be major incidents involving potent biocides, e.g. insecticides or highly persistant chemical, e.g. polychlorinated biphenyls or metals.

A number of laboratory tests have been devised which seek to identify the lethal properties of chemicals to representitive environmental species, notably earthworms, algae, daphnia, fish, a higher plant, and the chemicals biodegradation rate. Such data is clearly important in that it permits the identification of chemicals which are most likely to have a major environmental impact and the possible duration of their effects. For the many chemicals for which no such data exists, attention should be focussed on those chemicals which are likely to be highly persistant by virtue of high lipophilicity, chemical stability and/or steric hinderence of normal sites of biodegradation (Schmidt-Bleek (7)).

OTHER CONSIDERATIONS

As mentioned above the actual toxicity which occurs is dependent on a number of variables including: age, sex, disease it may also be influenced to a marked degree by the presence of other chemicals present. In the absence of additional information the toxicity experienced from exposure to a mixture of chemicals must be assumed to be the sum of the individual toxicities of each chemical. Some consideration should be given to the possible toxic impact of all other chemicals likely to be present in significant concentrations following a major incident.

PREDICTIVE VALUE OF PHYSICOCHEMICAL CONSIDERATIONS

For many chemicals of industrial importance the toxicity data are sparse or non-existant. Unfortunately, because of the rather poorly developed scientific basis of toxicology it is the exception rather than the rule where all the major toxic properties of a chemical can be predicted from physico-chemical considerations alone. However, certain general rules are apparant (Bridges & Beaton (8)).

i) Physical Properties

Lipophilicity may influence toxicity by:
- facilitating the uptake of chemicals by organisms including man:
- increasing the probability of access and adverse effects to the brain, foetus, etc.
- enhancing the likelyhood of accumulation of a chemical in fatty tissues.

Water solubility - great water solubility normally entails poor lipid solubility and hence poor absorption.

Molecular weight/particle size - as described above small particles <1μm are likely to gain access to the most effective portion of the lung for uptake, namely the alveolar region. In general low molecular weight <1000 dalton is more favourable to uptake by the gut, skin and lung than higher molecular weight chemicals.

Volatility - in combination with lipophilicity volatility enhances access to all body tissues. Narcotic effects and effects on excitable membranes such as the heart are common. Highly volatile chemicals once absorbed tend to be excreted primarily through the exhaled air.

ii) Chemical Properties

For certain types of toxic effect, e.g. mutagenicity and chloroacne some structure activity relationships are apparant.

Homologous Series. Some extrapolation of toxic properties between near neighbours in an homologous series is usually valid. However, the first member in a series is usually atypical.

Steric Features. The major pathways for degradation of chemicals, at least in mammalian organisms, are predictable qualitatively. Hence it can be predicted that if the sites for metabolic attack are blocked or sterically hindered a chemical will tend to persist in the human body and in the environment in general, e.g. dioxin.

Intrinsic Reactivity. Reactive chemicals tend to combine irreversibly with the proteins and other components of biological organisms. Frequently this results in adverse effects such as mutations, allergy, cell death. Such properties may be predictable qualitatively from chemical considerations alone.

Structural Resemblence to Endogenous Substances. If an industrial chemical has a closely similar structure to a normal component of the body, it may mimic some of the properties of this component with consequent toxic effects.

RANKING OF CHEMICALS FOR POTENTIAL TOXIC HAZARD TO MAN

The major advantage of using LC_x and LD_x data alone is that the findings are presented in a numerical form and define a single, well understood endpoint of obvious concern. Accordingly chemicals can be ranked, apparently without any requirement for expert advice. Such data, taken out of context of the conditions under which it was derived imply an accuracy which in reality is spurious. For other toxic responses such a simple presentation is not appropriate. None-the-less it is clearly important to incorporate such information into any toxic hazard rating scheme.

For a limited number of chemicals, inhalation hazard to man has been evaluated and the findings embodied in HSE, NIOSH and other guidelines in the form of STEL (Short Term Exposure Limits) and ceiling values. These incorporate consideration of both acute lethality and other acute toxicity findings. Although these recommended limits are intended to be related to safe working levels for adults, they may none-the-less be useful as a rough guide to the potential toxic hazard from the rapid release of these chemicals into the atmosphere.

For chemicals where such values have yet to be identified an alternative approach is to use the scheme presented in Table 2 in which the assessment is divided into compound specific (general) factors and site specific factors.

For each group of lesions a range of arbitary scores is assigned according to the severity of the effect. (For information sources on toxicology data see Bridges & Beaton (8)). To produce an overall intrinsic toxicity rating the scores for each group of lesions are added together. Where no direct data exists from which to identify a score for a particular factor three courses of action are available:

i) extrapolate from data on very closely related chemicals if this exists:

ii) assume a worst case score:

iii) take an average based on the factors for which information is available. For many chemicals, because of the very limited amount of data available, this is tantamount to using LD_{50} data only, in which case it may be inappropriate. The approach used is a simple one because the decision options arising from any information on toxicity are likely to be somewhat limited.

It should be emphasised that the actual scheme provided in Table 2 is still in the development phase and requires to be validated against real incidents before it, or an amended version of it, can be considered for general application. However, once an appropriate ranking system were agreed it

could be readily incorporated into data hazard sheets on chemicals allowing identification by non-experts of high hazard situations.

RANKING OF CHEMICALS FOR POTENTIAL TOXIC HAZARD TO THE ENVIRONMENT

The scheme proposed for assessing environmental impact is a very simple one because the amount and quality of information on the adverse effects of a chemical on the environment is generally much less than that which relates to possible human hazard. None-the-less the principles involved are very similar.

APPLICATION OF THE RANKING SYSTEMS

In assessing the actual hazard to man and to the environment which may arise from the sudden release of a chemical, the approaches used in Tables 2 and 3 must be combined with information on "worst case" dispersal considerations. This would enable the identification of a toxicity safety rating for each chemical in each plant, major storage vessel, transporting vehicle, etc. and could be clearly identified along with the fire and explosion safety rating.

CONCLUSIONS

The present method of identifying the toxic hazards from a chemical is based very largely on data on its lethal dose in rats by the oral route. Potent carcinogens are incorporated into some rating schemes although the selection of which carcinogens to include appears to be somewhat arbitary. A reappraisal of the present approach is necessary to take into account the following factors:

i) dispersal characteristics of each chemical:

ii) other possible serious toxic effects in man, e.g. narcosis, irritancy, teratogenicity, mutagenicity:

iii) the impact of the chemical on the environment.

The scheme proposed in the present paper enables this additional information to be taken into account and allows chemicals to be ranked according to their potential hazard. The scheme is still an experimental one that requires validation, and perhaps modification, before it can be adopted for practical purposes.

REFERENCES

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TABLE 1 CLASSIFICATION SYSTEMS FOR ACUTE TOXICITY

Figures shown are for acute oral LD_{50} values in rats expressed in mg/kg-1.
(NB: Other requirements not included in this Table).

Textbook Hodge & Sterner	Industrial chemicals EEC	Poison Law Japan	Pesticide Act USA	Transport of Goods United Nations	Pesticide Classification WHO
Extremely toxic <1	Very toxic <25	Designated poison <15	Category I <50	Group I <5	Extremely hazardous <5
Highly toxic >1 to 50	Toxic >25 to 200	Poisonous substance <30	Category II >5 to 500	Group II >5 to 50	Highly hazardous >5 to 50
Moderately toxic >50 to 500	Harmful >200 to 2000	Deleterious substance >300	Category III >500 to 5000	Group III Solids: >50 to 500	Moderately hazardous >50 to 500
Slightly toxic >500 to 5000			Category IV >5000	Liquids: >50 to 2000	Slightly hazardous >500
Practically non-toxic >5000 to 15000					
Relatively harmless >15000					

TABLE 2 HUMAN TOXICITY HAZARD ASSESSMENT - A POSSIBLE APPROACH

A. COMPOUND SPECIFIC FACTORS.

I: Lethality data[+]

a)	Inhalation LC_1 <0.1	Dermal LD_1 <5	Oral LD_1 <1	(Score 10)
b)	Inhalation " 0.1-0.5	Dermal " 5-10	Oral " 1-5	(Score 7)
c)	Inhalation " 0.5-5	Dermal " 10-100	Oral " 5-50	(Score 5)
d)	Inhalation " 5-50	Dermal " 100-500	Oral " 50-500	(Score 3)
e)	Inhalation " >50	Dermal " >500	Oral " >500	(Score 1) _____

II: Narcosis findings[‡]: Narcosis at <1 ppm (Score 6)
Narcosis at 1-50 ppm (Score 2)
No or a weak narcosis effect (Score 0) _____

III: Corrosivity, irritancy, sensitisation properties[†]:
Potent effect (Score 6)
Moderate effect (Score 2)
Weak-no effect (Score o) _____

IV: Teratogenicity, mutagenicity, chronic toxicity and carcinogenicity findings relevent to acute exposure:
Potent effect (Score 6)
Weak effect (Score 2)
No effect (Score 0) _____

B. SITE SPECIFIC FACTORS

V: Number and nature of probable exposed human population (excluding the work force)
Highly populated area (Score 6)
Moderately populated (Score 3)
Very sparsely populated (Score 0) _____

VI: Likelyhood of entry to drinking water sources
Probable (Score 6)
Likely (Score 3)
Very unlikely (Score 0) _____

TOTAL _____

(continued next page)

Table 2 (continued)

‡ If no data consider properties of close structural analogues.

+ If LD_1 data not available calculate from LD_{50}.

LD values are mg/kg body weight: LC values are mg/litre of air/4hrs.

Final ranking:

- If in category (a) for lethality or total score of > 30 consider as human hazard Category 1.
- If in category (b) for lethality or total score of 20-30 consider as human hazard Category 2.
- Total score of 12-19 = human hazard Category 3.
- Total score of 5-12 = human hazard Category 4.
- Total score of less than 5 = human hazard Category 5.

TABLE 3 ENVIRONMENTAL TOXICITY HAZARD ASSESSMENT

A. COMPOUND SPECIFIC FACTORS

I: Intrinsic toxicity data[+]:

Score 5 for very highly toxic to 0 for non-toxic) _____

II: Environmental Persistance[‡]:

Score 3 for high persistance to 0 for unlikely to persist) _____

III: Food chain accumulation:

Score 3 for marked accumulation in economically important species. Score 0 for non accumulation) _____

IV: Effects on BOD (Biological Oxygen Demand)

Score 3 for major effect to 0 for minimal effect) _____

B. SITE SPECIFIC FACTORS

V: Nature of probably immediately exposed population

Score 3 for extensive exposure to 0 for minimal exposure) _____

TOTAL _____

+ If no data consider properties of close structural analogues.

‡ If non-persistant consider the properties of the degradation products.

Final ranking: If score 14-17 consider as hazard category 1.
If score 10-13 consider as hazard category 2.
If score 7-10 consider as hazard category 3.
If score 4-6 consider as hazard category 4.
If score 0-3 consider as hazard category 5.