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Toxicological assessments in relation to major hazards

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Abstract

This paper outlines a general approach for determining the toxicological hazard posed by the release of a substance from a Major Hazard. The aim of the toxicological assessment is to derive a "toxic load" value and relationship which will be representative of all sets of exposure conditions predicted to produce a chosen Specified Level of Toxicity (SLOT). This "toxic load" can then be used as the basis for calculating the risk from the Major Hazard. Such risk calculations are currently an integral part of the assessment of Major Hazards carried out by the Health and Safety Executive of Great Britain. Emphasis is placed on the importance of obtaining and evaluating data from original reports and on maintaining a sound biological basis for the assessment. The approach is a pragmatic one, in that it is intended to represent the best that can be achieved under the usual prevailing circumstances of sparse data, with little or no direct information on human effects. The limitations of the approach and the assumptions made in its adoption are discussed, and reference is made to toxicological assessments produced for specific substances.

1. Introduction

In the United Kingdom, a considerable number of installations (chemical plants, warehouses, etc.) are designated as Major Hazards because of the presence of substantial quantities (individual or aggregate) of one or more substances having the potential to produce significant toxicological effects in the surrounding general human population in the event of an accidental release. Having identified that such a potential exists at a particular site, the crucial issue is then that of the likelihood that such a release could occur. Estimations of the likelihood of accidental releases and their consequences have obvious implications in relation to, for example, the operation of the site,

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proposed developments in the vicinity of the site, provision of information to the general public, and arrangement/planning of emergency services. In order to provide advice in these areas, the Health and Safety Executive (HSE) in Great Britain is making increasing use of quantified risk assessment. This entails the calculation of numerical values for the risks to an individual or a community of being exposed to amounts of released substance(s) which would result in certain levels of toxicity.

One of HSE's principal concerns in this field is the calculation of risks in the vicinity of Major Hazard sites in order to provide advice for land-use planning decision-making [1]. This paper focusses on the assessment and provision of toxicity data such that it can be used as the basis for calculating these risks.

We are aware that some aspects of the approach described in this paper are not universally accepted or routinely adopted by others working in this field. With this in mind, we feel that it is appropriate to state at the outset three principles which we feel are very important:

(i) The toxicological assessment should be regarded as a regulatory toxicology issue and on this basis the approach adopted should follow as closely as possible the best principles and standard, widely accepted practices of "mainstream" toxicology.

(ii) The results of risk analyses are frequently used as a basis for decision by people who are not experts in the fields of toxicology or risk analysis. Therefore, the various steps used in the analysis should be transparent and the end-result of each part of the analysis, including the toxicological assessment, should be easy to trace back to the original supporting data. This is also an essential element in achieving harmony between different risk analysts.

(iii) The objective of the toxicological assessment is to derive a prediction of toxicity in order to facilitate decision-making by the regulatory authority. Failure to make such decisions is not an available option. Clearly, we recognise that frequently the extent of the data available falls well short of ideal, and various assumptions are required if the above objective is to be realised.

This paper only addresses direct effects on human health arising from a substance released into the atmosphere. Adverse effects on the environment or indirect effects on human health mediated via the environment are not discussed.

2. Criteria defining the level of toxicity on which risk calculations are based

Calculations of individual risk from Major Hazards are based on the likelihood of a defined member of an affected population receiving an exposure equal to or greater than that required to produce a Specified Level of Toxicity

(SLOT). The particular SLOT on which risk calculations are based may vary, depending on the situation under consideration, and in some cases risk calculations relating to several different SLOTs may be appropriate.

Inevitably there must be a degree of compromise in the selection of the most appropriate SLOTs for various Major Hazard situations. In the case of land-use planning, criteria defining a SLOT which were based solely on lethality may not be sufficiently stringent; there would be no allowance made for any serious but sublethal effects on health, which may be of great concern (effects such as marked impairment of organ or tissue function or serious disfigurement). On the other hand, if risk calculations were based on only a low level of sublethal effects within the population, this approach could appear to be too stringent, especially for an accidental release which is in itself a rare phenomenon.

Such considerations indicate that for land-use planning, criteria defining the appropriate SLOT which are based on serious injury, as well as on death itself, are appropriate. The SLOT which HSE uses in this situation has therefore been defined as one where there is:

(i) Severe distress to almost everyone in the area;
(ii) A substantial fraction of the exposed population requiring medical attention;
(iii) Some people being seriously injured, requiring prolonged treatment;
(iv) Highly susceptible people possibly being killed.

The choice of these criteria, reflecting a range of individual health effects and a somewhat imprecise level of overall effect on the population, is set out in terms intended to be understood readily by the general public and in particular by those involved in the decision-making process. Some flexibility is necessary to account for variations in the toxic properties of different substances, in that some chemicals may produce more serious sublethal effects than others. These criteria also avoid creating a spurious impression of accuracy, particularly when one reflects on the extent and quality of toxicity information available for most of the substances that need to be considered.

We feel that the level of toxicity given above is a more comprehensive description of the likely overall impact on a population and allows greater flexibility, particularly when faced with poor quality data, when compared with probit expressions generated from and descriptive of mortality data only [2, 3]. Furthermore, the future trend in acute toxicity testing will be towards studies in which the maximum level of toxicity produced should be serious sublethal effects with, at most, only a small percentage of deaths [4]. Consequently, an approach based on a SLOT such as the one described above will be more receptive than a mortality-based probit approach to the type of data likely to emerge from future acute toxicity studies.

In defining a level of toxicity on which risk calculations will be based, attention has focussed on toxic effects which become apparent soon after exposure. It should be acknowledged that there is also the possibility of effects being produced, the consequences of which only become manifest a long-time

after exposure. In animal studies germ cell mutations, teratogenicity and even cancer have arisen following a single exposure to certain substances [5–7]. However, for almost all substances with such properties, single exposure dose-effect data are not available. In addition, at least for carcinogenicity, in view of the envisaged mechanisms of tumour production it is likely that for most substances the risk of cancer arising from a single exposure is very low. Therefore it is generally not possible to include these aspects of toxicity in the overall quantitative approach described here.

3. Identification of appropriate toxicological data for use in the assessment

In considering the human health hazard created by a postulated release into the air of a toxic substance from a Major Hazard, attention will be focussed primarily on effects arising from a single exposure to the airborne substance. It is necessary to attempt to relate the estimated atmospheric concentrations and durations of exposure following a release to the level of toxicity produced within the surrounding population. The data used should therefore be principally those contained in reports of accidental single exposure of humans to the airborne substance, or generated in single exposure inhalation studies in animals.

Toxicity data relating to routes of exposure other than inhalation should be used only with great caution. For example, in the absence of sufficient inhalation data it may be possible, in some instances, to make use of oral exposure data and to relate these values to "equivalent" inhalation exposure conditions. However, care should be taken to ensure that the toxicokinetics (absorption, distribution, metabolism and excretion) and sites of toxic action are (or are judged likely to be) comparable for the two routes. Such comparisons between routes cannot be made if substantial differences in toxicokinetics appear possible, or if the sites of toxic action differ between the two routes; the latter point is particularly important for substances exhibiting predominantly local effects (e.g. irritation, corrosion) on the respiratory or digestive tracts.

Some issues must be raised concerning the quality of toxicological data used in the analysis. Experience has shown that commonly used secondary sources of information may be unreliable, in that the toxicological values given may be inaccurate representations of the original results, or that the primary sources of such values are either difficult to verify or of doubtful quality. Therefore, in a thorough assessment all the data used should be obtained from the original reports. In obtaining these reports, it will also then be possible to consider the quality and reliability of the studies and hence of the results generated. Such considerations form an important aspect of the overall assessment process, and greater emphasis should be given to values for which the underlying scientific evidence is strongest.

Many of the points made in this paper, in relation to appropriateness and validity of toxicological data, are echoed in a recent European chemical industry publication [8].

4. The "TOXIC LOAD" concept

The purpose of the toxicological assessment is to define all the sets of exposure conditions (all pairs of values for atmospheric concentration and exposure duration) predicted to produce the SLOT of interest. This requirement can be satisfied most easily by developing a functional relationship between the exposure concentrations (c) and durations (t) producing the SLOT, such that the end-product of this relationship is a constant numerical value, i.e.

$$f(c,t) = \text{constant} \quad \text{(in appropriate units)} \tag{1}$$

The form of this equation and the units of the constant will vary according to the substance under consideration. The value emerging is not invariably equivalent to the administered "dose" which, in inhalation toxicology, is expressed as concentration × time. Therefore the above numerical constant has been termed the "TOXIC LOAD". Furthermore, the toxic load relating to the particular SLOT used by HSE in land-use planning considerations has been designated the "DANGEROUS TOXIC LOAD" (DTL).

The Dangerous Toxic Load relationship and constant are used by HSE in risk analysis, in terms of calculating the probability that the Major Hazard could create conditions satisfying the DTL in the area surrounding the site.

5. Deriving the toxic load and the relationship between c and t, for the chosen "SLOT"

5.1 Interpretation of results in humans and in animals

In theory, at least, the ideal assessment of the toxicity of Major Hazard substances would be based on accurate observations of effects in humans. However, for most substances, existing reliable data on acute effects arising from a single exposure in humans are sparse. In some cases, information is available on sublethal effects (e.g. carboxyhaemoglobin levels produced by exposure to carbon monoxide, sensory irritation to eyes or mucous membranes by irritant gases). In addition, for a few substances some information is available from their use in warfare (e.g., chlorine, phosgene), although the usefulness of the available information has been disputed [9, 10]. However, for most substances the data are limited to a few reports of accidental exposures, often involving only a few people and rarely containing accurate measurements or even estimates of exposure concentrations and times.

Consequently, heavy reliance has to be placed on the results of experiments on animals in attempting to predict the responsiveness of a human population. Knowledge of the toxicokinetics and toxicodynamics (the relationship between concentration in the body and adverse effects) of a substance at low exposure levels in humans and animals, and at higher exposure levels in animals, would be the best way of extrapolating to effects in man at higher exposure levels. However, at present there are insufficient data for Major Hazard substances to enable such approaches to be used in practice.

Another possible approach in animal-to-human extrapolation is the use of scaling factors based on physiological parameters to develop a relationship which can then be extrapolated to man by incorporating the appropriate value(s) for humans. However, the generality of such relationships and the validity of extrapolation is often in doubt.

Thus in general, extrapolation from laboratory animals to humans with any assurance of accuracy and reliability is fraught with difficulties, principally because of the absence of adequate information. Hence considerable caution and judgement are required in adapting animal results for use in risk analysis. For many substances it may be necessary to make the assumption that results from animal experiments will be representative of effects on the human population, in terms of both the nature of the effects produced and the dose–effect relationships observed.

The approach described in this paper is therefore a pragmatic one, representing the best that can be achieved under the usual prevailing circumstances of sparse data, with little or no information on human effects. In some cases the paucity of data on certain substances will make any analysis extremely tenuous, and in these situations further experimental work by manufacturers or their trade associations would be advisable if important decisions depend on the results. The need for further toxicological research in this area has also been emphasised elsewhere [8].

5.2 Gathering animal LC_{50} data

For the vast majority of Major Hazard substances the most readily available information on the toxic effects of the airborne substance is the atmospheric concentrations and exposure times producing deaths in laboratory animals. For certain substances, particularly where studies have been conducted to current internationally-agreed protocols, there may be more complete details relating exposure conditions to both death and to more specific toxicological end-points. However, some of the older toxicity studies contain only lethality information.

Therefore, the first stage in the process should be the gathering of animal LC_{50} values, each with an associated exposure time. Most animal experiments involve the use of small groups. The response of the group at the 50% mortality level will most accurately reflect the likely response of the population from which the group is drawn.

Collation of these LC_{50} and exposure time values will permit comparisons to be made between different species and between different strains within the

same species. From the available data, the most sensitive animal species and strain should normally be used to represent the prediction of human responsiveness, unless there is information indicating that other animal results will serve to model human responsiveness more reliably.

5.3 Transition from the LC_{50} and t values in the animal model to c and t values representing one set of exposure conditions for the chosen SLOT in the same animal model

Most acute inhalation toxicity studies have been (and are still) performed under conditions where the exposure concentration has been (is) varied but the exposure period has been (is) fixed. In the Major Hazard context one is concerned primarily with the scenario of exposure for a period of perhaps up to 60 minutes, although the nature and limitations of the data usually available means that one must attempt to make use of information from studies employing a duration of exposure which may fall anywhere in a range from a few (5–10) minutes up to several (4–6) hours.

Therefore, at this point in the toxicological assessment we will have selected an animal model represented by an LC_{50} value and associated exposure period. The next stage is to extrapolate from the exposure concentration producing 50% mortality to that producing a degree of toxicity comparable to the chosen SLOT, for the same exposure period and in the same animal species and strain. In the case of land-use planning considerations, this entails deriving a pair of c and t values estimated to produce serious toxic effects and a low percentage (normally taken to be 1–5%) of deaths in the animal model.

As exposure conditions producing a low mortality level within a population cannot, in practice, be observed directly because of the very large groups of animals required, the conventional method of deriving such parameters is by probit analysis [11]. Note that here we are referring to subjecting to probit analysis data from a specific study, where the exposure period is fixed and one is simply moving along a concentration axis from one level of effect to another.

With probit analysis, "best estimate" values relating to a low percentage mortality should be used, because the size of the confidence interval is very much influenced by factors inherent in the design and conduct of experimental studies, in addition to influence from the results obtained.

If the data on the selected animal species and strain are inadequate for such probit analysis, then the extrapolation to a set of c and t values relating to the SLOT in these animals must be approached more empirically, from a simple visual examination of the data.

Occasionally, substances may be encountered where the only available information is a tabulated LC_{50} value, with an associated exposure time. In such cases a possible approach is to estimate, for the species and strain under consideration, the ratio between the LC_{50} and LC_x, where x is a lower percentage of deaths, i.e. around 1–5% in the case of the SLOT used for land-use planning. The slope of the dose-effect curve, and hence this ratio, will vary depending on the substance and on the heterogeneity of the test animals.

Nevertheless, in a study of the acute toxicity of a large number of pesticides in rats of the same strain, sex and age, examined under fixed experimental conditions, many pesticides had an LC_{50}/LC_1 ratio of between 1.5 and 4 [12]. Ratios of a similar magnitude have also been obtained in studies with various lung damaging gases [cf.13–15]. In addition a new classification system for acute toxicity has recently been proposed, in which the criterion determining classification was a dose level producing serious toxic effects but minimal lethality, rather than the LC_{50}. In a subsequent study designed to examine the proposal, most of the substances considered were placed in the same category using either criterion, when the boundaries for classification on the basis of LD_{50} were four to five times the corresponding boundaries for classification on the basis of serious toxic effects but minimal lethality [16].

However, ratios of this type should be used to extrapolate from a dose producing 50% mortality to one producing a lower level of toxicity only in the absence of any other useful data, and even then only with full acknowledgement of their very general and approximate nature.

5.4 Adaptation of one set of c and t values relating to the chosen SLOT in the selected animal model to corresponding values relating to the same SLOT in the general human population

Having derived one set of c and t values relating to the appropriate SLOT in the chosen animal model, it is then necessary to examine whether such values can be considered representative of the corresponding parameters in the general human population.

At this stage any collateral evidence available on effects in humans, usually in the form of isolated case reports of accidental exposures or anecdotal statements relating to the experiences of medical practitioners in particular industries should be considered. Such evidence can be used to assess whether the derived c and t values relating to the SLOT are consistent with the almost invariably scant information available on human responsiveness, or whether some adjustment of the c and t values is required on the basis of such information.

Another issue to be raised at this point is that of population heterogeneity. Animal experiments, particularly those performed in more recent years, will have been conducted using groups of animals bred especially to limit the variability in response. In general such animals will be healthy young adult members of that population. By comparison, the general human population is extremely heterogeneous. Therefore if, for example, the LC_{50} in the general human population has been equated with the LC_{50} in a particular species and strain of animal, then given the increased spread in responsiveness within the human population it may be suggested that for levels of toxicity significantly below 50% mortality, the exposures producing these levels of effect may be lower for the human population than for the animal model.

Several reports have included proposals in the proportion of the human population that should be considered to be particularly vulnerable to health

effects from the release of a toxic substance [17,18]. Generally these are people at the extreme ends of the age range and people with physiological disabilities which may increase their sensitivity to the substance. It has been estimated that such people constitute about 25% of the general population.

However, such issues are mainly conjectural, in that there are no data on the relative sensitivities of different groups within the human population towards most, if not all, Major Hazard substances. In practice, the need to compensate for the heterogeneity of the human population must remain one of toxicological judgement, depending on the particular case under consideration. To a large extent the approach will be dependent on the amount of data available. Adjustment of the toxicity values to account for human population heterogeneity appears unnecessary where data exist for several animal species and strains, the most sensitive of which is taken to represent human responsiveness, as this in itself is a conservative approach. In contrast, some adjustment may be necessary where data are available in only one or two animal species/strains, and where the observed dose–response curve is particularly steep.

At the end of this stage in the analysis, one value will have been derived for c and one for t which, taken together, should represent an estimate of one set of exposure conditions predicted to produce the particular SLOT in the human population. It is then necessary to deduce the relationship between c and t, such that, if possible, the end-product of this relationship (the "toxic load") can be represented by a constant numerical value. This constant, together with the relationship between c and t , can then be used to predict all sets of exposure conditions (c and t values) for the chosen SLOT.

5.5 Derivation of the toxic load equation and constant

Theoretical considerations indicate that there are several forms of expressions relating the toxic load to a function of c and t [19]. The manner in which c and t are functionally related in producing a toxic load value for a particular SLOT should only be examined within a collection of data from the same study involving the same animal species and type of toxic effect. In addition, the toxic effect should be the same as that on which the c and t values are based. These are very important points. If data from different studies and/or different animal species are combined in a single analysis, then inter-species, inter-strain and inter-laboratory variation (factors which have already been taken into account earlier in the process) will also exert an unknown degree of influence on the derived relationship between c and t. In fact, the relationship thus obtained may be predominantly an expression of such variations and far removed from an expression of the true toxic load relationship. The importance of maintaining a constant type of toxic effect (such as mortality) lies in the fact that different toxic effects may show different degrees of dependency on c, relative to t. For instance, sensory irritation of the eyes and mucous membranes may be much more heavily dependent on c, relative to t, than lethality.

There has been little experimental work in this area. Acute inhalation toxicity experiments in laboratory animals, performed in the early years of this

century on a limited number of gases, obtained mortality results suggesting the following relationship [20]:

$$\text{Toxic Load} = c \times t \tag{2}$$

(The Haber Rule)

More recently, a literature survey of more than 30 substances, for which LC_{50} values had been determined in the same species for at least three different exposure periods, suggested two groups of substances, showing empirical relationships of [21]:

$$\text{Toxic Load} = ct \tag{3a}$$

$$\text{Toxic Load} = c^2 t \tag{3b}$$

Overall, experimental observations suggest that in many cases the following general relationship may hold for acute lethality [8,22]:

$$\text{Toxic Load} = c^n t \tag{4}$$

A recent review of acute inhalation studies on various substances, using lethality as an end-point, derived values for n ranging from 0.8 to 4.9 for individual studies on particular substances and animal species, although the strength of evidence underlying some of these values is questionable [22]. To introduce a note of caution, some of the values of n quoted in the risk assessment literature for particular substances must be regarded as very dubious [3, 18, 23]. Such values have often been derived from studies using non-lethality end-points or from combined treatments of vaguely-defined data.

The requirement at this stage is, therefore, a knowledge of the value of n which will relate variations in c and t to a constant, experimentally observed level of mortality within an individual animal species. The most suitable reference point is usually 50% mortality, since exposure conditions relating to this level of mortality are most readily available. A simple (logarithmic) plot of $\ln c$ against $\ln t$, each pair of c and t values relating to the production of 50% mortality, may permit derivation of n from the slope of the resulting line $(-1/n)$, since:

$$c^n t = \text{constant}, k \tag{5}$$

can be rearranged to:

$$\ln c = -\frac{1}{n} \ln t + \frac{1}{n} \ln k \tag{6}$$

However, it must be recognised that the general applicability of the $c^n t$ relationship is based on empirical observation more than fundamental biological principles. If the data available for a specific substance do not appear to fit such a relationship, then there may be very good reasons why this is the case

(e.g. the particular mechanism(s) of toxicity operating) and these should be explored further.

An alternative approach at this stage is to use probit analysis and the method of Maximum Likelihood to produce a description of the relationship between c, n and t in the form of a probit equation [11, 22]. For the reasons given above, each such analysis must be restricted to data relating to the same study, animal species and toxic effect. The simpler graphical method may be preferable because there is no requirement for computer programmes and visual presentation of the data allows one to readily observe deviations from a $c^n t$ relationship. However, the method of Maximum Likelihood will allow all experimental data points to be taken into account, whether or not reliable LC_{50} values can be calculated. It may therefore be applicable to a wider range of data sets and provide a more comprehensive description of the relationship between c, n and t.

Occasionally, sufficient data may be available on a particular substance to permit the derivation of several values for n, representing values for different animal species, or values from different studies in the same species producing very different sets of results which cannot be combined readily or justifiably. In this situation, comparison of the relative standards of the studies under consideration may suggest that one of the values for n is much more reliable than the others, based on strength of experimental evidence, and this value should be used. Otherwise an overall values for n may have to be derived, by taking an average of the values derived for individual species.

In some cases the data available on a substance may be insufficient to permit the derivation of n. In such situations, although use of the Haber Rule has been common practice in toxicology, consideration of the mechanism of toxicity of the substance in question and its similarity in this respect to other substances with better defined $c:t$ relationships may be a better basis for choosing a value for n. On occasion, it may also be appropriate to perform and compare separate risk analyses based on toxic load expressions obtained using the two values of n (1 and 2) commonly observed.

We now have one c and one t value representing one set of exposure conditions predicted to produce the chosen SLOT. We also have the exponent n which can be used to define a "toxic load" equation describing variation in c and t in relation to the production of this SLOT. Insertion of the values for c, t and n into the equation:

$$\text{Toxic Load} = c^n t \tag{7}$$

will produce a numerical value for the "toxic load" constant

6. Use of this approach to toxicological assessment

Detailed assessments for a number of specific substances (acrylonitrile, ammonia, chlorine, hydrogen fluoride, hydrogen sulphide, nitrogen dioxide,

sulphuric acid mist) have been prepared using the approach described in this paper. The "dangerous toxic load" (DTL) values so derived have been used in quantified risk analyses of Major Hazards and the toxicological assessments have been (or are soon to be) published [24–30].

Disclaimer

The comments expressed in this publication are the views of the authors and may not necessarily be the views of HSE.

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