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Use of toxicity information in risk assessment for accidental releases of toxic gases

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Abstract

Decision-making regarding the management of accidental chemical releases requires toxicologic input in the form of specific chemical concentration limits ("toxicity values"). Toxicologic concerns include protection against lethality and other irreversible effects, serious health effects that could tax medical delivery systems, and impairment of respiration, vision, judgement or mobility. Currently there are a number acute exposure guidelines developed by expert committees for application to occupational or military settings or for the general population. The values for many chemicals span a 100-fold range. Thus, evaluation of existing guidelines is needed to identify those which adequately protect the public. An alternate approach would be development of clearly defined procedures for identifying toxicity values. Such procedures could be used by government agencies to incorporate new scientific information as well as site-specific concerns, without having to reconvene an expert committee. Development of toxicity values could be substantially improved with more experimental data on nonlethal endpoints and with explicit accounting for sensitive subpopulations, such as children and people with chronic respiratory disease.

1. Introduction

Accidental releases of volatile chemicals are commonplace. The United States Environmental Protection Agency (EPA) reported that from 1982 to 1988, 10 933 accidents occurred involving toxic chemicals resulting in 10 803 injuries and 288 deaths [1]. These have resulted from facility accidents or explosions, transportation accidents, or from improper storage or disposal. The worst such incident occurred in 1984 in Bhopal (India) when approximately 35×10^3 kg of methylisocyanate were released over several hours killing 2,500–5,000 and injuring 60 000–200 000 [2]. Another well publicized but less serious accident occurred in 1976 in Seveso (Italy) when a reaction vessel manufacturing 2,4,5-trichlorophenol exploded and released a chemical cloud containing approximately 1,3 kg of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin over a wide region [3]. In Texas City, Texas, the accidental shearing of a valve in 1987 released hydrogen fluoride and required approximately 1,000 individuals to seek medical atten-

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tion. Of the accidents noted by the EPA, 17 released chemicals in similar volume-to-toxicity ratios as occurred in Bhopal. These incidents prompted local air districts to consider potential acute exposures as well as routine emissions when granting an operating permit for a new industrial facility, and to begin evaluating existing facilities' potential for a catastrophic release.

Toxicity values are used as input for numerous decisions related to accidental chemical releases, including:

(1) establishing safe storage volumes and levels;
(2) calculating maximum transport quantities;
(3) estimating vulnerable zones;
(4) planning responses to an accidental release;
(5) determining evacuation routes;
(6) triggering a call to emergency responders;
(7) notifying government authorities or the public;
(8) sheltering the public in place;
(9) ordering evacuation; and
(10) allowing re-entry into an affected area.

There is a strong dependence between the toxicity value chosen and the resulting "vulnerable zone" or evacuation area dimensions, which have been reported to be proportional to the inverse of the concentration limit squared [4]. In the context of this paper, the uses for toxicity values can be categorized as either for emergency planning or response.

Emergency planning encompasses factors (1)–(7) above. Decisions about these concerns should be based on a toxicity value that is protective against any serious injury or health impact. Emergency response involves weighing the risk of chemical injury against the risks involved in taking drastic actions; this encompasses factors (5)–(10) above. Clearly the risk of evacuation should be weighed against the risk of exposure. Thus, toxicity values used in emergency response situations may be different from those used for planning. Furthermore, the use of emergency response personnel to manage an incident may have to be weighed against other concerns requiring their attention.

2. Toxicological outcomes to be addressed by emergency guidelines

Most dose–response information relevant to emergency planning derives from controlled experimental animal studies, since industrial or other accidents involving toxicity to humans are rarely accompanied by exposure measurements. The limited number of toxicological studies must be used to address many types of injuries that could result following a single acute exposure. Lethality is a major, but not the sole, concern in toxic releases. Lethality may be a useful index to determine the potential imminent hazard in a particular situation. However, most decisions should target prevention of injury, not simply fatality, and exposure guidelines should reflect this public health dictate.

Prevention of fatalities requires considering not only lethal concentrations themselves, but concentrations resulting in toxic responses that could lead to lethality if not properly attended to, such as impairment of mobility, vision or judgement. For example, neurological injury (including incapacitation through neurological dysfunction or narcosis, muscle weakness, or severe disorientation) could prevent escape or possibly result in life-threatening action by the person exposed. Similarly, severe eye or respiratory tract irritation could result in disorientation by loss of sight or blurred vision, or to impaired mobility secondary to difficulty breathing. A third example includes irrational panicky responses to highly objectionable or frightening odors which may hamper evacuation efforts.

It is axiomatic that the public should be protected from irreversible health effects, which we define here generally as manifestations of toxicity that would not reverse within a week without substantial medical intervention (e.g. blood transfusions, dialysis, administration of antidotes or intubation). Thus, irreversible effects would include serious toxicity that may last at least one week even with medical treatment. This category could overlap those listed above.

Evaluation of a chemical's toxicity after acute exposure should also encompass the potential to produce cancer and reproductive harm. Although cancer is generally associated with chronic exposure, a single exposure to a high concentration of a carcinogen may result in a delayed neoplastic response, as has been demonstrated experimentally with nitrosourea, hydrazine and other alkylating agents [5]. Thus, an evaluation of possible carcinogenic risks should be considered in evaluating potential hazards of accidental releases.

Reproductive effects can occur following single exposures within critical periods during pregnancy. Exposure during a specific critical period can result in characteristic congenital anomalies and other effects. Thus, emergency planning values should be developed to avoid adverse reproductive responses.

Another class of biological endpoints would be those resulting in serious, but self-limited or reversible effects for which most individuals would seek medical attention; a large number of individuals requiring such attention could significantly tax medical care systems. Thus, exposure concentrations likely to produce such effects should be averted. In addition to some of the outcomes listed above, another example from this category would include moderate respiratory irritation resulting in cough, inspiratory pain and phlegm, but not bronchospasm or respiratory distress. These symptoms would be considered reversible in most individuals, but might require significant medical intervention in sensitive individuals with asthma, chronic bronchitis or emphysema.

3. Available toxicity values and their application

One of the factors involved in emergency planning to avert or manage toxic gas releases is consideration of "acceptable" levels for a once-in-a-lifetime ex-

posure. As described below, there are several possible sources of "acceptable" values, none of which is ideal. Published values applicable to acute exposure are limited and have significant practical shortcomings. While standard procedures exist for quantitative cancer risk assessment [6], there is nothing comparable to evaluate the potential toxicity from acute exposure to noncarcinogens. The lack of generally acceptable acute exposure levels or of standard procedures to calculate such levels encourages arbitrariness in emergency planning. As shown in Table 1, the value chosen can vary 100-fold or more. The primary standards and guidelines available are discussed below.

The immediately dangerous to life or health (IDLH) values, developed by the Standards Completion Program of the U.S. National Institute for Occupational Safety and Health (NIOSH) and the U.S. Occupational Safety and Health Administration (OSHA), were formulated for the purpose of respirator selection, not emergency planning [7]. The IDLH values are intended to allow workers to escape within 30 minutes, without irreversible harm, in the event of a respirator failure. A recent review of the applicability of IDLH values to emergency planning found that many of the IDLH levels were comparable to concentrations producing death or severe toxicity in animals [8]. The application of a ten-fold uncertainty factor to the IDLH has been advocated by EPA to estimate a level of concern (LOC) for emergency planning [9]. However, such an approach would not necessarily protect public health, since IDLH values range several orders of magnitude in their ability to predict a lethal or severely toxic endpoint [8]. The lack of consistency between the IDLH values and other toxic endpoints argues against the use of a single uncertainty factor.

Some potentially useful values are the threshold limit values determined as short-term exposure limits (TLV-STELs) or time-weighted averages (TLV-TWAs), and ceiling limits developed by the American Conference of Governmental Industrial Hygienists (ACGIH) [10]. Similar values developed by NIOSH are short-term or ceiling concentrations. These occupational exposure guidelines have been designed for healthy workers and some of them are based on long-term exposures, so their applicability to emergency planning is limited. The advantage of these values is that they are available for a large number of chemicals. Furthermore, guidelines based on acute endpoints can provide useful insight into the level of injury that might result following exposure. Consequently, although TLV-STELs and TLV-TWAs are not universally applicable, a case-by-case evaluation may show their level of protection to be appropriate for the public in emergency planning and response situations.

Other published values are emergency exposure guidance levels (EEGLs) and the short-term public emergency guidance levels (SPEGLs) formulated by the Committee on Toxicology of the National Research Council (NRC) for the U.S. Department of Defense [5, 11–18]. Of all the available toxicity values, these are the most completely documented. However, EEGLs and SPEGLs were developed for use in narrowly defined circumstances of military opera-

TABLE 1

Comparison of guidelines applicable to emergency response from various organizations[a]

Chemical compound	NIOSH/OSHA[b] IDLH	AIHA[c] ERPG-2	NAS[d] EEGL	ACGIH[e] STEL or ceiling	NIOSH[f] STEL or ceiling	ACGIH[g] TLV-TWA	Level[h] of concern
Acrolein	5	0.5	0.05	0.3	0.3 (15 min)	0.1	0.5
Ammonia	500	200	100	35	35 (15 min)	25	50
Arsine	6	NA[i]	1	NA	0.0005 (15 min)	0.05	0.6
Carbon disulfide	500	NA	50	NA	10 (15 min)	10	50
Chlorine	30	3	3(2)[j]	3	1 (5 min)	1	3
1,1-Dimethylhydrazine (UMDH)	50	NA	0.24[j]	NA	0.06 (120 min)	0.5	5
Hydrazine	80	NA	0.12[j]	NA	0.03 (120 min)	0.1	8
Hydrogen chloride	100	20	20(1)[j]	5 (ceiling)	5 (ceiling)	NA	10
Hydrogen fluoride	30	20	NA	3 (ceiling)	6 (15 min)	NA	2
Hydrogen sulfide	300	NA	10-50[k]	15	10 (10 min)	10	30
Nitrogen tetroxide (as NO_2)	50	NA	1[j]	5	1 (15 min)	3	5
Phosgene	2	0.2	0.2	NA	0.02 (15 min)	0.1	0.2
Sulfuric acid (mg/m^3)	80	10	1	NA	NA	1	8

[a]All values are given in ppm unless otherwise noted.

[b]IDLH values are based on a 30-minute exposure [7], developed by National Institute for Occupational Safety and Health (NIOSH) and the Occupational Safety and Health Administration (OSHA).

[c]Developed by the American Industrial Hygiene Association (AIHA) and called emergency response planning guidelines (ERPG); based on a 60-minute exposure for ERPG-2 [19].

[d]Developed by National Academy of Science (NAS) for the military and National Aeronautics and Space Administration (NASA), except as noted; based on a 60-minute exposure, except as noted [11-18].

[e]Developed by American Conference of Governmental Industrial Hygienists (ACGIH) [10]. Values are 15-minute short-term exposure limits (STELs), except for ceiling values which are maximum ceiling values and are as such maximum exposure limits.

[f]Ceiling exposure values recommended by NIOSH [7] for workers. Exposure time in parentheses.

[g]Threshold limit values (TLVs) based on a time-weighted average (TWA) exposure for a work day [10].

[h]Level of concern advocated by U.S. Environmental Protection Agency [9].

[i]NA-not available.

[j]Public emergency guidelines developed by the U.S. National Academy of Sciences [11-18, 40].

[k]The 10 ppm value is for a 24-hour exposure, while the 50 ppm is for a 10-minute exposure [14].

tions or space travel [5]. The EEGLs are intended to prevent irreversible harm to military personnel, while SPEGLs are designed to protect the public in the event of a disaster involving military facilities. Only a few SPEGLs have been developed, and approximately 40 EEGLs are available. Finally, since the EEGLs focus on military or NASA scenarios values do not exist for many commercially important chemicals such as hydrogen fluoride.

Emergency response planning guidelines (ERPGs) have been developed under the auspices of the American Industrial Hygiene Association (AIHA) [19]. At the time of writing, 20 ERPG documents have become available. These guidelines represent threshold concentrations where exposure above the stated level is likely to produce toxicity. In contrast to guidance values developed by the EPA, NIOSH or National Academy of Science (NAS), ERPGs do not include safety or uncertainty factors, and are therefore likely to be higher than comparable values developed by government agencies. "The values derived for ERPGs should *not* be expected to protect everyone but should be applicable to most individuals in the general publication... the focus is on the highest levels not showing the effects described by the definitions of the ERPG levels."

Published guidance values for a given chemical may range over several orders of magnitude (see Table 1). The reason for this large range stems from the varied purposes of the standards and whether they incorporate margins of safety. For the purpose of protection of public health, the most appropriate guidelines appear to be the SPEGLs, since they apply to single acute exposures and incorporate a margin of safety. The SPEGLs take into account the wide range of susceptibility of the general public, including sensitive populations such as children, the aged and persons with serious debilities. In estimating SPEGLs and EEGLs all adverse effects are evaluated and the most seriously debilitating, work-limiting or sensitive one is selected as the basis for guidance [5]. The EEGLs are designed for military personnel, who represent one of the healthiest segments of society and are trained to work in hazardous and potentially life-threatening situations. Thus, the NAS Committee on Toxicology suggested an additional uncertainty factor of two- to tenfold be applied to calculate SPEGLs from EEGLs. While the EEGLs and SPEGLs generally represent upper limits where toxic effects are not likely to occur, the ERPGs demarcate threshold levels above which toxic effects may occur [19]. This difference in approach may require the application of a safety or uncertainty factor by the user following careful analysis of the guideline. This is apparent when comparing ERPG-2 values (for the public) and EEGLs (for the military) which are both intended to protect against irreversible effects. As shown in Table 1, the ERPG-2 for acrolein is 0.5 ppm while the EEGL is 0.05 ppm; the ERPG-2 for ammonia is 200 ppm, while the EEGL is 100 ppm; and the ERPG-2 for sulfuric acid is 10 mg/m^3 while the EEGL is 1 mg/m^3. Thus, the ERPG approach suggests that the public would be considered safe from an exposure to a chemical when it would be detrimental to military personnel.

Where the NAS has developed public exposure values (i.e. chlorine and hydrogen chloride), the comparable ERPG-2 values developed by AIHA are higher.

The composition of expert committees charged with developing exposure guidelines represents another potentially problematic area in evaluating existing guidelines. The NAS Committee on Toxicology has consisted of eminent scientists and public health professionals from a broad-based cross-section of organizations. Unlike other guidelines, the membership and formal affiliations of the committee members are described in each NAS document. The ERPGs have been developed primarily by industry-based scientists, although recently academia and government representatives have been added to the AIHA ERPG committee. The ACGIH committee is primarily composed of representatives of government and academia. Apostolakis [20] has observed that the most controversial aspect of using expert opinions is the selection process, which should ensure representation of all groups having a vested interest in the outcome. Thus, use of any guidance value developed by an expert committee requires some examination of the criteria for choosing the experts, and an indication that a balanced committee was selected. The listing of the expert committee in the NAS documents allows such an examination, while the AIHA, ACGIH and NIOSH guidelines do not.

Most of these values are not updated systematically. Thus, emergency planning agencies are not only faced with a confusing choice among different potentially "acceptable" levels, but also have no recourse regarding the interpretation of new, relevant scientific information. Furthermore, emergency planning agencies may require a different exposure time, scenario, or combination of chemicals not envisioned in the original guideline.

Review of guidelines for a few specific chemicals can illuminate some of the different underlying toxicological criteria used which resulted in the range of values. For ammonia the values reported in Table 1 range from 25 to 500 ppm. The 25 ppm TLV-TWA and the 35 ppm TLV-STEL values [10] are intended to protect against eye and respiratory tract irritation. The 100 ppm level is a concentration that some might find annoying and eventually frightening, but would result in little reflex lacrimation and would not be directly incapacitating [17]. However, education of military personnel on the properties of ammonia was expected by the NAS committee to reduce fright and panic. The ERPG-2 value of 200 ppm is intended to avoid serious health effects. The 500 ppm level [21] is based upon the statement that 300–500 ppm is the reported maximum short exposure tolerance [22]. Thus, ACGIH values are based upon prevention of acute irritation. The 100 ppm level is to prevent incapacitating lacrimation, and higher levels are designed as maximum tolerable exposures.

For sulfuric acid the values reported in Table 1 range from 1 to 80 mg/m^3. The TLV-TWA value of 1 mg/m^3 is to prevent pulmonary irritation (acute) and injury to teeth (chronic) [10]. The EEGL of 1 mg/m^3 is also designed to prevent pulmonary injury or irritation [11], but it is more stringent than the

TLV-TWA since the EEGL is a one-hour guideline. The ERPG-2 of 10 mg/m^3 is based on the absence of chronic toxic effects in rats after two years of exposure. However, the guideline does not reference the lung changes observed in monkeys at 4.8 mg/m^3, which is cited in the earlier EEGL committee recommendations. The 80 mg/m^3 level [21] is based upon a 1950 study which reported that 87 mg/m^3 is lethal to guinea pigs after 2.75 hours of exposure. Thus, while the 80 mg/m^3 IDLH is based on an early lethality study, the 1 and 10 mg/m^3 guidelines were developed from a review of essentially the same literature. The different conclusions drawn appear to be based on the emphasis placed on certain studies and the degree of health protection allotted by the various review committees.

The impact that the choice of toxicity value has on hazard analysis is illustrated in Fig. 1. In this figure a ten-minute release of 4.5 kg (10 lbs) of arsine is modeled from a hypothetical facility near San Diego, California, using the

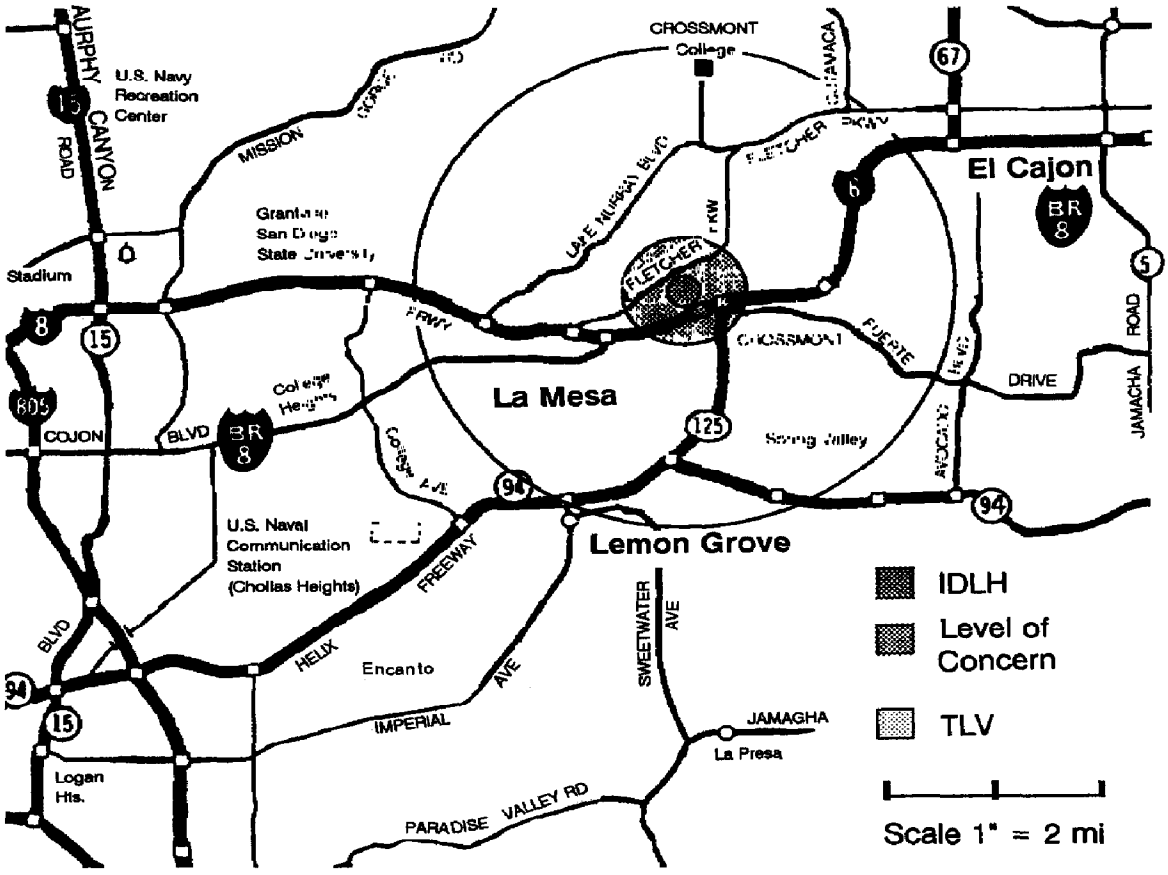

Fig. 1. A release of arsine is modeled from a hypothetical facility near San Diego, California. The vulnerability zone near the facility is modeled using CAMEO II [23] for three toxicity values, the immediately dangerous to life and health level (6 ppm), the EPA level of concern (0.6 ppm), and the American Conference of Governmental Industrial Hygienists' TLV-TWA (0.05 ppm).

screening assumptions suggested by the EPA [9]. Using the computer program CAMEO II [23], the vulnerable zone near the facility is estimated for three toxicity values, the IDLH (6 ppm), the EPA level of concern (0.6 ppm) and the ACGIH TLV-TWA (0.05 ppm). The toxicity levels vary by a factor of 120. In contrast, the area of the vulnerable zone varies by a factor of 200 (0.34 versus 68 square kilometers). Finally, the population within the vulnerability zone can increase dramatically when the larger zones encompass residential areas. Although screening assumptions were used, it is clear that the choice of toxicity value significantly affects the size of the vulnerable zone and the estimated population affected.

4. Importance of time and calculation of exposure

Inter-relationships between time, concentration and response are complex, and there are limited data in this area. Experimental studies of the same duration as a desired human guideline are preferred but rarely available. For example, many one-hour standards are based on experimental results using four-hour exposures. Haber's rule (concentration, c, $\times$ time, t, $=$ constant) is often applied in developing standards for exposure durations different from experimental data. However, when the outcome is mortality, this rule is not necessarily a good predictor of the response [24]. Acute lethality data from experimentally exposed animals suggest logarithmic relationships for several chemicals. Equivalent responses were observed when concentration to the nth power multiplied by exposure duration ($c^n \times t$) was considered constant, where n was a chemical-specific parameter between 0.8 and 3.5 [24–27]. In fact, the original Haber publication was limited to assessing the relative $c \times t$ toxicity of gases and did not extrapolate toxicity values across different exposure times [28]. Furthermore, Haber compared only eight chemicals and did not report the exposure durations.

Without chemical-specific and endpoint-specific information for various exposure concentrations and durations, it is difficult to extrapolate across time. Based on data from Ten Berge et al. [24], one health-protective approach would be to assume that $n=3.5$ (the values reported for chlorine and nitrogen dioxide) when extrapolating to shorter time periods if chemical-specific information is not available. This approach may overestimate the potency of a chemical in some cases. When extrapolating to longer time points, using $n=0.8$ (the value reported for 1,1,1-trichloroethane) will generate lower values, i.e. more health-protective levels. In all cases, it is important to evaluate the primary literature on which the original guideline is based, since the guideline itself may represent an extrapolated time point. Furthermore, if an existing guideline represents a ceiling value or an allowable level of exposure up to a given time point (e.g. 30 or 60 minutes), one should be cautious about exceeding the level during briefer exposures.

A related issue that arises is how to apply a 30- or 60-minute guideline to a variable concentration over time. Consider the hypothetical chlorine exposure shown in Fig. 2. A simple approach to assess the potential impact of the exposure is to rigidly apply a guideline, such as 3 ppm for 60 minutes, as a level not to be exceeded. This approach would lead to the conclusion that the chlorine exposure in Fig. 2 may result in incapacitating irritation. Since the total exposure is likely to be the overriding issue governing toxicity, one could integrate the area under the curve ($\int c\,dt$) and compare the area to 180 ppm min

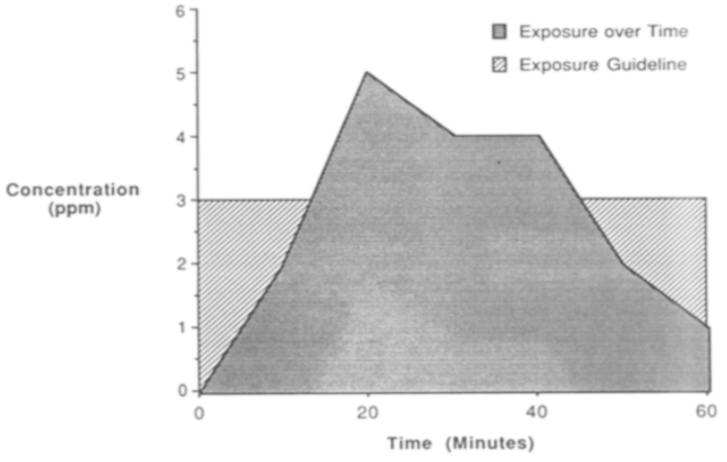

Fig. 2. An exposure to a release of chlorine is plotted in terms of concentration over time. The concentration rises and peaks at 20 minutes, then declines (shaded area). This exposure is compared to a guideline of 3 ppm for 60 minutes, intended to prevent incapacitating irritation.

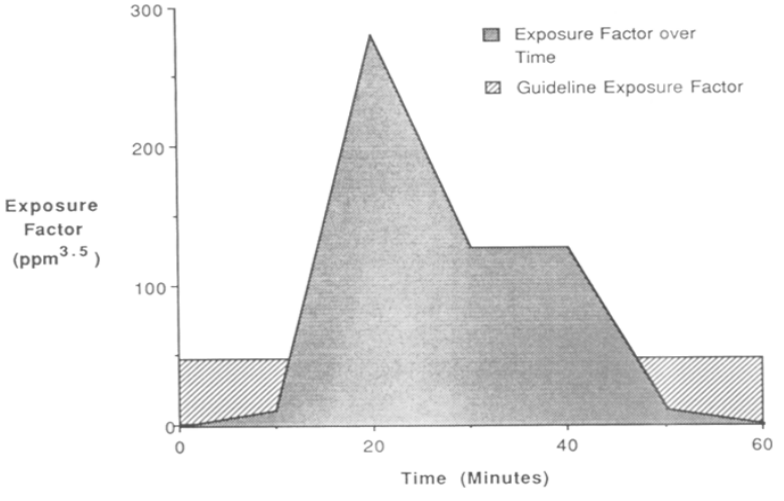

Fig. 3. An exposure to a release of chlorine is plotted in terms of concentration$^{3.5}$ versus time. This is based on the empirical evidence indicating that chlorine exposure should be based on $c^{3.5} \times t$ and not $c \times t$. This exposure is compared to a guideline exposure of $(3\ \text{ppm})^{3.5} \times 60$ minutes to prevent incapacitating irritation.

(60 min×3 ppm), as shown in Fig. 2. The area under the curve is 175 ppm min, so using this rule of thumb the chlorine exposure would not result in incapacitating irritation. However, as indicated above, concentration×time is not a constant for chlorine; instead (concentration)$^{3.5}$×time is a constant based on lethality studies. The expression $c^n \times t$ should be considered the exposure factor [24]. Thus, one would have to construct a curve as shown in Fig. 3 and evaluate $\int c^n dt$, where c is the concentration and n is empirically determined. Using this technique, the guideline would be equivalent to an exposure factor of 2806 ppm$^{3.5}$ min. The area under the chlorine exposure curve would be 5587 ppm$^{3.5}$ min or twice the guideline exposure. Consequently the total chlorine exposure by this comparison indicates the potential for incapacitating irritation.

5. Quantitative procedures

Clearly the major purpose of any toxicity value should be to provide guidance such that adverse health effects will not occur in exposed persons. However, for accidental releases the purpose must be more precisely defined. For example, we can define exposure levels called emergency medical planning levels (EMPLs) as "the maximum airborne concentration to which almost all individuals could be exposed for up to one hour, without developing any serious health effects requiring medical consultation, or without experiencing impairment of ability to take protective action". Such a definition would include serious, reversible as well as irreversible health effects. The definition of such values should state if they are to be used to evaluate the potential hazard or an accidental release during a planning/evaluation phase for a specific facility or area, or as a basis for risk management decisions in the event of a chemical release emergency. It would be prudent to develop exposure levels tied specifically to major emergency response alternatives, e.g. public warning or evacuation, if adequate data are available.

For any quantitative procedure, studies on a specific chemical applicable to emergency planning need to be identified by reviewing the primary toxicological and medical literature. The most applicable studies would provide a quantal concentration–response relationship for a serious, nonlethal health effect. However, studies describing the concentration–response relationship for minor toxicological responses or lethality would also be considered.

Two procedures for determining toxicity values will be discussed here: the uncertainty factor approach [29] and the practical threshold approach. The uncertainty factor approach is based on determining the maximum dose level causing no observable adverse effects (NOAEL). The NOAEL is an estimate of a threshold level for toxic effects and is determined directly from the observations reported in the study. The NOAEL is then divided by uncertainty factors (UFs) to estimate an acceptable potential public exposure. If an NOAEL was not determined in the study then the lowest observable adverse effect level

(LOAEL) is used. This LOAEL is commonly divided by a UF of 10 to estimate an NOAEL. Uncertainty factors have historically been multiples of ten and account for:
(1) potentially greater susceptibility to toxicity of humans compared with laboratory animals (10);
(2) the large range of individual variability in the human population (10); and
(3) other deficiencies in the study design (2–10) [29,30].

The practical threshold method [31], assumes a log–probit concentration–response relationship to identify the concentration expected to produce a one-in-one-hundred response (TC_{01}) via a maximum likelihood estimate (MLE). The log–probit model provides a good fit for most acute experimental data. The 95% lower confidence limit on concentration of the TC_{01} can be a considered a practical threshold (PT) for most acute effects. For a toxic response with a specific threshold, 1% approaches the margin of useful extrapolation for acute noncarcinogenic data due to the limited number of animals used in most experiments. Use of the 95% lower confidence limit on concentration takes into account the variability of the test population. Other studies are identified which provide information on areas of uncertainty involved in extrapolation, such as the influence of exposure duration on the concentration–response curve (discussed above). Other areas include the relationship between the severity of the response in the study identified as the most appropriate for extrapolation, to the response of concern in the human population, relative species sensitivity, and the dose of toxicant delivered to the target tissue. Using this information, data-specific adjustment factors are obtained from published studies and applied to the PT in the following manner:

$$\text{Ambient level of concern} = PT/(TAF \times RSF \times SEF \times TTR)$$

where PT is the practical threshold; TAF is the time adjustment factor; RSF is the response severity factor; SEF is the species extrapolation factor; and TTR is the target tissue ratio. Arsine is used as an example to illustrate these two methods.

6. Example of quantitative approach: arsine

Arsine is a toxic gas which has resulted in numerous injuries and fatalities due to its ability to destroy red blood cells [32]. Although most injuries have resulted from its accidental production, currently it is used as a doping agent in the semiconductor industry. Two studies on arsine were identified as the best available for concentration–response extrapolation. Levvy [25] evaluated the lethal response for arsine in mice at various concentrations and exposure times. In this study, lethality was found to be a function of concentration to approximately the second power (i.e. $c^2 \times t = k$). This information was used to calculate TAFs for experimental exposures that were not less than or greater

than 60 minutes in duration. Using this study, a PT was calculated to be 5.3 ppm for 60 minutes. Peterson and Bhattacharyya [33] observed hematological responses to arsine exposures in mice, and from these data we calculated a comparable 60-minute PT of 4.9 ppm. In addition, Peterson and Bhattacharyya [33] provided some information on relative concentrations producing no adverse effect, a serious effect and lethality. From these data an RSF of 2.9 was used to estimate a concentration likely to result in a serious response from experimentally lethal concentrations [25]. A SEF of 4.3 was derived as an estimate of species sensitivity for the lethal response and an SEF of 10 was derived for a hematological effect, using data from Gates et al. [34]. Assuming that the primary toxic effect of concern for arsine is hemolysis, the target tissue dose was also considered in the analysis. This was done by taking into account ventilation rates, blood counts, blood volumes and body weights of various experimental animal species and human populations. Using these physiological parameters we calculated a TTR of 2.1, which represents the increased target site dose which an active child could receive in comparison with a mouse breathing the same concentration of arsine.

Incorporating the above factors, the total adjustment to the practical threshold is 26.2 ($2.9 \times 4.3 \times 2.1$). For the purposes of emergency planning, the level to protect against hemolysis (for up to a 60-minute exposure), was calculated to be 0.2 ppm, using either the Peterson and Bhattacharyya data (4.9/26.2) or the Levvy data (5.3/26.2). Using the uncertainty factor approach a total uncertainty factor of 10 000 would be applied to the Levvy data. This is based on a factor of 10 for animal-to-human extrapolation, a factor of 10 for human variability, a factor of 10 for converting lethality to a more appropriate endpoint of hemolysis and a factor of 10 to convert the LOAEL to NOAEL. Based upon the results reported, it is estimated that at 25 ppm for a 60-minute exposure, 33% of the animals would have died. Thus, 25 ppm is divided by 10 000 to achieve a value of 0.0025 ppm for emergency planning and response. For the Peterson and Bhattacharyya data [33], a total uncertainty factor of 100 would be used. This is based on a factor of 10 for the animal-to-human extrapolation and a factor of 10 for human variability. Applying this to an NOAEL of 5 ppm produces a value of 0.05 ppm for emergency planning and response.

These values can be compared with those reported in Table 1, which range from 0.0005 to 6 ppm. The 0.0005 ppm value [7] is based upon the limit of detection for arsenic compounds due to its potential carcinogenicity. The 0.05 ppm value based on chronic toxicity is "the same for other inorganic arsenic compounds, which are considered substantially less toxic" [10]. The 1 ppm level [11] is based upon asymptomatic concentrations estimated in the 1940s [22,34]. The 6 ppm level is based upon the statement that 6–30 ppm is the "maximum concentration that can be inhaled in 1 hour without serious consequences" [21, 22]. Thus, the two lower values are not based upon the acute toxicity of arsine. The difference between the two higher levels is the choice of

an asymptomatic level versus a nonserious exposure level. However, it should be kept in mind that these two levels do not consider the data of Peterson and Bhattacharyya [33]. The concentration of 0.2 ppm for the general public calculated in this example is five-fold lower than the EEGL. This is reasonable due to the greater variability in sensitivity to arsine in the public as a whole compared with select military personnel. Also there is a greater ventilation rate to blood volume ratio in children compared to adults. The values of 0.05 and 0.0025 ppm developed using the uncertainty factor approach are much lower and are based on generic assumptions that can be improved upon with the extrapolation approach described above.

7. Future needs

There are many issues that can be addressed to improve toxicity values used in emergency planning and response. These values need a more explicit definition of purpose and description of application. This requires a multidisciplinary discussion of accidental releases among toxicologists, physicians, community representatives, industry scientists and government representatives. Currently, none of the guidelines provide clear definitions of irreversible, serious or incapacitating health effects. Guidelines should differentiate between applications for response and planning.

A major limitation is the lack of toxicity data for nonlethal endpoints of concern in emergency planning and response, as noted above. The absence of experimental data on other outcomes has forced some emergency guidelines to be based on the extreme endpoint of lethality. Other uncertainties exist in the extrapolation of animals data to humans and of limited human studies to the human population as a whole, but these uncertainties are common to most toxicological risk assessments. Existing toxicological endpoints need to be clearly applied to the acute human exposures. One such example is the RD_{50} (respiratory rate depression of 50%) calculated using mice and correlated to occupational standards for irritants [34–39]. This rich database could be very useful in developing toxicological values for irritants.

The target receptor of concern in an accidental release also needs redefinition. Classical toxicology has focused on a 70 kg healthy adult male when estimating toxicity. However, after an accidental release people likely to be exposed may not be limited to this population, but may include children playing, elderly individuals on a walk, and pregnant women. Information on the susceptibility of various other subpopulations needs to be developed. Recommended guidance levels must take into account known sensitive groups. While idiosyncratic reactions cannot be predicted, impacts on those with common chronic conditions such as asthma need to be considered.

Finally, once the purpose of the value is defined, the development of these guidance values needs to be done without the direct influence of risk manage-

ment decision-makers. These guidance values should be developed for the risk managers, who can then evaluate the potential impact of a release and determine appropriate management strategies to mitigate the impact.

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