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Derivation of a toxicity reference value for nitrogen trichloride as a disinfection by-product

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ABSTRACT

Nitrogen trichloride is a highly volatile chlorination disinfection by-product, very commonly found in the air of indoor swimming pools. The aim of this work is to characterize the hazard associated with it and to determine the concentration at which health effects appear, for application in health risk assessments for users of indoor swimming pools. Hazard identification was based on a literature survey and analysis of animal and human studies, with special attention paid to their methodological quality and to reports of a dose–response relationship. A toxicity reference value was derived for respiratory effects, based on human data from both general and occupational data. We selected a lowest-observed-adverse-effect-level of 0.355 mg/m^3 based on objective measurements rather than self-reported effects. Two uncertainty factors were applied to take into account both intra-species variability and the use of a concentration with an effect rather than a no-observed-adverse-effect-level. A toxicity reference value of 4×10^{-3} mg/m^3 for nitrogen trichloride is proposed for repeated short exposures. Alternative values based on animal data range from 0.01 to 0.03 mg/m^3.

1. Introduction

Chlorination is commonly used to disinfect water. When chlorine reacts with organic matter present in water, it generates disinfection by-products (DBPs) (Deborde and von Gunten, 2008; Westerhoff et al., 2004). One of the most commonly measured of these is nitrogen trichloride (Zwiener et al., 2007). Nitrogen trichloride is a chlorinated compound with the formula NCl_3 (CASRN 10025-85-1 and RTECS No. QW974000). It is a yellow oily liquid, highly reactive in its pure form, with a pungent odor. Its molar mass is 120.37 g/mol, its melting point 40 °C, boiling point 71 °C, and vapor pressure 19.95 at 25 °C (OSHA, 2007). Its Henry's law constant is 435 M/atm (Holzwarth et al., 1984). Several synonyms are often used in the literature, such as "nitrogen chloride" or "trichloramine". In this paper, we use the formula "NCl_3" to refer to this chemical. Toxicological data for it are sparse in the literature, and no human toxicity reference value (TRV) — not any reference concentration (RfC), minimal risk level (MRL) or reference exposure level (REL)[1] — is available in the toxicological databases. It is known to have a strong potential for irritation (Gagnaire et al., 1994), and short-term exposure causes ocular irritation and coughing. Based upon irritation studies in mice in 1994, Gagnaire et al. recommended a TWA-TLV (8-h time-weighted-average threshold limit value) of 0.5 mg/m^3 and a STEL (15-min short-term exposure limit) of 1.5 mg/m^3 for workers (Gagnaire et al., 1994). Epidemiological data indicate that NCl_3 may increase the risk of respiratory inflammation and asthma among people, including children, who are chronically exposed at indoor chlorinated swimming pools (Bernard et al., 2003; Jacobs et al., 2007). The aim of this paper is to derive a TRV from current published data for the purpose of assessing the acute and chronic risks associated with exposure to NCl_3 among swimming pool users and workers.

2. Methods

Our bibliographic survey of the Pubmed and Toxline databases from the National Library of Medicine website as of September 2009 (http://www.nlm.nih.gov/databases/), used the following search terms: "CASRN[2] 10025-85-1" or "nitrogen chloride" or "nitrogen trichloride" or "trichloramine". We selected the studies reporting health effects in animals or humans.

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[1] The RfC is the reference dose derived by the US Environmental Protection Agency, the MRL the minimal risk level derived by the US Agency for Toxic Substances and Disease Registry, and the REL the reference exposure level derived by the California EPA Office of Environmental Health Hazard Assessment. In this paper, all these values are referred to as toxicity reference values (TRVs). They are estimates of the inhalation exposure to the human population, including sensitive subgroups, at which there is likely to be no appreciable risk of deleterious effects during a specified time.

[2] Chemical Abstract System Registry Number.

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2.1. Hazard identification

For each study, we analyzed the protocol, type of study population, exposure characterization or dosing (type of measurements and sampling, duration and route of exposure, etc.), effects studied, and response observed. We summarized the populations' principal characteristics, the study observations, and confounding factors.

2.2. TRV derivation

For each relevant exposure route, we chose the most sensitive endpoint as a *critical effect*[3] to analyze the dose–response relation. To derive the TRV, we chose studies according to the following criteria:

- Human data were preferred over animal data (when both were available) to avoid interspecies extrapolation, as recommended by the International Programme on Chemical Safety (IPCS, 1999). Animal data were considered for analysis of the mode of action and the consistency of the data.
- Studies with objective effect measures (e.g., respiratory function or laboratory parameters) were preferred over studies that used subjective symptoms (such as a simple comfort questionnaire).
- Studies with quantitative exposure data and specific measurement of NCl_3 (rather than total chlorine) were preferred.
- NCl_3 was the main irritant chemical found in the atmosphere.
- Studies with statistically significant differences in response among several exposure groups or compared with a control were preferred.

Finally, the assessment was based on expert judgment that considered, as recommended by the World Health Organization, the timing, biological plausibility, and consistency of the observations and characteristics of any dose–response relation, and which took bias and confounding into account (WHO working group, 2000).

Applying a "lowest-observed-adverse-effect-level" (LOAEL) approach, we chose as the *critical dose* the lowest dose corresponding to a statistically significant increase of the critical effect in the study population. Next, in accordance with the conventional approach suggested by the current U.S. EPA's IRIS guidelines, uncertainty factors were applied to this critical dose (Kimmel, 1990; U.S. EPA, 1994; Pohl and Abadin, 1995). The uncertainty factors include an extrapolation from the LOAEL to a No-observed-adverse-effect-level (NOAEL), two factors that took interspecies and interindividual variability into account, and sometimes a factor that considered the poor quality or inadequacy of the database. Default health-protective values of 10 were applied when no data were available. Specific values (e.g., 1, 3, or 5) rather than the default values were used when justified by knowledge of variability, uncertainty, and mode of action. Similarly, the traditionally recommended adjustments of the critical dose (allometric or dosimetric and temporal adjustments) (U.S. EPA, 1994, 2002) took into account the chemical, toxicokinetic, and toxicological properties of NCl_3.

3. Results

3.1. Toxicological assessment

The physicochemical properties of NCl_3 indicate that it can be readily volatilized from water and thus explain why health effects studies, especially among humans, use the inhalation route. Only one study has assessed its oral toxicity — in rats exposed to 0.2–90 ppm in drinking water (Nakai et al., 2000). No clinical signs were observed, but biochemical and mild histological effects appeared at 0.23 mg/kg/d in females and at 0.29 mg/kg/d in males. No information is available for the dermal route. Consequently, we conclude that the inhalation route is the route of concern for health risk assessments.

3.1.1. Effects in humans

Table 1 summarizes the 13 available studies. Four were performed after workers complained and reported symptoms of irritation in industrial facilities where NCl_3 and chlorinated derivatives were likely to be found in the air, such as food processing plants (Sanderson et al., 1995; Héry et al., 1998; King et al., 2006; Massin et al., 2007). In two of these four studies, chloramine levels were individually characterized and ranged from 0.0057 to 1.1 mg/m^3 (mean values) (Héry et al., 1998; King et al., 2006). The lower concentration was associated with self-reported upper respiratory tract symptoms among workers in a poultry processing plant (King et al., 2006). Nonetheless, because the highest concentration measured in this plant was 0.15 mg/m^3 and chlorine was also detected, it is not possible to determine whether there was any causal relation between NCl_3 and the self-reported complaints. Two other occupational studies have investigated pulmonary function with objective measurements (spirometry or bronchial challenge test with methacholine) (King et al., 2006; Massin et al., 2007). One reported a significant decrease in lung function among exposed workers (King et al., 2006), but the association was with chlorine and not NCl_3 exposure. Finally, there is no occupational study in an industrial facility that met our selection criteria. The only direct associations between NCl_3 and respiratory effect concern self-reported symptoms, while associations with objective measurements have been shown only with chlorine or a global index exposure, but not directly with NCl_3.

One study was conducted after an outbreak among children who attended a party at a hotel pool. It collected only self-reported symptoms, by questionnaire. The results show that entering the swimming pool area and swimming in the pool were both strongly associated with respiratory symptoms (cough, eye and throat irritation, and difficulty in breathing) (Kaydos-Daniels et al., 2008). Only water samples were available and NCl_3 was not measured directly.

The other eight studies were conducted in swimming pools where NCl_3 was measured alone or with other volatile organic compounds, such as chlorine or aldehydes (see Table 1). NCl_3 has been linked to symptoms of irritation in workers (Héry et al., 1995; Massin et al., 1998; Thickett et al., 2002; Jacobs et al., 2007) and in swimmers (Carbonnelle et al., 2002; Bernard et al., 2003, 2006). Complaints reported by employees of 13 swimming pools with mean NCl_3 concentrations of 0.15–0.87 mg/m^3 (Héry et al., 1995) appeared at concentrations exceeding 0.5 mg/m^3. Another study of 334 lifeguards reported a significant association between upper respiratory irritation reported by questionnaire (eyes, nose, throat, or dry cough) and NCl_3 levels as low as 0.14 mg/m^3 (Massin et al., 1998): at this level, the prevalence of irritation of the eyes, nose, and throat was, respectively, 50%, 11%, and 16% and showed a significant concentration–response relation, which rose to 86%, 60%, and 28% in the group exposed to a concentration greater than 0.5 mg/m^3. In view of the subjective character of the effects and because there was no unexposed control group, it is difficult to conclude definitively that there was a positive effect. Inflammation of the lungs was also observed in swimmers. Mean concentrations of approximately 0.35 and 0.5 mg/m^3 of NCl_3, respectively, were associated with an increase in lung epithelium permeability in trained and recreational

[3] The critical effect is "the first adverse effect, or its known precursor, that occurs to the most sensitive species as the dose rate of an agent increases" (U.S. EPA, IRIS Glossary http://www.epa.gov/ncea/iris/help_gloss.htm#c).