Regulatory Toxicology and Pharmacology 81 (2016) 33–38

Contents lists available at ScienceDirect

Regulatory Toxicology and Pharmacology

journal homepage: www.elsevier.com/locate/yrtph

An approach for the development of emergency response levels for halogenated hydrocarbons

George M. Rusch

Risk Assessment and Toxicology Services, 6900 Corral Gate Lane, Sarasota, FL 34241, USA

ARTICLE INFO

Article history:
Received 7 March 2016
Received in revised form
23 June 2016
Accepted 24 June 2016
Available online 28 June 2016

Keywords:
Halogenated hydrocarbons
Emergency response
Guideline levels
Default guideline levels
Emergency guideline levels

ABSTRACT

Emergency exposure guidance levels have been developed for many halogenated hydrocarbons. These can be employed in the event of accidental releases or terrorist actions. However, for a chemical release involving a substance without existing guidance levels, there is a need to be able to develop one rapidly. Two data sources are available, the Acute Exposure Guideline Levels (AEGL) and Emergency Response Guideline Levels (ERPG). The subset of halogenated hydrocarbons and related substances included in these data sources represent 30 chemicals and 41 risk assessments. The ratios for serious toxicity/annoyance level and for potential lethality/serious toxicity were calculated. On reviewing the results, the geometric means provided the best basis for extrapolation. When the geometric means of the ratios of ERPG-3/ERPG-2 and AEGL-3/AEGL-2 were calculated their combined mean was 4.40. The geometric standard deviation for the combined data set was 2.00 suggesting the data were homogeneous. Likewise, calculation of the geometric means for ERPG-2/1 and AEGL-2/1 the combined ratio was 3.93. The geometric standard deviation for the combined set was 1.46, again suggesting homogeneity of the data. The review described in this paper confirmed that the time default "n" values of 3 and 1 (ten Berge et al., 1986) are appropriate for extrapolation to shorter and longer exposure times, respectively.

1. Introduction

Exposure to chemicals can occur as a consequence of normal background levels originating from releases during production or use or as a consequence of an accidental, unplanned release. Risk assessments for exposures resulting from anticipated, frequent releases are normally described in occupational exposure guideline level documents such as TLVs, WEELs or PELs (TLVs, 2015; WEELs and ERPGs, 2015; OSHA, 1989). These are guidance levels for repeated exposure over a working life time.

Where the release is accidental, exposures can occur to either or both the individuals working at the site where the chemical is being produced or used and the general public in the area of the release. Depending on the magnitude of the release, the number of people exposed and the area impacted may be either small or extensive. It is critical to be able to rapidly evaluate the seriousness of the exposure. When the exposures occur at a plant site, frequently plant safety personal can determine the hazard and recommend appropriate action. If the exposure occurs off site, e.g. a transportation accident, or a release from a plant site, First Responders are called upon to provide guidance. When the substance released has emergency exposure guideline levels either derived by a producer or by a committee such as the AEGL or ERPG committees and the data are available, the First Responder has guidance to determine appropriate action. Where that information is not available, it is important to have a means to estimate hazardous exposure levels. This manuscript provides an approach that can be used to estimate these levels for a specific class of chemicals, halogenated hydrocarbons. Halogenated hydrocarbons were selected because many are volatile, produced in large quantities, and transported over great distances. While the toxicity of most of the finished products has been studies extensively, many of the intermediates have not been studied in great detail.

In the development of emergency exposure guidance levels, the data on which these levels are based should be appropriate for the situation in which they are to be applied. These are rare or infrequent exposures resulting from an accidental or terrorist release. Both the American Industrial Hygiene Association's Emergency Response Planning Committee (AIHA ERP, 2006) and the (EPA) Federal Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances (AEGL, 2011) have developed guideline

E-mail address: George.rusch9@gmail.com.

http://dx.doi.org/10.1016/j.yrtph.2016.06.021
0273-2300/

levels specifically for rare accidental releases. The data presented in this manuscript were collected from the AEGL and ERPG data bases and represent all of the halogenated hydrocarbons that have been reviewed by these two committees. The exposure scenarios being evaluated are accidental releases with potential exposure to the public. When data for the specific substance do not exist, it is possible to extrapolate from existing data bases when those data bases are robust and appear to represent responses reasonably expected to be seen from exposure to the substance being evaluated. Where there is a fairly robust data set for the chemical under evaluation, extrapolation, using data bases from other chemicals, is even more straight forward. At the request of the American Society for Heating Refrigeration Air Conditioning Engineers' (ASHRAE) committee for Refrigerant Safety Classification, SSPC 34's Toxicology Subcommittee, this manuscript was prepared to provide a default method to estimate appropriate safety levels for accidental releases of refrigerants that do not have AEGL or ERPG guidance levels.

While the best approach is to always start with high quality appropriate data on the chemical in question or from a similar chemical, some times these data do not exist. In an emergency, such as described in the TEEL process (TEELs, 2008), the only option is to extrapolate from data that have been carefully reviewed. Even though the comparisons may be limited, they will be of more value than having nothing to use for a comparison. It is better to have substances of similar toxicity in the data base being used for extrapolation to default risk assessment values than substances of unknown similarity. The advantage of having a large data base is that it will tend to be a better predictor than one of limited scope. The Acute Exposure Guideline Levels for Hazardous Substances (Standing Operating Procedures, 2001; AEGL, 2011) and the Emergency Response Planning Guidelines (WEELs and ERPGs, 2015) data bases combined consist of approximately 200 substances and over 285 data sets. This combined data base contained 41 sets of emergency response guideline values that represented 30 different halogenated hydrocarbons. This subset of values for halogenated hydrocarbons provides a robust basis for the development of default values for similar substances.

2. Method

Since this manuscript primarily discusses the class of substances known as halogenated hydrocarbons and two related materials (two acid chlorides; benzoyl chloride and methylchloroformate), both the AEGL and ERPG data bases were reviewed and halogenated hydrocarbons and related substances identified. These, by themselves, consisted of a robust group with 30 members and 41 chemical specific reviews. This grouping provided a class specific set of values containing both saturated and unsaturated substances and both highly toxic and relatively non-toxic substances.

Both AEGLs and ERPGs involve three different exposure levels. The AEGL/ERPG-1 is an annoyance level. The AEGL/ERPG-2 is a threshold for serious toxicity or impairment of escape. The AEGL/ERPG-3 is a conservative estimate of a potentially lethal level. A proposal was presented to the ERP committee to determine the approximate relationship between the three levels as a means for estimating these default levels. This proposal initially involved calculation of the mean, standard deviation and median for the ratios of levels 2/1, 3/1, and 3/2 and was expanded to include the geometric mean and geometric standard deviation. Both the AEGL and ERPG data bases were used. Some chemicals appear in both data bases. Since the evaluations on these duplicate chemicals were conducted independently, both sets of data were used. The results of this evaluation have been reviewed by the ERPG committee. It was agreed that using mean ratios did not give robust results since the standard deviations for these ratios were large and the values were subject to large influences from outlier values. The medians and geometric means were not influenced in this way and appeared to better represent the distribution of the values without being overly influenced by outlier values. When the geometric standard deviation for the combined data set was calculated, it was 2.00 for the level-3/level-2 ratios and 1.46 for the level-2/level-1 ratios suggesting a good fit of the data. Thus the geometric means were used as the basis for the default calculations.

These calculations were performed using the programs in the 2007 Microsoft office data base. As it was concluded that the geometric means and standard deviations best represent the data only these values are presented here.

3. Results and discussion

The estimation of the "Point of Departure" for the risk assessment on a specific chemical was based in part on the publication: "Establishing a Point of Departure for Risk Assessment Using Acute Inhalation Toxicology Data" (Rusch et al., 2009). It involves taking 1/3 of the lowest lethal exposure in an animal acute inhalation study as an estimate for a non-lethal level and applying an adjustment factor to that number to include a safety factor to go from animals to humans, to derive a level 3 value. This could only be done in cases where more than 50% of the animals survived that exposure (i.e. less than 50% lethality). The determination of a safety factor in this risk assessment typically must rely on a toxicologist's professional judgment and in most cases would fall between 3 and 10. As noted in the paper referenced above, most often a value of 3 can be used.

The results from the ratio calculations for level 3/level 2 (Tables 1 and 2) and level 2/1 (Table 3) are presented below. The interim and final AEGL values are very similar and have been combined. The only difference between these two is that the final values have been reviewed by a National Research Council Subcommittee. The differences between the ERPG and AEGL result from slight differences in the definition of the terms, mostly the level 3, where ERPGs are closer to threshold values and as such they are slightly higher. Given that most dose response relationships are log normal, the geometric mean appeared to represent the best fit. For the data analyzed so far, the two approaches appear to yield similar results.

The final step in the process was to recommend an approach for estimation of a factor to be used in time extrapolation to develop values for different exposure periods. The AEGL committee has relied on a publication by ten Berge (ten Berge et al., 1986) which reviewed the results from 15 studies where these data were available. Ten Berge reported that the range for the values of "n" in the equation $C^n * t = K$ was between 0.8 and 3.12, where C is concentration; n is the experimentally derived slope for the dose response curve; t is the time for the exposure and K is a constant was between 0.8 and 3.12. They then applied limits from 1 to 3 when doing time extrapolations. There are 52 chemicals in the complete AEGL data base for which time extrapolations were made based on real data. Of these, 26 were in the range of 0.7–1.3; 12 were in the range of 1.5–1.9; 11 were between 2.0 and 2.5 and only 3 were above 2.5. The median for all n values is 1.3 while the

Table 1
AEGL-ERPG 3/AEGL-ERPG-2 comparison of median and geometric mean with geometric standard deviation for halogenated hydrocarbons.

Parameter	Final ERPG	Combined AEGL	Combined AEGL & ERPG
Median	4.00	3.25	4.00
Geomean	4.48	4.29	4.40
Geostdev	1.82	2.19	2.00