Available online at www.sciencedirect.com
ScienceDirect
Regulatory Toxicology and Pharmacology 47 (2007) 261–273
Regulatory Toxicology and Pharmacology
www.elsevier.com/locate/yrtph

Evaluation of acute inhalation toxicity for chemicals with limited toxicity information

Roberta L. Grant *, Bernard J. Kadlubar, Neeraja K. Erraguntla, Michael Honeycutt

Texas Commission on Environmental Quality, P.O. Box 13087, MC168, Austin, TX 78711-3087, USA

Received 19 July 2006
Available online 31 January 2007

Abstract

A large reference database consisting of acute inhalation no-observed-adverse-effect levels (NOAELs) and acute lethality data for 97 chemicals was compiled to investigate two methods to derive health-protective concentrations for chemicals with limited toxicity data for the evaluation of one-hour intermittent inhalation exposure. One method is to determine threshold of concern (TOC) concentrations for acute toxicity potency categories and the other is to determine NOAEL-to-LC_{50} ratios. In the TOC approach, 97 chemicals were classified based on the Globally Harmonized System of Classification and Labeling of Chemicals proposed by the United Nations into different acute toxicity categories (from most toxic to least toxic): Category 1, Category 2, Category 3, Category 4, and Category 5. The tenth percentile of the cumulative percentage distribution of NOAELs in each category was determined and divided by an uncertainty factor of 100 to derive the following health-protective TOC concentrations: 4 $\mu g/m^3$ for chemicals classified in Category 1; 20 $\mu g/m^3$ for Category 2; 125 $\mu g/m^3$ for both Categories 3 and 4; and 1000 $\mu g/m^3$ for Category 5. For the NOAEL-to-LC_{50} ratio approach, 55 chemicals with NOAEL exposure durations $\leqslant$24 hour were used to calculate NOAEL-to-LC_{50} ratios. The tenth percentile of the cumulative percentage distribution of the ratios was calculated and divided by an uncertainty factor of 100 to produce a composite factor equal to 8.3×10^{-5}. For a chemical with limited toxicity information, this composite factor is multiplied by a 4-hour LC_{50} value or other appropriate acute lethality data. Both approaches can be used to produce an estimate of a conservative threshold air concentration below which no appreciable risk to the general population would be expected to occur after a one-hour intermittent exposure.

Keywords: Acute; Inhalation; Threshold of concern; Globally Harmonized System; LC_{50}; Cramer; Air permit review; NOAEL

1. Introduction

The Texas Clean Air Act (Chapter 382 of the Texas Health and Safety Code) authorizes the Texas Commission on Environmental Quality (TCEQ)[1] to conduct air permit reviews of all new and modified facilities to ensure that the operation of a proposed facility will not cause or contribute to a condition of air pollution. Air permit reviews typically involve evaluations of best-available-control technology and predicted air concentrations related to proposed emissions from the new or modified facility. In a conservative evaluation, worst-case emission rates are

* Corresponding author. Fax: +1 512 239 1794.
E-mail address: rgrant@tceq.state.tx.us (R.L. Grant).

[1] *Abbreviations used:* AEGL, Acute Exposure Guideline Level; ATSDR, Agency for Toxic Substances and Disease Registry; ESLs, effects screening levels; GHS, Globally Harmonized System of Classification and Labeling of Chemicals; GLC_{max}, maximum ground level air concentrations; GM, geometric mean; GSD, geometric mean standard deviation; hr, hour; LC_{50} or LD_{50}, the concentration or dose of a chemical which causes the death of 50% of a group of test animals; ln, natural logarithm; LOAEL, lowest-observed-adverse-effect level; LTB, lower tolerance bound; MRL, minimal risk levels; NOAEL, no-observed-adverse-effect level; N–L ratio, NOAEL-to-LC_{50} ratio; NOEL, no-observed-effect level; OEHHA, California Office of Environmental Health Hazard Assessment; POE, point of entry; REL, reference exposure level; TC, toxicity category; TCEQ, Texas Commission on Environmental Quality; TOC, threshold of concern; UF, uncertainty factor; UTB, upper tolerance bound.

0273-2300/$ - see front matter
doi:10.1016/j.yrtph.2006.11.003

modeled to predict resulting short-term and long-term chemical-specific maximum ground level air concentrations (GLC_{max}). In the review of proposed emissions, federal/state standards and chemical-specific effects screening levels (ESLs) developed by TCEQ toxicology staff are used for criteria and non-criteria pollutants, respectively. ESLs are chemical-specific air concentrations set to protect human health and welfare and are used in the air permitting process to assess the protectiveness of emission rate limits. Short-term ESLs are developed to evaluate acute intermittent exposures of one hour (hr) whereas long-term ESLs are developed to evaluate chronic exposures. The Texas Health and Safety Code is comprehensive. Therefore, ESLs are developed for as many air contaminants as possible, even for chemicals with limited toxicity data. There is a need to develop conservative, health-protective concentrations for chemicals with limited toxicity data for the review of short-term GLC_{max}s taking into consideration that ambient air exposure is dependent on meteorological conditions and peak exposures that could occur several times per day.

The purpose of this paper is to present two different approaches to establish health-protective air concentrations for chemicals with limited toxicity information for the general public via the inhalation route of exposure. This paper focuses on one-hour intermittent exposure scenarios that are normally the basis for air permit reviews. A method proposed by Munro et al. (1996) for establishing a threshold of concern (TOC) via oral exposure for chemicals in different toxicity potency classes will be discussed followed by an adaptation of a procedure proposed by Layton et al. (1987) and Venman and Flaga (1985) that involved the calculation of the ratios of no-observed-adverse-effect levels (NOAELs) to oral LD_{50} data for different chemicals. The LD_{50} is the dose of a chemical which causes the death of 50% of a group of test animals. Health-protective air concentrations derived using these two approaches are presented and compared to published short-term toxicity values.

1.1. A threshold of concern approach

Munro et al. (1996) proposed a method for establishing a threshold of concern (TOC) based on grouping chemicals into three structural classes that correlated with chronic oral toxicity potency. Using a system devised by Cramer et al. (1978), organic chemicals were classified in Cramer Class I (least toxic class), II (intermediate class), and III (most toxic class). Munro obtained no-observed-effect levels (NOELs) from chronic, oral animal studies for over 600 chemicals and calculated the fifth percentile of NOELs for each structural class. The fifth percentile NOEL for each structural class was divided by an uncertainty factor (UF) of 100 to account for animal-to-human uncertainty and human variability to establish a conservative threshold dose below which no appreciable risk to human health would occur. The threshold dose could be used for chemicals with limited toxicity information to determine if toxicity testing should be conducted if potential exposure levels were higher than the conservative threshold dose. The approach assumes that the proposed threshold dose for a chemical with limited toxicity information will not be significantly lower than the fifth percentile NOEL divided by an UF of 100. The TOC approach was initially used for food additives and for the evaluation of packaging material (FDA, 1995; Kroes et al., 2000, 2004; Munro, 1990; Munro et al., 1996). Other investigators have used this approach for other products such as food flavorings, personal and household care products and pharmaceutical compounds (JECFA, 1993, 1995, 1997; Kroes et al., 2004; Blackburn et al., 2005; and Dolan et al., 2005).

The TOC approach has mainly been used to evaluate chronic oral exposure. However, the basic approach of Munro et al. (1996) could be used to develop a TOC for other routes of exposure such as inhalation exposure. Ford et al. (2006) investigated the inhalation TOC approach for the evaluation of tobacco additives (i.e., low molecular weight volatile compounds) where inhalation is the relevant route of exposure. They collected chronic inhalation NOAELs for approximately 350 chemicals categorized into the three Cramer structural classes. There was a good correlation with the oral database for those chemicals not causing respiratory tract point-of-entry (POE) effects but there was not a good correlation with the oral database for approximately 33% of chemicals that caused respiratory POE effects. Ford et al. (2006) concluded that the use of the chronic inhalation database, with the removal of those substances with NOAELs based on respiratory POE effects, allowed the determination of inhalation TOCs. Although the Cramer structural class categories were useful for establishing a TOC for the chronic inhalation route, a method to predict respiratory POE effects for chronic inhalation exposure must be developed and used in conjunction with the Cramer structural categories.

The basic approach of Munro et al. (1996) was followed to establish a TOC approach for the review of short-term GLC_{max}s. However, the basic approach was altered in that the acute inhalation database included NOAEL data, not NOEL data, and the chemicals were classified using acute lethality data and the Globally Harmonized System of Classification and Labeling of Chemicals (GHS) proposed by the United Nations (UN, 2005). The GHS classification system is designed to predict acute toxicity potency and is more appropriate for developing an acute TOC approach.

1.2. A NOAEL-to-LC_{50} ratio approach

One of the first steps in determining toxic inhalation potency is to determine the concentration of a chemical in air which causes the death of 50% (one half) of a group of test animals (LC_{50}). Acute lethality data have been used to determine concentrations that are predictive of an increasing likelihood of lethality for the general public (i.e., acute emergency exposure guideline levels (NRC, 2001) and temporary emergency exposure limits (Craig