Determining Acute Health Hazard Ratings in the Absence of Applicable Toxicological Data

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Introduction

Health, safety and emergency planning professionals have a responsibility to identify hazards associated with chemicals and to find a way to transmit that information to chemical users, emergency responders and others. Health hazard information is one of these important pieces of information that needs to be transmitted. Many schemes that have been developed to transmit health hazard information rapidly including the National Fire Protection Association (NFPA) diamond as described in NFPA 704, *Identification of the Hazards of Materials for Emergency Response* (1) and the *Hazardous Materials Identification System* (HMIS) (2) from the National Paints and Coatings Association. We will briefly discuss these two major systems and then we will look at options to determine health hazard ratings when toxicological data are not available.

Comparison of NFPA and HMIS

The NFPA and HMIS rating schemes are well defined, well understood, and widely used. In both cases, health hazards are identified by a number where the number scale indicates the degree of relative hazard and ranges from "0" (minimal hazard) to "4" (extreme hazard). These systems are similar in that they primarily base their numerical ratings on LC_{50} and LD_{50} data from toxicological studies on specific species. The HMIS system, however, goes further and identifies chronic health hazards, such as carcinogenicity, by using an asterisk while the NFPA diamond is silent on the issue. The advantage of using both systems is that they provide, at a glance, a significant amount of health hazard information associated with the chemical product in question. What also makes these systems so versatile is that criteria used to make health hazard rating determinations are well described so that individuals can determine the appropriate rating for their chemical products when ratings are not available.

Importance

What makes the health hazard rating even more important is that various organizations are considering their use as triggers that would mandate various activities. For instance, the Department of Energy (DOE) recently issued revision DOE O 151.1C, *Comprehensive Emergency Management System* (approved 11/2/2005), which invokes the use of the NFPA health hazard rating to determine when a chemical is sufficiently hazardous to require further analysis for emergency planning purposes. This change in approach will require DOE sites to evaluate thousands of chemical products that are unrated. This change in DOE policy was an impetus for this paper.

Currently, the tradition is to use a list-based approach to hazard evaluation. One would check the list-of-choice for the hazards associated with the particular chemical and mitigate accordingly. If the product was not on any of the established lists, then it was generally viewed as relatively non-hazardous. We are now starting to see a paradigm shift away from the "lists" towards evaluating each chemical on its' own merits. As previously mentioned, DOE has abandoned a list-based methodology and now uses the NFPA health hazard rating to determine whether a chemical is sufficiently hazardous to require further analysis for emergency planning purposes. This approach may be applied equally to a small municipality evaluating the hazards associated with a local manufacturing process, or an agency as large as Homeland Security evaluating the potential risk associated with a chemical in the hands of terrorists.

Developing a Rating

The NFPA and HMIS rating systems are primarily based on a chemical's acute toxicity. Three different possible methods of introducing the chemical into the body are evaluated with the hierarchy being inhalation, absorption, and ingestion. Inhalation is used to provide information should a chemical gas, vapor, or particulates be inhaled and is based upon the rat model. Absorption is used to provide information should a chemical be spilled on the skin; the rating value for the relative toxicity of a chemical for this pathway is determined using the rabbit model. Ingestion is used to provide information on the toxicity of a chemical should it be directly ingested or trapped in nasal mucous and subsequently swallowed. As with inhalation, the rat model is used to determine the relative toxicity for ingestion.

When one has a chemical or chemical product that requires a health hazard number assigned, one typically looks at data available in reference materials such as the Material Safety Data Sheet (MSDS), Sax's Dangerous Properties of Industrial Materials (3), or the Registry of Toxic Effects of Chemical Substances (RTECS)(4) to determine what toxicological data is available. If available, the toxicology data is matched to the NFPA or HMIS criteria and a rating is assigned.

Sources of Toxicological Data (List is Not All Inclusive)

Manufacturers' Material Safety Data Sheet;
Sax's Dangerous Properties of Industrial Materials (3);
Registry of Toxic Effects of Chemical Substances (RTECS) (4);
The Agency for Toxic Substances and Disease Registry (ATSDR) (5);
The International Agency for Research on Cancer (IARC) (6);
National Toxicology Program (NTP) (7);
National Institute of Occupational Safety and Health (NIOSH) (8);
The Risk Assessment Information System (RAIS) (9);
Toxicology Data Network (TOXNET) (10).

Inappropriate Approaches

Using Exposure Limits

A potential source of information to help determine health hazard ratings would be either exposure limits or emergency exposure guidelines. Exposure limit data would include ACGIH threshold limit values (TLVs) and Occupational Safety and Health Administration (OSHA) permissible exposure limits (PELs). In principle, TLVs and PELs are similar in nature. The following discussion of TLVs applies to PELs.

Contrary to what some may think, TLVs may or may not be related to relative acute toxicities. Table 1 shows the relative acute oral toxicities of systemic toxins and their respective TLV. As can be seen, arsenic has a very low TLV but a fairly low toxicity. One could argue that the low TLV would stem from arsenic's carcinogenicity. However, benzene, another carcinogen, does not share a similar low TLV. Iron carbonyl has TLV on par with oxalic acid, but oxalic acid is 300 times less toxic.

Chemical	TLV	LD_{50}/ LC_{50}
Arsenic	0.01 mg/m^3	763 mg/kg (oral)
Benzene	1.6 mg/m^3	930 mg/kg (oral)
Iron Carbonyl	0.8 mg/m^3	25mg/kg (oral)
Oxalic Acid	1 mg/m^3	7500 mg/kg (oral)
Methyl iodide	12 mg/m^3	76 mg/kg (oral.)

Table 1 - Comparison of TLV Values with Acute Toxicity Values for the Rat

From this data, one can see how TLV data cannot be used as an indicator of a chemical's relative toxicity. Examples present in the table are systemic toxins that were chosen to eliminate any argument that other routes of entry for a given chemical (e.g., inhalation) would prove to be more toxic which would justify a lower TLV. Relatively nontoxic carcinogens were chosen as examples to show how a very low TLV may not be entirely due to a chemical's carcinogenicity. Likewise, chemicals having almost identical TLVs and over two orders of magnitude in their toxicities would indicate that more information is factored into TLVs than simply acute toxicity. It is interesting how the second most acutely toxic product on the list (i.e., methyl iodide) has the highest TLV. Taken together, it would appear that TLVs cannot be used to gauge the relative toxicity of a chemical in an effort to assign health hazard values.

Another difficulty with using TLV data to determine health hazard ratings is that TLVs change while toxicity values generally do not change. Over the last few years chemicals such as n-butyl glycidyl ether, hydrogen fluoride, and tetrahydrofuran have had their TLVs reduced and other chemicals such as 2-methoxyethyl acetate, calcium carbonate, carbon disulfide, Portland cement, n-propanol, and vanadium pentoxide are proposed to have their TLVs lowered for the year 2006. Some of the reductions are on an order of magnitude and reductions of this size could result in health hazard ratings changes if TLV values are used to generate them. If one is to use TLV data to determine health hazard ratings, then one must factor added cost into the program to address the change in health hazard ratings when TLVs are changed. Confusion may also ensue when health hazard ratings are changed.

Using Emergency Exposure Guidelines

Emergency exposure guidelines include Acute Exposure Guideline Levels (AEGLs), Emergency Response Planning Guidelines (ERPGs) or Temporary Emergency Exposure Limits (TEELs).

Emergency exposure guidelines are designed as a tool to assist in the development of emergency response strategies for protecting workers and the general public against the harmful effects of specific chemicals and substances. AEGLs are developed through a collaborative effort of the public and private sectors worldwide and are published by the U.S. EPA after peer review (11). A limited number of AEGLs have been developed through a collaborative effort. Similarly, the American Industrial Hygiene Association (AIHA) established a peer review process to develop and publish Emergency Response Planning Guidelines (ERPGs) (12). Because of the limited numbers of AEGLs and ERPGs available, the Department of Energy (DOE) established a system to create Temporary Emergency Exposure Limits (TEELs) to provide interim criteria to support emergency planning (13).

Each set of emergency exposure guidelines has defined levels of varying health effects.

> "Level 1 values are those airborne concentrations below which a person may be exposed up to one hour without any other than mild transient health effects.
>
> Level 2 values are those airborne concentrations below which a person could be exposed to up to one hour without developing irreversible or other serious health problems that would prevent the individual from taking protective actions.
>
> Level 3 values are those airborne concentrations below which nearly all persons could be exposed for up to one hour without experiencing or developing life-threatening health effects."

While NFPA health hazard ratings deal with toxicity of acute exposures, the emergency exposure guidelines (AEGLs, ERPGs, TEELs) take into account other factors and a wide range of susceptibility of the general public, including sensitive populations such as children, the aged, and those with serious debilitating diseases. TEELs, in order to account for interspecies differences, use a weighted value for the available toxicity data for any route of entry, based on a relative correlation to rat toxicity data. (TEEL Rev. 21 Introduction, pages 5-6)(13) These differences limit the ability to directly correlate emergency exposure criteria to NFPA health hazard ratings.

Table 2 gives examples of the difficulties that arise when attempting to compare TEEL values with NFPA Ratings. Hydrazine Hydrochloride has a very low TEEL-1 and TEEL-2 value, indicating a chemical of serious concern. However, the NFPA rating based on oral toxicity is a 2 (a moderate hazard). The opposite scenario is observed with Nicotine sulfate where the NFPA rating is severe and the TEEL is moderate.

Chemical	TEEL-1 Value	TEEL-2 Value	LD_{50} (oral)	LC_{50}	NFPA Rating
Hydrazine Hydrochloride	0.025 mg/m^3	0.04 mg/m^3	128 mg/kg	N.D.	2
Nicotine Sulfate	9 mg/m^3	9 mg/m^3	50 mg/kg	22 mg/m^3	4
Diethylene Glycol	30 mg/m^3	50 mg/m^3	12565 mg/kg	N.D.	0
Warfarin	0.3 mg/m^3	20 mg/m^3	1.6 mg/kg	320 mg/m^3	4

Table 2 - Comparison between TEEL Values and Toxicities in the Rat
NFPA acute health hazard rating is given per NFPA criteria
N.D. – Not Determined

Another argument that is sometimes made is that using different TEEL values can yield more relevant health hazard rating values. As can be seen in Table 2, this is not the case. Some values such as those for nicotine sulfate do not vary from TEEL-1 to TEEL-2 and others, such as hydrazine hydrochloride or diethylene glycol, roughly double in value between TEEL-1 and TEEL-2. Some compounds, such as warfarin, have their values increase by a factor of almost 100 when going from TEEL-1 to TEEL-2.

From the above information, it is clear that emergency exposure guidelines cannot be used to develop meaningful health hazard ratings.

Problematic Approaches

Use Data for Other Animal Species

When no applicable toxicological data is available, one may opt to use data for other animal species. This may not provide accurate rating values based upon the HMIS or NFPA criteria for the chemical in question. Relative toxicities can vary by up to a factor of 100 (Table 3) when measured in various species. For example, acrylic acid taken orally is approximately 100 times more toxic in the rat than in the mouse. Similarly, ethylene bromide is ten times more toxic in the rat than in the rabbit. One may opt to use one animal model as being the most conservative case because it appears the animal is more susceptible to toxins than other species, but this is not the case either. Theobromine is much more toxic in the cat than in the rat and methoxychlor is more toxic in the mouse than in the rat. Similar difficulties exist when one attempts to draw comparisons between other routes of entry (e.g., inhalation, absorption) between species or other routes of entry within a given species.

Chemical	Animal	LD_{50} (oral)	Animal	LD_{50} (oral)
Acrylic Acid	Rat	33.5 mg/kg	Mouse	2400 mg/kg
Methylene Bromide	Rat	108 mg/kg	Rabbit	1,000 mg/kg
Theobromine	Rat	1265 mg/kg	Cat	200 mg/kg
Methoxychlor	Rat	1865 mg/kg	Mouse	510 mg/kg

Table 3 - Comparison of Toxicities for Different Animals

One may argue that, in some cases, extrapolating between species in an effort to obtain accurate health hazard ratings based upon NFPA and HMIS criteria can be performed, but this argument poses an interesting dilemma. If one attempts to extrapolate relative toxicities of a chemical between species, then one must have a good understanding of the toxicological properties of that chemical. In order to have a good understanding of toxicological properties between species, then a significant amount of toxicological testing must have occurred. If this testing has occurred, then LD_{50} values are likely available, which would make extrapolation between species unnecessary. If LD_{50} values are not available, necessitating an attempt at extrapolating between species, then there is likely not enough information present to indicate whether or not the extrapolation would be valid.

A similar argument could be made for attempting to extrapolate between other routes of entry between species or between routes of entry within a given species. If one compares the toxicity of nicotine sulfate (LD_{50} oral, 50 mg/kg; LC_{50}, 22 mg/m^3) and warfarin (LD_{50} oral, 1.6 mg/kg; LC_{50}, 320 mg/m^3) and their toxicities based upon routes of entry, one can see that no simple relationship can be observed between them. Based on the above information, any attempt to extrapolate between either routes of entry or species should be, at best, be regarded as being suspect.

On rare occasions, extrapolating relative toxicities between species can be used if one understands when its use is appropriate. If a toxin such as an organophosphate neurotoxin or cyanide has a mechanism of toxicity that is universal between species, then their relative toxicities should be similar. What is also required is the knowledge that the mechanisms of uptake and distribution are similar. In the case of potassium cyanide, mechanisms of absorption, distribution and toxicity are similar between species and its LD_{50} (oral) for the rat, mouse, and rabbit exhibits a narrow range of 5 to 8 mg/kg. Because the toxicology of cyanide is simple and well understood, extrapolations between species may be valid. The difficulty is knowing when universal mechanisms are present for a toxin and when this approach is valid. Because of this difficulty, this approach should only be taken when no other information or method is available and should be applied by an individual or group who possess the necessary qualifications. Also, ratings derived by extrapolating between species should be annotated to indicate that the assigned value is derived and not based upon actual toxicological data for the compound in question.

Evaluating Structural Similarities

Inorganic Compounds

Estimating a chemical's toxicity based upon structural similarities of other chemicals with known toxicities may work well with a few simple salts but is usually not effective. Several pieces of information must be known for this estimation to work well. First, there must be no question as to which half of the salt is responsible for the toxic effect. While it would be sensible to relate the toxicities of sodium cyanide with potassium cyanide, it would not make sense to draw conclusions about the toxicity of mercuric cyanide by analyzing potassium cyanide. Second, there must be no known toxicological interaction (e.g., potentiation, synergism, antagonism) between each half of the salt. Third, the ability of the body to absorb the toxin is based upon numerous factors, such as solubility, that must be understood. Some inorganic compounds, such as cadmium sulfide (LD_{50} rat is 7,080 mg/kg), are relatively insoluble in water or stomach acid and that would inhibit their absorption into the body. This, in turn, renders them far less toxic than more soluble compounds such as sodium sulfide (LD_{50} rat is 208 mg/kg) or cadmium chloride (LD_{50} rat is 88 mg/kg). Similarly, inorganic complexes such as ferricyanide cannot be compared to simple cyanide salts.

Organic Compounds

Estimating toxicities of organic compounds can be even more difficult than the case for inorganic compounds. In some cases, the functional group (e.g., alcohol, nitro, aldehyde, acid) is the source of toxicity. As a general rule, when the molecule becomes larger, the effect of the functional group becomes diluted and the toxicity decreases (Table 4). Formic acid is three times more toxic than acetic acid, and methylamine and methyl iodide are about four times more toxic than ethylamine and ethyl iodide. In each of these cases, adding a carbon onto a molecule resulted in a larger molecule that was less toxic. This is not, however, true in all cases. Acetonitrile has fewer carbons than propionitrile, but the propionitrile is far more toxic.

Another argument that is sometimes made is that the more functional groups present on a molecule, the more toxic it will be. This is also not the case (Table 4). Phenol has approximately the same oral toxicity that of other dihydroxybenzenes (such as 1,2-benzenediol) and ethylamine is much more toxic than 1,2-ethanediamine.

Chemical 1	LD_{50}	Chemical 2	LD_{50}
Formic Acid	1100 mg/kg	Acetic Acid	3300 mg/kg
Methylamine	100 mg/kg	Ethylamine	400 mg/kg
Methyl iodide	76 mg/kg	Ethyl Iodide	330 mg/kg
Acetonitrile	2460 mg/kg	Propionitrile	39 mg/kg
Phenol	317 mg/kg	1,2-Benzenediol	260 mg/kg
Ethanediamine	400 mg/kg	1,2-Ethanediamine	1200 mg/kg

Table 4 - LD_{50} (oral) values of Chemicals Containing Specific Functional Group

If no consistent toxicological relationships can be found when one compares similar simple organic molecules, then one should not expect to see a consistent set of toxicological relationships when a complex molecule and its derivatives are compared. Using strychnine as an example, one can see that adding a hydroxyl group on carbon number four has little effect on the resulting compound's toxicity (Table 5). If one instead adds the hydroxyl group to carbon number two, then the relative toxicity goes down about fifty-fold. The same effect is observed when an amino group is added to carbon number 2, but the relative toxicity observed by adding bromine to this carbon is an order of magnitude greater than either the hydroxyl or amino derivative. These differences in toxicity likely stem from the added functional groups affecting the ability of the molecule to bind to the site that mediates the molecule's toxicity. Because of this, one cannot make assumptions about the relative toxicity of a complex compound based upon structural similarities to other complex compounds.

Strychnine Derivative	LD_{50}
Strychnine	0.474 mg/kg
4-Hydroxystrychnine	0.556 mg/kg
2-Hydroxystrychnine	22.1 mg/kg
2-Bromostrychnine	2.8 mg/kg
2-Aminostrychnine	19.7 mg/mg

Table 5 - LD_{50} values (subcutaneous, mouse) for Strychnine and Its Derivatives

This method can work for some inorganic or organic salts. As stated earlier, this works well when the ion responsible for the toxic effect is well known and understood while the rest of the complex is known with certainty not to participate in any toxicological response. In the afore-mentioned example of cyanide salts, one can take the relative toxicities of sodium cyanide, potassium cyanide, gold cyanide, etc., and use those to estimate the toxicity of lithium cyanide. However, if one does not have a good understanding of chemistry, then one might incorrectly assume that ferricyanide salts are as toxic as simple cyanide salts. Also, one must understand the toxicology of both ions. One needs to realize that the relative toxicity of sodium oxalate comes from the oxalate ion and cannot be compared to that of mercuric oxalate due to the toxicity of both the oxalate and mercuric ions. As in the case of extrapolating health hazard ratings between species, ratings derived by extrapolating between similar salts should be annotated to indicate that the assigned value is derived and not based upon actual toxicological data for the compound in question.

Determining Relative Toxicities Based Upon Constituents (Mixtures)

Attempting to determine relative toxicities by evaluating individual components in a mixture should be used with great caution. While this method may work when the toxic effects of chemicals in a mixture are additive, or when the solvent is pure water, it will not work in other cases. When chemicals interact to cause negation (1 + 1 = 0), potentiation (1 + 0 = 4), or synergism (1 + 1 = 4), their overall effect cannot be predicted. For example, dilute hydrochloric acid is a simple irritant, but, if a small amount of "harmless" surfactant is added, then the dilute hydrochloric acid/surfactant mixture

becomes corrosive. Because one can never tell with certainty how chemicals in a mixture will interact within the body, attempts to determine the relative toxicity of chemical mixtures may likely result in error. Because of the many uncertainties involved, this method should only be attempted by qualified individuals or groups and ratings obtained should be annotated to indicate that the assigned value is derived and not based upon actual toxicological data for the mixture in question.

Appropriate Approaches

Clearly, there is no easy solution on how every chemical that has not undergone a toxicological evaluation should be evaluated for health hazard rating numbers. Since every proposed method has strengths and weaknesses, one should adopt a process that would allow the analyst to carefully evaluate available data and determine appropriate health hazard rating numbers. In developing this process, one should be aware that the level and amount of resources available will determine which methods can be used. Some methods will require a fair amount of research by a person who is knowledgeable in chemistry and/or toxicology. If a person or persons with these qualifications are not available, then these more involved methods should not be attempted.

MSDS Estimated Values

One method for determining health hazard rating numbers when no toxicological data exist is to simply use the estimated values from an MSDS. When multiple MSDS are available and their estimated health hazard ratings vary, one should use the most conservative value. One advantage of using this approach is that, while using estimated health hazard values from MSDS does not place the liability of these numbers' accuracy on the manufacturer, it does tend to absolve the user of any fault if the values prove to be in error. A second advantage to this method is that it requires little expertise. A third advantage of using this method is that, due to the similarity of hazard rating criteria, either HMIS or NFPA approximate health hazard ratings can be used. One must, however, be aware of a minor drawback to this method. If one adopts this method, then one must use the manufacturer's hazard rating number when it is clearly in error until one can get the manufacturer to correct the value.

Data Mining

RTECS (4) is viewed as being a comprehensive listing of toxicological studies, It is typically consulted to find toxicological data to help with health hazard rating determinations. What is not so well known is that toxicological studies have been performed that have not been published. These studies will not appear in RTECS, but may be helpful in assigning health hazard ratings. The difficulty is in finding these studies. Some websites, such as the ones describing the generation of AEGLs and ERPGs, can be used. The AEGL and ERPG processes seek to obtain all published and relevant unpublished LC-50/LD-50 data through industry-trade associations and from individual companies in the private sector. This information appears in the supporting documents published for final AEGLs and ERPGs and can be sources of toxicity data that

can be used along with the NFPA 704 quantitative guidelines to determine the numerical health hazard rating. Also, one may want to identify any ratings that stem from unpublished sources so that users know there may be some uncertainty related to the rating or that data used to generate ratings came from an "unconventional" source.

Quantitative Structure Activity Relationship (QSAR) Methodologies and Computer Programs

Also known as quantitative structure-property relationships (QSPR), QSAR methodology based programs utilize electronics and lipophilicity properties to predict the biological activity of a compound. When the required parameters are not known for the compound of interest, one would data-mine for other compounds in the same class and use the available data to predict the properties. Generally, the more similar compounds used in developing the model, the better the prediction. These computational chemistry methods have been used successfully to predict biological activity, including LD-50 values. (16, 17).

While these types of programs are widely used in the pharmaceutical industry as predictors to determine which analogs of a particular drug warrant further investigation, they are not widely used in general industry because of the cost of the programs and associated hardware, and the time involved in mining for the data needed to develop the model. Lastly, these data are derived values and, as with any statistical method, false correlations are possible.

Use Other NFPA Rating Criteria

NFPA 704 allows the use of other data in the determination of health hazard ratings. Some of these ratings, such as corrosives, cryogens, or liquefied gases that can cause frostbite being rated a "3"; sensitizers, lachrymators, and severe irritants being rated a "2"; and mild irritants being rated a "1"; are fairly well known and can be used. What is less well known is that transportation hazard classifications can be used to develop health hazard ratings. Products classified as being "Poison – Inhalation Hazard" per the U.S. Department of Transportation (2.3 – Toxic/Poison/Poisonous) (14) can be provided a health hazard rating of "3" or "4". Similarly, products that, according to United Nations Criteria (15), fall into categories called Packing Groups I, II, or III can be provided a health hazard rating of "4", "3", or "2", respectively.

Noting the Unknown

One last approach that can be taken when no toxicological data exists to support the generation of health hazard ratings is to use a symbol indicating that no information is available. This symbol may be a blank, question mark or anything else one chooses. While this is the most accurate methodology, it is clearly the weakest in that it leaves the user with no data. What would be required to help workers when no health hazard data is available would be default instructions that might include directions to treat all chemicals with unknown health hazard ratings as being rated a "3" for handling purposes.

Conclusions

Determining health hazard rating numbers for chemicals for which no applicable toxicological data exist is both important and difficult. If accurate ratings are not determined or available, then either extra work resulting in the consumption of scarce resources or the potential exposure of workers to unidentified hazards will result. Blindly using information from sources that have various limitations and weaknesses can lead to inaccurate health hazard rating numbers and would not lend itself towards accomplishing the goal of protecting the worker at a reasonable cost. What is required is a process that carefully analyzes applicable data and allows the analyst to determine reasonable health hazard rating numbers. If the resources and expertise are available then data mining for toxicological data is the preferred choice. If data mining is not possible, or does not yield useful results, then the use of the UN packing group criteria or QSARS listed above should be the next choice. That failing, then the only remaining option is to give the health hazard a rating of "?" for unknown.

References:

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6 - The International Agency for Research on Cancer (IARC)

7 - National Toxicology Program (NTP)

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