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Concentration-time extrapolation of short-term inhalation exposure levels: dimethyl sulfide, a case study using a chemical-specific toxic load exponent

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Abstract

Objective: Dimethyl sulfide (DMS, CAS 75–18-3) is an industrial chemical. It is both an irritant and neurotoxicant that may be life-threatening because of accidental release. The effects of DMS on public health and associated public health response depend on the exposure concentration and duration. However, currently, public health advisory information exists for only a 1 h exposure duration, developed by the American Industrial Hygiene Association (AIHA). In the present work, the AIHA-reviewed data were computationally extrapolated to other common short-term durations.

Methods: The extrapolation was carried out using the toxic load equation, $C^n \times t = \mathrm{TL}$, where C and t are exposure concentration and duration, TL is toxic load, and n is a chemical-specific toxic load exponent derived in the present work using probit meta-analysis. The developed threshold levels were vetted against the AIHA database of clinical and animal health effects induced by DMS.

Results: Tier-1 levels were derived based on human exposures that resulted in an easily detectable odor, because DMS is known to have a disagreeable odor that may cause nausea. Tier-2 levels were derived from the lower 95% confidence bounds on a benchmark concentration that caused 10% incidence (BMCL_{10}) of coma in rats during a 15 min inhalation exposure to DMS. Tier-3 levels were based on a BMCL_{05} for mortality in rats.

Conclusion: Emergency responders and health assessors may consider these computationally derived threshold levels as a supplement to traditional chemical risk assessment procedures in instances where AIHA developed public health advisory levels do not exist.

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Disclaimer

The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the Agency for Toxic Substances and Disease Registry.

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Keywords

ERPG; AEGL; n-value; toxic load; TLE; health guidance value; inhalation; inhalation exposure; volatile organic compound; dimethyl sulfide

Introduction

The magnitude of adverse effects caused by short-term inhalation exposures to volatile hazardous substances depends both on concentration of the substance in the air and on duration of exposure. Because combinations of these two factors are almost infinite, to measure and tabulate all of them is implausible. Therefore, extrapolation across exposure durations is of prime concern to health risk assessors and first responders. It is also important for emergency planning, including industrial sites design and construction, and in chemical detector/sampler manufacturing.

From the public health perspective, the plethora of adverse health effects due to inhalation exposures can be roughly divided into two groups: effects from intense short-term exposures to highly toxic substances that are clearly adverse and may develop rapidly, and effects from prolonged low-level exposures to contaminated air that may not be evident immediately, but could manifest over time. The latter type of exposures and associated delayed health effects are addressed by Minimal Risk Levels (Chou et al. 1998) and Reference Concentrations (USEPA 1994). Short-term exposures of high intensity, however, typically represent an immediate threat to the public and may even be life threatening. Scientific risk assessment of such short but intense-concentration exposures is provided by multiple institutions, including the U.S. Environmental Protection Agency (NRC 2001), American Industrial Hygiene Association (AIHA 2016), Department of Energy (DOE 2016), and others. There are differences among these programs in the depth of scientific assessment, coverage of the chemical space, the purpose of guidance, and methodology.

Emergency response at the Agency for Toxic Substances and Disease Registry (ATSDR) and the National Center for Environmental Health (NCEH) is driven by rigorous scientific judgement on a case-by-case basis. In the course of this process, usually the scientific information from USEPA is reviewed first and, when unavailable, supplemented by the scientific assessments of AIHA and other organizations. Unlike USEPA, AIHA provides recommendations for 1h exposures only, which may be insufficient for many real-world chemical emergencies. This disparity motivated the authors to explore a framework for extrapolation of AIHA information to other short-term exposure durations without sacrificing scientific rigor. In the present work, concentration-time extrapolation using chemical-specific toxic load exponents is examined using dimethyl sulfide (DMS) as a case study.

Purified DMS is a flammable (NFPA 704 class 4) colorless volatile liquid lighter than water and poorly water-soluble. It boils at about 37 °C releases irritating toxic vapors. Its vapors are heavier than the air, with a flash point of < −30 °C. It is manufactured primarily for the use in petrochemical and insecticide syntheses, but also as a gas odorant, dimethyl sulfoxide precursor, catalyst impregnator and solvent for anhydrous mineral salts (Pohanish 2012).

DMS is found as a byproduct at paper mills, oil refineries and at waste management facilities.

Being a part of the global sulfur cycle (Pham et al. 1996), DMS is ubiquitous with an olfactory limit of detection in the ppb range (Katz and Talbert 1930; Wilby 1969). It is discharged into the atmosphere by marine life and decomposition processes (Kappler and Schäfer 2014; Pham et al. 1996). In mammals, it is a catabolite, which may result in blood-borne halitosis (Harvey-Woodworth 2013). Trace concentrations of DMS are naturally present in many foods, including milk, beer, processed cabbage, asparagus, corn and seafood items. Its consumption is FDA approved as a flavoring adjuvant (21 CFR 172.515).

As concentration increases, the smell of DMS turns noxious, inciting a bad taste in the mouth, nausea and vomiting (Uzhdavini 1986; Vento 1966). Further increase in concentration may cause irritation of mucosa, eyes, and skin; prolonged topical application may cause necrosis (Uzhdavini 1986). At air volume (i.e. molar) concentrations of ~1% and higher, DMS is known to cause deadly central nervous system (CNS) effects, including diaphragmatic paralysis and coma, accompanied by asphyxia because of oxygen depletion at very high concentrations of DMS. Coroners from Japan and Russia (Terazawa et al. 1991; Vento 1966) report lung edema and visceral hyperemia in victims that have succumbed to paper-mill byproduct exposures rich in DMS (up to 80%).

Small amounts of absorbed DMS are quickly metabolized, while larger absorbed quantities of DMS are also exhaled (Sandmeyer 1981) and cause inhibition of enzymes, such as carbonic anhydrase and blood catalase, decrease oxygen consumption and lower the body temperature of laboratory animals (Koptyaev 1967; Schwimmer 1969). These facts suggest that overexposure to DMS may have additional adverse systemic effects beyond clinically observed CNS and respiratory depression.

In the field, DMS vapors are typically assessed using gas chromatography in combination with one of several detection methods. Of them, flame photometric detection is the mostly widely used method (Farwell and Barinaga 1986). Field instruments of this type are relatively simple and inexpensive. They are especially appropriate for the detection of DMS at high concentrations in the ambient air, because the signal output of the device is proportional to the square of sulfur concentration. DMS detection methods of higher sensitivity include mass-selective detection (Thornton et al. 1990), sulfur-specific electron capture detection (Johnson and Lovelock 1988), sulfur chemiluminescence detection (Ivey and Swan 1995) and atomic emission detection (Sullivan and Quimby 1990). The limit of detection of these methods in the most sensitive instrumentation is in the parts-per-trillion range, but such instruments, especially those based on mass spectrometry, are bulky, complex and service-dependent, and may be expensive.

DMS is produced and used in multi-ton quantities in chemical industry (USEPA, ECHA). Despite its wide use, current short-term exposure recommendations are limited to a 1 h exposure. In the present work, these exposure recommendations are extrapolated to additional durations needed for emergency response by means of a novel chemical-specific TLE calculated using a probit meta-analysis. This process represents a framework that could

be used to extend the risk assessment of other chemicals with multiple short-term inhalation incidence studies but lacking multi-duration guidance.

Materials and methods

Similar to hydrogen sulfide (HS) and methyl mercaptan (MM), DMS is a volatile sulfur compound. Therefore, its properties are similar but non-identical to those of HS and MM. Comparison of AIHA's Emergency Response Planning Guideline (ERPG) values for DMS with Acute Exposure Guideline Levels (AEGLs) for 1-hour exposures of HS and MM suggests that DMS causes specified health effects at concentrations higher than the latter ones. Neither ERPGs nor AEGLs provide guidance for DMS at other exposure durations. However, its mode of action (MOA), in many respects, resembles that of these structurally similar (Figure 1) and more amply studied congeners with a better understood MOA (Almeida et al. 2008).

Common health effects due to DMS exposures include offensive odor, mild irritation, nausea, coma and respiratory arrest. Therefore, short-term inhalation exposure levels for DMS were developed using information published by the AIHA Guideline Foundation's Emergency Response Planning Committee (AIHA 2016) with due consideration of the guidance from the National Academy of Sciences (NAS) and technical support documents for HS and MM published by the AEGL Committee (NRC 2001, 2010, 2013).

An AIHA ERPG document for DMS (AIHA 2016), along with citations therein, served as the basis for the DMS toxicological database (DMSDB). An independent literature search using PubMed and Scopus did not reveal any additional primary sources for animal inhalation studies. DMSDB contained relevant peer-reviewed journal studies and industrial reports. The ERPG document provides a succinct rationale for selecting (or not selecting) acute, one-hour, one-time inhalation concentrations at three health effects severity tiers: ERPG-1 (discomfort/mild transient health effects), ERPG-2 (disabling/injury), and ERPG-3 (life threatening). For each tier, the AIHA Emergency Response Planning Committee attempts to adopt a chemical-specific recommended exposure level as "the maximum airborne concentration below which nearly all individuals could be exposed for up to 1 h without experiencing or developing" health effects typical of this tier (AIHA 2014). This definition is reciprocal to the NAS interpretation of AEGL as "the airborne concentration (expressed as ppm (parts per million) or mg/m^3 (milligrams per cubic meter)) of a substance above which it is predicted that the general population, including susceptible individuals, could experience" health effects typical of the given tier (NRC 2001). Because both definitions describe essentially the same critical threshold exposure level, ERPGs are often used interchangeably with AEGLs in public health practice, especially when a chemical-specific AEGL is unavailable. Both ERPGs and AEGLs are not designed for repeated or prolonged exposures, because they are derived from short-term toxicological or epidemiological studies. Similar considerations apply to the present framework for short-term inhalation exposure levels, which are aimed at extrapolating the 1 h ERPGs to other exposure durations.

At short-term inhalation exposures, the NAS recommends using the toxic load equation for concentration-time extrapolation (NRC 2001), $C^n \times t = \mathrm{TL}$, where C is exposure concentration, t is exposure duration, TL is a constant toxic load that causes a specified health effect, and n is a chemical-specific toxic load exponent (TLE, n-value). The toxic load equation is a consequence of bivariate generalized linear model (GLM) fitted to laboratory binomial incidence data collected in experiments with probit design (Finney 1977, p. 50–81). Ideally, the TLE is estimated from the GLM fit, when appropriate laboratory data are available (ten Berge et al. 1986). For many chemicals, however, properly designed incident data are unavailable. For them, either a surrogate TLE derived by alternative methods, or a default TLE is used (NRC 2001). For DMS, no single study provided data that complied with a statistically significant GLM model. In the present work, a meta-analytical TLE for DMS was derived by pooling data from three published studies.

Laboratory data are measured within a certain precision, including binomial incidence data in experiments with probit design. When the laboratory data are modeled, the uncertainty propagates on parameter estimates. Because GLM is fitted directly to laboratory incidence data, it provides appropriate confidence intervals (CIs) on the TLE. To the contrary, regression-estimated TLEs are good only as point estimates with undefined uncertainty. The NAS guidance (NRC 2001) does not mention this important distinction in point versus interval estimation of a chemical-specific TLE. However, when “no empirical exposure concentration–exposure duration relationship data are available to derive a value of n”, it recommends using default TLEs, which de-facto represent an interval estimate: $\hat{n} = 1$ “represents the estimate of the lower boundary of the value of n” and $\hat{n} = 3$ “an estimate of the upper boundary of the value of n”. Consequently, when an interval estimate of a chemical-specific TLE is available, using the lower 95% confidence bound on TLE for extrapolation from shorter to longer durations and the upper 95% confidence bound for extrapolation from longer to shorter durations would constitute an approach coherent with the intent of NAS guidance (NRC 2001). Because the available DMS data allowed interval estimation of TLE, two n-values given by the lower and upper 95% confidence bounds, respectively, were used in the present work for concentration-time extrapolation.

Generalized linear models (GLM) were originally applied in short-term inhalation toxicology as probit and logit analyses, which were subsets of the methodology. In modern terms, they are known as GLM with probit and logit link functions, respectively. GLM encompasses these two cases, but the GLM framework is broader than that. In addition to the Gaussian inverse normal cumulative density function (normal icdf or probit) link function, NAS also considers Weibull icdf (NRC 2001). Weibull and probit analyses were carried out using the USEPA Benchmark Dose Software 2.6.0.1 (USEPA 2012, 2016a), SAS JMP® 13.2.1 (SAS Institute, Cary, NC), and MATLAB® R2016b (MathWorks, Natick, MA). In all univariate analyses of the present report, the probit model fitted data adequately, while the Weibull model failed to converge. Of the other models available in USEPA Benchmark Dose Software, the models either failed to converge, did not fit as well as the probit model according to the Akaike Information Criterion, or gave very similar estimates (logit model). Alternative statistical methods (such as substituting t with a parametric function of time) may be useful for other chemicals (Brown and Foureman, 2005), but DMS

lacks the experimental data needed to solve models of additional complexity. Data published as graphs were digitalized using DigitizeIt™ 2.0.5 (Bormann, Braunschweig, Germany).

NAS favors benchmark concentration (BMC) analysis over the traditional no-observed-adverse-effect-level (NOAEL)/lowest-observed-adverse-effect-level (LOAEL) approach (NRC 2001). For tier-3 effects, NAS recommends using the lower 95% confidence bound on a BMC that causes 5% incidence ($BMCL_{05}$) as a point of departure (POD) or, when unavailable, a benchmark concentration that causes 1% incidence (BMC_{01}). For tier-2 and −1 effects, NAS is less specific. However, effects of these levels of severity are also addressed by BMD guidance (USEPA 2012), which endorses $BMCL_{10}$ as POD. Accordingly, in the present study $BMCL_{05}$ and $BMCL_{10}$ were used as PODs for tier-3 and −2 effects, respectively.

Results and discussion

Derivation of a chemical-specific TLE for DMS

The DMSDB contained information sufficient for derivation of a chemical-specific TLE. Binomial outcome data on mortality (Schoenig 1967b; Tansy et al. 1981) and coma (Zieve et al. 1974) in rats exposed to airborne DMS were extracted from the DMSDB and pooled. Pooling was possible, because coefficients at dummy variables in a categorical regression GLM were found to be statistically insignificant (p-values=.507 and .800). These data, pooled from two distinctive health effects, nevertheless complied with a single-plane probit model (Figure 2). The model resulted in an estimate of chemical-specific n_{DMS}=3.26 (95% CI: 2.89–3.64). It is similar to the AEGL Committee n-value for HS, which is the structural analog of DMS. The HS n-value estimates are n_{HS}=4.4 for rat (NRC 2010), n_{HS}=2.93 (95% CI: 2.44–3.61) for mouse (Péry et al. 2010), and meta-analytical n_{HS}=2.2 (95% CI: 1.6–2.7) for combined species (ten Berge et al. 1986).

In the present study, the lower confidence bound on the DMS TLE, n_1=2.89, was used for extrapolation from shorter to longer durations and the upper confidence bound, n_2=3.64, for extrapolation from longer to shorter durations. An additional TLE for tier-2 (disabling) effects could not be calculated because of lack of incidence data for these effects at multiple durations.

Summary of DMS toxicity in humans

Acute mortality: Two men working in a paper production plant were exposed to DMS and immediately collapsed after entering a storage tank (Terazawa et al. 1991). One was already deceased when retrieved, and the other succumbed a day and a half later. An autopsy performed 27 h after the accident on the 25-year-old man, who was already deceased when retrieved, revealed DMS in lungs, blood, brain, liver, kidneys, spleen, heart muscle, muscle and adipose tissue. A sample of the atmosphere taken after the accident also detected DMS but in a less than 1 ppm concentration. After performing animal experiments and comparing data, the cause of the victim’s death was deemed a combination of DMS poisoning and asphyxia due to a lack of atmospheric oxygen displaced by DMS. The gas would have been present at about 50% or more in the atmosphere of the tank at the time of the accident.

Paper mill workers filled barrels with odorant-sulfone, a byproduct of turpentine refinement that contained DMS, dimethyl disulfide (DMDS), and MM (Vento 1966). Typically, the odorant-sulfone mixture contains DMS and DMDS in proportions of up to 80% and up to 0.5%, respectively, and the rest is MM. The employees worked without respirators. Forced ventilation in the shop was inoperative. After the lunch break, a worker entered the work area and blocked a valve controlling the odorant-sulfone flow. Suddenly he felt sick, attempted to escape, but collapsed near the door, where he was found unconscious. He was rushed to a hospital, where he was pronounced deceased. Post-mortem examination revealed lung edema and visceral hyperemia. Autopsied cavities and organs of the deceased, along with blood taken for laboratory examination, emanated a pungent, disagreeable odor. Volatile sulfur compounds were distilled from the blood by vapor. The distillate had a pungent odor of decomposed vegetables typical of DMS. The distillate responded to laboratory organosulfur reagents, including potassium chlorate, barium chlorate and mercuric chloride. Addition of these reagents resulted in precipitation of chloro(methylthio)mercury (CH_3SHgCl) and a $2(CH_3)_2S \cdot 3HgCl_2$ complex, indicative of MM and DMS, respectively (Vento 1966).

Nonlethal toxicity: Kangas et al. (1984) analyzed air samples collected at Finnish kraft and sulfite cellulose mills and reported DMS concentrations ranging 0–14 ppm. Over 15 cellulose mill workers had reported headache or trouble concentrating; however, in addition to DMS, the workers were simultaneously exposed to MM, HS, and DMDS. Therefore, the reported symptoms could not be clearly attributed to only one specific chemical of the mixture at any concentration.

Olfactory effects: A number of authors published an odor detection limit for DMS. Nishida et al. (1979) exposed groups of 8–11 individuals ranging from 18 to 40 years of age to five chemicals of offensive odor, including DMS, and three pleasant-smelling chemicals. Mixtures of DMS with MM and methylamine were also tested. The response was ordinal. The individuals rated odors on a scale of intensity from 0 to 8, where 0 indicated “no smell at all” and 8 an “extremely strong” smell. The response was modeled following the Weber-Fechner law. The authors report the odor intensity of pure DMS (I) as $I = 2.5 \times \log(C)+2.98$, where C is DMS concentration. An odor detection limit that follows from this equation is 6.4×10^{-2} ppm. The authors also estimated the odor detection limit based on PPT50 (an odor threshold perceptive to 50% of population). It was determined as the geometric mean of the odor appearing and odor vanishing points, 0.076 ppm (90% CI: 0.007–0.794) and 0.063 ppm (90% CI: 0.010–0.398), respectively. The resulting estimate is 6.3×10^{-2} ppm (90% CI: 0.010–0.437). No other health effects were noted.

Vento (1966) suggests that the odor detection limit for DMS is less than 3×10^{-2} ppm but gives no experimental details.

Wilby (1969) exposed 33 individuals on the roof of a 13-story building in Los Angeles to 18 sulfur compounds, including DMS, at 12 concentrations representing a 100-fold range. The individuals reported the presence of odor on a binary scale. For each individual, an odor recognition threshold was determined based on three trials. From the distribution of responses, the mean and median odor threshold concentration was estimated as 2.5×10^{-3}

ppm (with a standard deviation of 2.2×10^{-3} ppm, although the shape of the distribution does not appear normal) and as 2.1×10^{-3} ppm, respectively. One of the 33 individuals detected DMS at 2.5×10^{-4} ppm and three individuals at 9.8×10^{-3} ppm. All other responses were between these concentrations. No other effects were noted.

Leonardos et al. (1969) derived a recognition odor threshold for DMS of 1×10^{-3} ppm. A panel of four trained staff members was selected from a pool of 15 observers with more than a year of analytical odor work. Odor recognition took place in a test room of 13,200 L with "odor-free background". At least five concentrations designed in accordance with the Weber–Fechner law were tested.

Katz and Talbert (1930) conducted the most sensitive study. Six individuals were exposed to DMS at a range of concentrations via a nosepiece. The response was ordinal. Individuals rated the intensity of the odor on a 0–5 scale of intensity, where 0 corresponds to "no odor" and 5 to a "very strong" odor (Supplementary material S2). The authors modeled the response following the Weber–Fechner law. Because this uses the logarithm of concentration, "results usually agree in order of magnitude". The authors' estimate of the odor detection limit for DMS is 1.6×10^{-4} ppm. It is the most sensitive odor detection limit. For that reason, the report of Katz and Talbert (1930) was adopted as a key study for the derivation of tier-1 short-term inhalation exposure levels.

NAS recommends against establishing tier-1 levels based on "perception of a disagreeable odor, taste, or other sensations (mild sensory irritation)" (NRC 2001). Even "mild lacrimation or coughing" is not sufficient evidence. Although the noxious smell of DMS and its level of detection can serve as a warning sign of exposure, reliance on sensory perception alone would be in disagreement with the NAS description of tier-1 effects. However, in addition to olfactory perception, DMS also stimulates retching and the emetic reflex. Katz and Talbert (1930) classify the DMS odor as "somewhat sweet at low concentrations but foul", which may lead to the physiological effect of nausea. Similarly, both Vento (1966) and Uzhdavini (1986), report that DMS exposures cause nausea and vomiting, but the authors do not specify an exact concentration range. Therefore, the middle category of the Katz and Talbert (1930) scale that corresponds to "easily noticeable" odor intensity was identified as the highest no-observed-effect-level (NOEL) and used as the POD for derivation of tier-1 DMS exposure levels. Exceeding levels of exposure may result in a "strong" odor on the Katz and Talbert (1930) intensity scale and, therefore, present a risk of nausea.

In addition to olfactory effects, Katz and Talbert (1930) also studied nasal and eye irritation. For DMS, both effects were observed at concentration of 6200 ppm, which is higher than the studied olfactory range of purified DMS. At this exposure level, one-out-of-four-level nasal irritation was reported by two out of six observers, and ¼-level eye irritation by 4/6 observers. The duration of exposure was "the few seconds of testing" in olfactory and nasal irritation experiments and a "10 seconds exposure for eyes" irritation. The former exposure durations were kept at a minimum to avoid saturation of osmoceptors and subsequent olfactory fatigue.

Delayed health effects.—No developmental, reproductive, genotoxicity, or carcinogenicity studies were available regarding human exposure to DMS.

Summing up human studies: Data concerning human exposures to DMS are scant. Case reports of deaths from accidental exposure to DMS are available; however, definitive exposure durations and concentrations are not reported. Nonlethal toxicity data are limited to odor detection or odor identification studies that have no accompanying health effects information, except for mentioning that the strong odor of DMS is malodorous to the extent of nausea and vomiting. Data on developmental and reproductive toxicity, genotoxicity and carcinogenicity in humans were unavailable.

Summary of DMS toxicity in animals

Acute mortality: DMS showed toxicity upon oral, cutaneous and inhalation administration. Schoenig (1967a, 1967b) reports an acute oral median lethal dose (LD_{50}) of 1.0 ± 0.2 g/kg (recalculated from digitalized data using BMDS as 1.1 g/kg with a 95% CI of 0.6–1.7 g/kg; probit *p*-value .546) and an acute dermal LD_{50}>10.2 g/kg. In the inhalation study, four groups of five male and five female Sprague–Dawley rats were exposed to DMS at concentrations of 18,500, 42,100, 81,500 and 195,000 ppm, followed by a 14-day observation period (Schoenig 1967b). The study was devised with a 4 h design. However, all animals in the high concentration groups died in the course of exposure, and at the lowest concentration, the experiment was terminated at 3 h because of paucity of the DMS exposure material. Therefore, the effective times of exposure in this study varied. They were 180, 240, 70 and 18 min from the lowest to highest concentration group, respectively. Animals were exposed in a 70-L acrylic inhalation chamber designed to introduce animals to the test atmosphere after 99% of the nominal vapor concentrations were established. Mortality incidence from this study is provided in Supplementary material S3. The author reports a 4-hour median lethal concentration (LC_{50}) of 45,250 ppm estimated using a graphical method of Litchfield and Wilcoxon (1949). In the present work, the LC_{50} was recalculated to 43,310 ppm with a 95% CI of 36,717–52,153 ppm by fitting a univariate probit model (*p*-value . 9998) using BMDS. The probit slope was estimated to <di> on the natural semi-logarithmical scale, which characterizes the mortality-concentration relationship as “steep” (Ruijten et al. 2015). In addition to mortality, the author describes nonlethal effects observed in the course of exposure (see the next section).

For bivariate concentration-time modeling, the Schoenig (1967b) mortality data alone were not amenable to probit analysis. Convergence of the model was not achieved, perhaps, because of sparseness of the dataset in two dimensions.

White female rats of unspecified strain were exposed to DMS for 30 min at concentrations 1,100, 5,600, 13,000, 29,000, 31,000 and 54,000 ppm (Ljunggren and Norberg 1943). Mortality in 1/1 rats was observed after exposure to DMS at 54,000 ppm for 15 min. This study, including nonlethal effects observed at lower concentrations, is described in more details below.

Mice of unspecified strain were exposed to DMS concentrations of 68,000, 116,000, 236,000, 340,000 and 506,000 ppm (Terazawa et al. 1991). Because the exposure

concentrations were chosen intentionally high, to mimic exposure conditions attributed to human fatalities under investigation, the onset of adverse effects was extremely short, from 7.8 to 64.8 s. As a result, the experiment duration times ranged from 40 to 458 s (Supplementary material S4). Two adverse effects were monitored: astasis and respiratory arrest. Animals were exposed individually, five at each concentration, as indicated by the footnote to Supplementary material S4. Expositions took place in a 3-L desiccator. DMS concentrations were sampled using a micro-syringe inserted in an adhesive vinyl tape closing a small outlet on the fringe of the desiccator. Because at a given concentration animals were exposed for different durations, the toxic load received by each animal was different. Therefore, experiments by Terazawa et al. (1991) do not comply with probit design, but the collected data may be amenable to mixed modeling. However, at present, BMDS (USEPA 2012, 2016a) does not support this type of modeling.

In another inhalation study, rats were exposed to DMS for 3 and 9 min at 218,500 ppm (Dow 1957). At 3 min, rats experienced increased respiration, nasal irritation, and then coma. After removal from exposure, rats showed signs of nervous system depression but recovered. At 9 min, rats became comatose immediately with labored respiration; only 2/4 animals survived.

Groups of five male and female Sprague–Dawley rats were exposed to DMS for 4 h at concentrations ranging from 800 to 48,000 ppm, followed by a 14-day observation period (Tansy et al. 1981). Exposures took place in a 75-L glass chamber designed to permit continuous observation during the exposure and ensure uniform spatial distribution of gas mixtures. The authors report a 4-hour LC_{50} value of 40,250 ppm (re-estimated as 40,311 ppm with a 95% Wald CI of 38,028–42,237 ppm from a fitted univariate probit model with a goodness-of-fit p-value of .9996). All animals found alive 24 h post exposure survived until the end of the 14-day observation period. Because the experiment design of this study was similar to that of Schoenig (1967b), mortality incidence data from both studies were combined (Table 1). Categorical probit analysis of the combined data showed that probit slopes of these two datasets cannot be distinguished ($p = .9922$), and the categorical variable was insignificant ($p = .2152$). Consequently, these datasets were pooled. The concentration-response relationship is shown in Figure 3. Its steepness is indicated by the probit slope >2 (Ruijten et al. 2015). Across the DMSDB, the Tansy et al. (1981) study is perhaps both the best designed and reported. Therefore, this study (together with supplemental data of Schoenig (1967b)) served as a key study for the derivation of tier-3 short-term inhalation exposure levels and as a supporting alternative for tier-2 levels. In addition, the AEGL Committee has preferred the study of Tansy et al. (1981) as the key study for derivation of AEGLs-3 for MM.

When possible, NAS recommends using $BMCL_{05}$ as POD for tier-3 effects, and when $BMCL_{05}$ is unavailable, BMC_{01} can be used (NRC 2001). Probit analysis of pooled Tansy et al. (1981) and Schoenig (1967b) data resulted in $BMCL_{05}$=26,109 ppm (Supplementary material S5), which was more conservative than BMC_{01}=28,977 ppm. Both estimates were in the range between the highest NOAEL of 24,000 ppm and LOAEL of 36,000 ppm. Because the $BMCL_{05}$ is both recommended by NAS and more health-protective than BMC_{01}, it was chosen as POD for derivation of tier-3 short-term inhalation exposure levels.

Selyuzhitskii (1972) reports a LC_{50} value of 12.44 (10.0–39.0) ppm for mice of unspecified strain and sex exposed to airborne DMS for 2 h. A 4-hour LC_{50} of 19.72 (15.2–25.6) ppm is also reported for an unspecified strain and sex of rat. No experimental details are provided, except that statistical estimation followed the method of Litchfield and Wilcoxon (1949). These numbers, along with those cited by Uzhdavini (1986), are in conspicuous disagreement with aforementioned studies. Because experimental details in these publications are absent, and because of similar unexplained discrepancies noted for other chemicals mentioned in these reports, the Selyuzhitskii (1972) estimates were treated as outliers.

Nonlethal toxicity: White female rats of unspecified strain were exposed to DMS for 30 min at concentrations 1,100, 5,600, 13,000, 29,000, 31,000 and 54,000 ppm, followed by a 24 h observation period (Ljunggren and Norberg 1943). In each experiment, only one rat was exposed in a 7.6-L gas chamber. The concentration of DMS was determined in samples taken with a special gas pipette. No effects were observed at 1,100 ppm. Mortality in 1/1 rats was observed after the first 15 min of exposure to 54,000 ppm DMS. Data from this study are summarized in Supplementary material S6.

Four groups of five male and five female Sprague–Dawley rats were exposed to DMS for 18, 70, 180 and 240 min at concentrations 195,000, 81,500, 18,500 and 42,100 ppm, respectively, followed by a 14-day observation period (Schoenig 1967b). Nonlethal adverse effects were observed and recorded in addition to mortality described above. However, unlike mortality that is reported quantitatively, the nonlethal effects are described qualitatively, with a time range of the effect onset and its duration without quantifying the effect by animal. The onset of adverse effects after the start of exposure to DMS occurred at 30 min for 18,500 ppm, 10 min for 42,100 ppm, 8 min for 81,500 ppm and 1 min for 195,000 ppm. The sequence of observed adverse effects was rather consistent. Either tremors or hyperpnea began first, followed by unconsciousness and then by variable effects that included salivation, frothy nasal discharge, cyanosis, and dyspnea (Supplementary material S7). Prior to that animals experienced a period of “generalized inactivity”, which was interpreted as a discomforting but non-adverse effect. For the second and third concentration groups, a period of hyperactivity preceded generalized inactivity.

Male Holtzman or Sprague–Dawley rats were exposed to DMS for up to 15 min at various concentrations (Zieve et al. 1974). Each animal was individually exposed in a 4-L glass desiccator with the opening in the lid covered by a rubber septum through which DMS was injected into the chamber. Comatose animals were removed from the chamber. Coma was defined as complete loss of the righting reflex. All comatose animals recovered consciousness within 30 min post exposure. Based on these experiments, the authors report an approximate CD_{50} (coma induction in 50% of animals) of 96,000 ppm for DMS, and blood concentrations of DMS in comatose animals >7 μmol/mL. Measured blood concentrations varied in the range 2–12 μmol/mL. The variation was caused, perhaps, either by differences among individuals in the blood/gas partition coefficient, ventilation rate, or blood/tissue partitioning of DMS. At a given exposure concentration of DMS the spread of blood concentrations was 3–8 μmol/mL or 1.5–4.25 fold. A ratio of the comatose threshold of 7 μmol/mL to the minimal measured blood concentration varied in the range 1–3.5 fold. It

suggests that variations across the population in DMS toxicokinetics can be reasonably expressed by the geometrical half of the default uncertainty factor (UF) of 10.

DMS exposure concentrations and associated binary outcomes were determined from Figure 4 published by Zieve et al. (1974). The extracted data are shown in Table 2. Based on these data, CD_{50}=95,089 ppm with a 95% Wald CI of 87,467–102,490 was calculated from a fitted probit model (Pearson's *p*-value .818).

The study of Zieve et al. (1974) does not report NOAEL, which reduces confidence in imputations from the fitted model at low concentrations. Therefore, coma incidence data from the Zieve et al. (1974) study was supplemented by those from the Ljunggren and Norberg (1943) and Schoenig (1967b) reports (Table 2). The Zieve et al. (1974) data alone and pooled with the Schoenig (1967b) data complied with a probit model, goodness-of-fit *p*-values were .8176 and .9724, respectively. However, pooling either of these with the Ljunggren and Norberg (1943) data was not as successful, because of single-animal design of the Ljunggren and Norberg (1943) study (*p*-values .0557 and .0344, respectively). A concentration group at 54,000 ppm was especially problematic, because 1/1 design designates 100% incidence typical of the highest tested concentrations of DMS (Table 2). To alleviate the problem, a remedy described by Parham and Portier (2006) was applied: the concentration group at 54,000 ppm and the nearest concentration group at 42,100 ppm were combined together into a single-concentration group with a geometric mean of 47,680 ppm and 1/11 coma incidence. After this, goodness-of-fit of the fitted probit model became acceptable, as characterized by p=.9549. A concentration-incidence relationship of the model (Figure 4) was identified as steep, because the probit slope was >2 (Ruijten et al. 2015).

Ljunggren and Norberg (1943) and Schoenig (1967b) experiments were not designed to comprehensively study non-lethal effects of DMS. Therefore, the Zieve et al. (1974) study supplemented with data from Ljunggren and Norberg (1943) and Schoenig (1967b) was adopted as a key study for tier-2 calculations. Using the pooled coma incidence data, a $BMCL_{10}$ (USEPA 2012) of 47,408.8 ppm for incapacitation was obtained (Supplementary material S8). It was used as POD for derivation of tier-2 short-term inhalation exposure levels.

In skin and eye irritation experiments with albino rabbits, Schoenig (1967b) found DMS to be moderately irritating to eyes and minimally irritating to skin.

Delayed health effects: No developmental and reproductive studies or carcinogenicity studies regarding animal exposure to DMS were available in AIHA's DMSDB.

Summing up animal studies: Animal toxicity data for DMS are rather limited. Mortality studies are available for rats and mice, and suggest a steep concentration-response relationship for dimethyl sulfide, $b_2 \times n > 2$ (Ruijten et al. 2015), where b_2 and n are parameters of the multivariate probit equation, $Pr = b_0 + b_2 \times \ln(C^n \times t)$, that fits the experimental incidence data (ten Berge et al. 1986). In studies of rats, a 3-hour exposure to 18,500 ppm and 4-hour exposure to 24,000 ppm caused no mortality (0/10), but a 70-min exposure to

81,500 ppm caused 100% mortality. Similarly, a 15-min exposure to 54,000 ppm caused 100% rat mortality (Ljunggren and Norberg 1943). However, the latter was a single-animal study. A 9-min exposure to 218,500 ppm and 4-hour exposures to 39,000 and 42,000 ppm caused 50% mortality in rats (Dow 1957; Tansy et al. 1981). The 4-hour LC_{50} was estimated at 40,920 ppm (recalculated from pooled data of Tansy et al. (1981) and Schoenig (1967b) using BMDS). A hundred percent mortality in mice was observed during DMS exposures ranging from approximately 40–450 s at concentrations of 68,000–506,000 ppm (Terazawa et al. 1991). Comparison of mouse and rat data suggests variation in sensitivity to DMS across species is limited. Nonlethal adverse effects due to DMS exposures include salivation, nasal discharge, astasis, tremors, hyperpnea, dyspnea, cyanosis, and unconsciousness. For 15 min DMS exposures, a median coma-inducing concentration, CD_{50}=95,089 ppm, was determined in rats (recalculated using BMDS from data of Zieve et al. (1974)). Information on DMS genotoxicity is limited, with no indication of genotoxic effects. No reproductive and developmental toxicity data or carcinogenicity studies on DMS were located.

Summary of DMS toxicity in cellular and in vitro *assays*

DMS is not mutagenic in the Ames *Salmonella typhimurium* test using strains TA100, TA1535, TA98, TA1538, TA2637, TA1537, TA102, TA104 and TA97 regardless of activation using rat liver microsomal S9 fraction (Hakura et al. 1993). Solutions of up to 0.6% DMS did not indicate genotoxicity in the Umu-Chromotest – failed to induce *umu* gene expression in *Salmonella typhimurium* TA1535/pSK1002 (Nakamura et al. 1990). In bacteria, *umu* genes are involved in SOS reparation of DNA, similar to ubiquitous homologs of the recA archetype.

Derivation of short-term inhalation exposure levels

Reports of Katz and Talbert (1930), Zieve et al. (1974), and Tansy et al. (1981) served as key studies for derivation of DMS tier-1, −2, and −3 short-term inhalation exposure levels for the reasons explained in previous sections. Information concerning the derivation process is summarized in Table 3 and Supplementary material S9.

POD selection: Tier-1 levels were based on an exposure to 1.9 ppm DMS that causes a sensation of an “easily noticed odor” after one inhalation (Katz and Talbert 1930). This endpoint was deemed as the highest available NOAEL for tier-1. Exposures at the next higher level of 44 ppm are perceived as “strong odor” and, thus, they were associated with a risk of nausea (Uzhdavini 1986; Vento 1966) and categorized as a tier-1 LOAEL. At lower exposure levels of 0.084 ppm and 0.0037 ppm, participants detected only a “faint” or “very faint” odor. These levels were interpreted as lower NOAELs. They are similar to odor detection limits identified in other studies, which are 0.063 ppm (Nishida et al. 1979), <0.03 ppm (Vento 1966), and 0.0021 ppm (Wilby 1969).

Tier-2 levels were based on the study of Zieve et al. (1974), in which rats were exposed to a range of DMS concentrations for up to 15 min. The incidence of coma was surveyed. Because the Zieve et al. (1974) study did not cover the low-concentration region of concentration-response curve, it was supplemented by coma data interpreted from Ljunggren and Norberg (1943) and Schoenig (1967b) reports. The datasets were pooled as described

above. Probit analysis of the pooled incidence data resulted in a $BMCL_{10}$ estimate of 47,409 ppm (Figure 4, Supplementary material S8), which served as POD for derivation of tier-2 levels. It is higher than the highest available NOAEL of 31,000 ppm and lower than lowest available LOAEL of 54,000 ppm (Ljunggren and Norberg 1943). It is also marginally lower than a surrogate LOAEL of 47,680 ppm described in a previous section.

Tier-3 levels for DMS were based on a 4 h study in rats of Tansy et al. (1981), which is the most comprehensive mortality study. A $BMCL_{05}$ of 25,895 ppm followed from a probit model fitted to the study incidence data (Table 1, Figure 3). It served as POD for derivation of tier-3 levels. On the concentration-response curve, the POD was positioned intermediary between the exposure level of 24,000 ppm, after which all rats have survived, and 36,000 ppm, which caused mortality in two out of 10 animals; a 4-hour LC_{50} in rats is greater than 40,000 ppm (Schoenig 1967b; Tansy et al. 1981). The obtained $BMCL_{05}$ is in a good agreement with the Schoenig (1967b) study. The author observed no mortality at the exposure level of 18,500 ppm for 3 h, while four out of 10 rats died per a 4 h exposure at 42,100 ppm. Another shorter duration study reported no rat mortality at 31,000 ppm after a 30 min exposure, while an exposure to 54,000 ppm caused death of a rat on the 16th min of exposure (Ljunggren and Norberg 1943). This information is not directly comparable to the selected POD but requires concentration-time extrapolation (see below). Extrapolation of the POD to 30 min suggested a concentration of 45,848 ppm, which is between the observed mortality and no-mortality levels.

Concentration scaling: Because in all severity tiers the selected PODs represent expected levels of “no effect,” LOAEL to NOEL extrapolation was unnecessary. Animal-to-human extrapolation was carried using a default UF of 10 (NRC 2001) for tier-2 levels and a UF of 3 for tier-3 levels. Similar to HS and MM, different treatment of the tiers was warranted because of distinctions in MOA. For tier-2, the toxicity endpoint is coma. It is a CNS effect, which clearly involves both the toxicokinetic and toxicodynamic components. In the tier-3 effects, however, presence of the toxicokinetic component is likely less significant, because postmortem examinations describe lung edema, i.e. a life-threatening effect at the point of entry, to which toxicokinetics is less relevant (Schoenig 1967b; Terazawa et al. 1991; Vento 1966). Likewise, the AEGL Committee uses UF = 3 for animal-to-human extrapolation of AEGLs-3 for both HS and MM (Supplementary material S10 and S11). These volatile compounds are similar to DMS in chemical structure (Figure 1) and cause similar health effects – these thiols are irritants, asphyxiants and CNS poisons with a comatose MOA (NRC 2010, 2013). Noteworthy, the AEGL Committee uses UF = 3 for animal-to-human extrapolation of AEGLs-2 for HS, because unlike DMS, the Committee’s assessment is based on a point-of-entry adverse effect that is independent of toxicokinetics – perivascular edema, significant increase in protein content and lactate dehydrogenase activity in the lung lavage fluid (NRC 2010).

Individual variability in the population was accounted for by the same UF = 3 in all three tiers. For tier-2 and −3, the full UF of 10 did not apply, because of the steepness of the concentration-response curve, as indicated by the estimate of probit slope >2 (Ruijten et al. 2015). A steep probit slope implies a narrow window of response in the animals tested; therefore, there is less variability between individuals of the same species. For tier-2, data of

Zieve et al. (1974) also provide direct support for the chosen UF (see above). The AEGL Committee also uses an intraspecies UF of 3 (Supplementary material S10 and S11) for HS and MM (NRC 2010, 2013), whose structural (Figure 1) and MOA similarity with DMS additionally supports the present assessment. Olfactory receptors differ among individuals by about 1/3 (Mainland et al. 2014). Accordingly, diversity in the population was accounted for by using UF = 3 in the derivation of tier-1 exposure levels.

Concentration-time extrapolation: No time scaling was required for derivation of tier-1 DMS levels, because when the odor is strong and offensive, contribution of olfactory fatigue to organoleptic perception is expected to be insignificant during short-term inhalation exposures. Tier-2 and −3 levels were extrapolated from POD using the toxic load equation (refer to Materials and methods). Temporal scaling was performed using the lower and upper 95% confidence bounds on the derived DMS TLE: n_1=2.89 extrapolation from shorter to longer durations and $n_{2=}$3.64 for extrapolation from longer to shorter durations (Supplementary material S1, Figure 2). There was one exception, though. In tier-3, temporal extrapolation to the shortest exposure duration of 10 min resulted in a level inconsistent with select data from the Ljunggren and Norberg (1943) and Terazawa et al. (1991) reports. Ljunggren and Norberg (1943) identified rat mortality at the level of 54,000 ppm during a 15 min exposure. However, extrapolation from the tier-3 POD suggests a higher threshold exposure level of 55, 465 ppm. Similarly, Terazawa et al. (1991) observed mouse mortality on the 3.42 min of exposure to 68,000 ppm, whereas the extrapolated level is 83,255 ppm. In view of these inconsistencies near the 10 min mark and following NAS recommendations, thresholds for exposures shorter than 30 min, including at 10 min, were “assigned the same value as that extrapolated for the 30-min” (NRC 2001). An additional TLE for tier-2 effects would be desirable, but was not able to be calculated with currently available incidence data for DMS. Because the majority of health effects from studies independent to this derivation are compatible (*vide infra*), a single TLE for tier-2 and −3 levels may be justified.

Alternative calculations: When the concentration-response relationship for mortality is steep, as in the case of DMS, tier-3 levels may serve as PODs for derivation of tier-2 levels (NRC 2001). In this case, NAS recommends scaling tier-3 levels down to tier-2 by a factor of 3. The derived short-term inhalation exposure levels are compared to the alternative (Supplementary material S12) in Table 4. The table shows that both derivation methods are in reasonable agreement, but the alternative method is slightly less health-protective. However, similarity of the values is also remarkable, because the directly derived tier-2 levels and the alternative values were extrapolated in different directions: from 15 min and 4 h experiments, respectively. This suggests self-consistency of studies in DMSDB, published information, and derivation procedures adopted in the present work, especially taking into account that the alternative method provides a link between tier-2 and −3 data.

Validation of short-term inhalation exposure levels

The derived short-term inhalation exposure levels were vetted against the gamut of information comprised in DMSDB. The analysis was carried out using the levels of tested exposure (LTE) plots, on which all categories of laboratory-tested health effects were mapped. This analysis was aimed to examine the consistency of PODs, methodology, and

the derived values in relation to the full range of relevant health effects described in the literature.

Categorization of health effects related to DMS exposures: For the LTE plots, results of laboratory tests were categorized into “effect” and “no effect” groups for the three NAS severity tiers (reversible/discomfort, irreversible/disabling, mortality). In addition, each of the groups was split into high- and low-confidence subgroups. The low-confidence subgroup contained information discounted because of either insufficient statistical power of the study, inferior laboratory quality of work, or study design and other contradictions and doubts in published results of the study. The lower level of confidence was denoted by smaller size of the symbols in the LTE plots.

Study exclusions: A study by Selyuzhitskii (1972) reported a 2 h LC_{50} for mice of 12.5 ppm and a 4 h LC_{50} for rats of 19.8 ppm. The author provided little experimental details, and the reported findings are grossly inconsistent with other reports on volatile thiols, including DMS (AIHA 2016). As such, information from the Selyuzhitskii (1972) study was not included in the LTE plots.

LTE plots: DMSDB information about animal mortality caused by exposures to DMS is summarized in Figure 5. It demonstrates that animal PODs are positioned intermediary in a short range between the “effect” and “no effect” levels across the examined time range and concentrations. However, the short-term inhalation exposure levels derived from these animal PODs are well separated from the effect-level region in the LTE plot, which is consistent with the common view of humans as a more sensitive species. An AIHA ERPG-3 is located close to the short-term inhalation exposure level of the same duration, but ERPG-3 is marginally less protective. Also, a “blind” extrapolation using the default methodology (NRC 2001) from ERPG-3 to 10 min may result in an insufficiently health-protective threshold exposure level, because its back-extrapolated POD would be above a mortality concentration level at 15 min (Ljunggren and Norberg 1943).

Information collected for DMS tier-2 effects is more abundant but less quantifiable than for tier-3 effects (Figure 6). As expected, descriptive but not well-quantified animal data are more congested when graphed. In addition, the spectrum of tier-2 effects and their interpretation is wider than a clear-cut effect of mortality. As a result, a single line does not appear to divide the tier-2 data between “effect” and “no effect” levels (Figure 6). However, the line of animal PODs that bisects this area appears as a reasonable compromise between “effect” and “no effect” levels and follows the direction of scatter of the mapped laboratory data. Thus, independent data that have not been used in TLE derivation support the derived TLE when mapped on the LTE plots (this data could not be used in TLE derivation because of the studies’ design). It also suggests that the choice of initial “seed” POD was likely correct in a sense that all available health-effects data are approximately equipartitioned by the trace of PODs. Similarly to tier-3, the proposed tier-2 short-term inhalation exposure levels are well detached from the region of animal effect. ERPG-2 and the 60-min short-term inhalation exposure level for tier-2 health effects are identical.

Validation sources for tier-1 effects due to DMS exposures are scant. Figure 7 shows that at very short exposure durations eye irritation occurs at much higher concentrations than the derived short-term inhalation exposure level. Whether concentration-time extrapolation by means of the toxic load equation applies to irritation effects caused by DMS is unknown, but with rare exceptions, time-dependent progressive development of the irritation response is rare (Neilson 1991). Therefore, the proposed critical tier-1 health effect, which is a risk of nausea due to the noxious odor of DMS appears to be well-protective of eye irritation and possible visual impairment that may obstruct evacuation and other protective actions. Occupational and residential health guidance values available for DMS (Supplementary material S15) share much similarity with the developed tier-1 short-term inhalation exposure levels (Figure 7) and ERPG-1 being almost the same.

Conclusions

DMS is a hazardous volatile substance that may represent a public threat upon uncontrolled releases. The AIHA provides recommendations only for one-hour exposures, but in emergencies, other durations of exposure are also possible. By 42 U.S.C. § 9604 (i)(1)(D) the ATSDR is required to provide appropriate assistance in cases of hazardous substances emergencies (regardless of duration of exposure). To this end, short-term inhalation exposure levels developed for 10 min, 30 min, 1 h, 4 h and 8 h exposure durations for the three health-effects severity tiers (Table 3) represent an extension of AIHA efforts.

In the present work, computationally derived short-term inhalation exposure levels were developed using the toxic load equation and a chemical-specific TLE. A novel TLE for DMS was derived in the present study using generalized-linear-model fitting to binomial incidence data. Consistency of the TLE was vetted in the LTE plots using the whole body of information on health effects due to DMS exposures (Figures 5 and 6). In addition, it agrees favorably with known *n*-values of other volatile thiols. The derived TLE was consistent with information on both the tier-3 and tier-2 effects. Therefore, for DMS the same TLE appears to be appropriate for concentration-time extrapolation regardless of severity of a health effect.

Information on health effects caused by DMS inhalation exposures was borrowed from the AIHA sources (AIHA 2016). To this information, methods recommended by NAS (NRC 2001) were applied. When possible, these methods were extended past routine practices of the AEGL Committee to reflect the current level of computational toxicology method development. The derived knowledge was transformed into novel reference exposure levels, which were validated graphically using LTE plots. They demonstrate that the short-term inhalation exposure levels are in good agreement with the range of known health effects caused by DMS exposures in laboratory animals and in humans (Figures 5–7). The approach detailed here could be generalized to other chemicals with single duration guidance and thus fill a data gap in short-term inhalation toxicology.

DMS is the simplest thioether. Its mode of action is similar to that of HS, thioalcohols, and other mono- and polythioethers (Almeida et al. 2008; Uzhdavini 1986); however, by short-term inhalation, DMS appears to be less toxic than better studied volatile thiols

(Supplementary material S10 and S11). The calculated short-term inhalation exposure levels appear to be in good agreement with available DMS health guidance values (Figures 5–7). Therefore, emergency responders and health assessors may consider these calculated reference levels as an adjunct to other chemical risk assessment methods and practices. Compounded uncertainty of default extrapolation (Table 3) has the potential to unduly bias the response and resource allocation in emergencies. For example, preparations for a life-threatening emergency based on a default extrapolation of ERPG-3 would underestimate the risk of a 10-min exposure almost 2-fold (9,100 ppm versus 4,600 ppm). On the other hand, for an 8-h exposure, default extrapolation would grossly overestimate the risk at 625 ppm versus 2,000 ppm. Similarly, for an emergency leading to incapacitation after a 30 min exposure, default extrapolation from ERPG-2 would slightly underestimate the risk (1300 ppm versus 1200 ppm), but it would grossly overestimate the disabling risk at 8 h (a default extrapolation level of 125 ppm versus 500 ppm). Thus, based on the available scientific literature and computational concentration-time extrapolation, the proposed short-term inhalation exposure levels appear to adequately complement the known health guidance for DMS. When the established health guidance values do not exist for exposure durations shorter or longer than 1 h, use of these evidence-based computationally derived values may allow for more informed decisions for the best possible public health outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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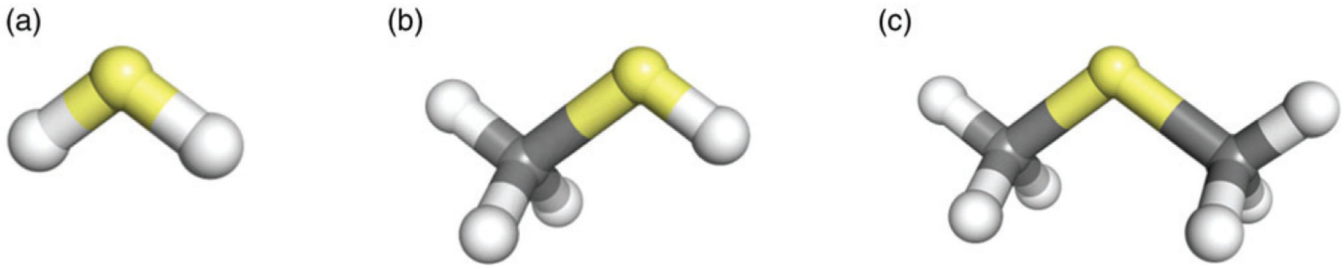

Figure 1.
Ball-&-stick representation of (a) hydrogen sulfide (HS), (b) methyl mercaptan (MM), and (c) dimethyl sulfide (DMS).

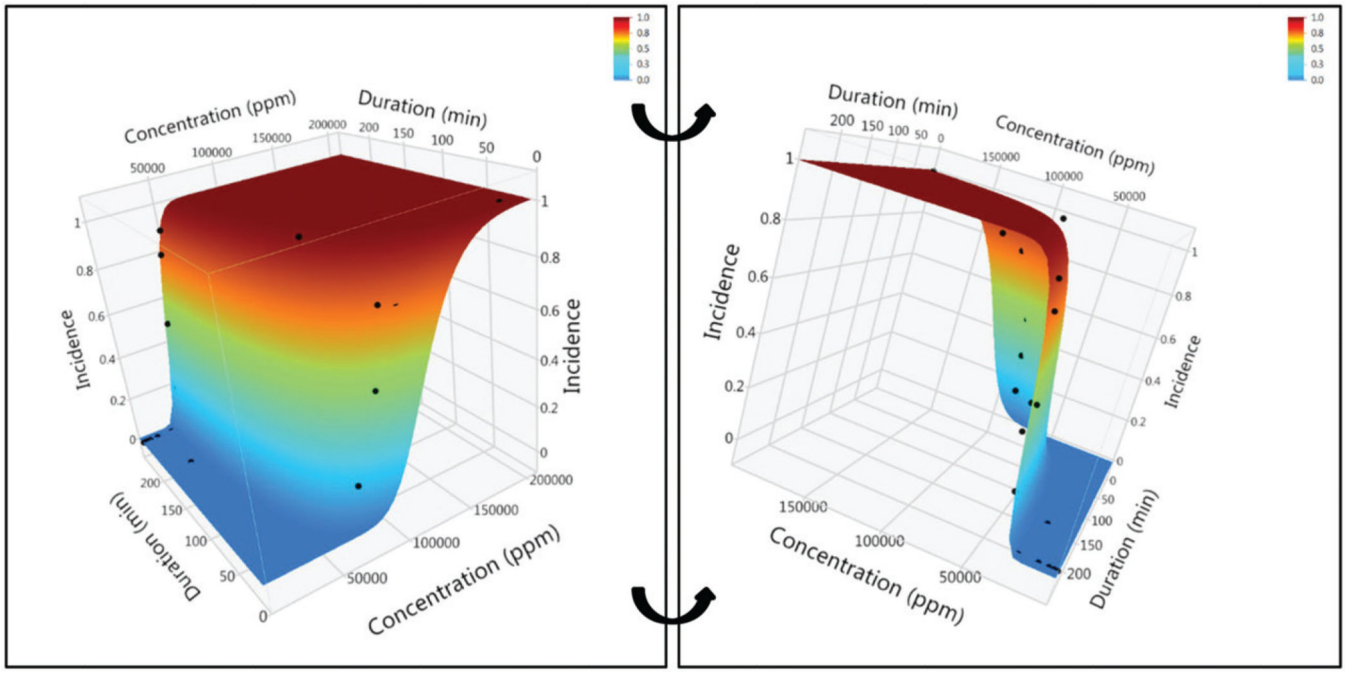

Figure 2.

Generalized linear model with probit link function fitted to pooled DMS binomial incidence data of Schoenig (1967b), Tansy et al. (1981) and Zieve et al. (1974). The pooled data was fitted using a single-plane probit model (Supplementary material S1). The right panel is a 90-degree rotation of the three-dimensional graph.

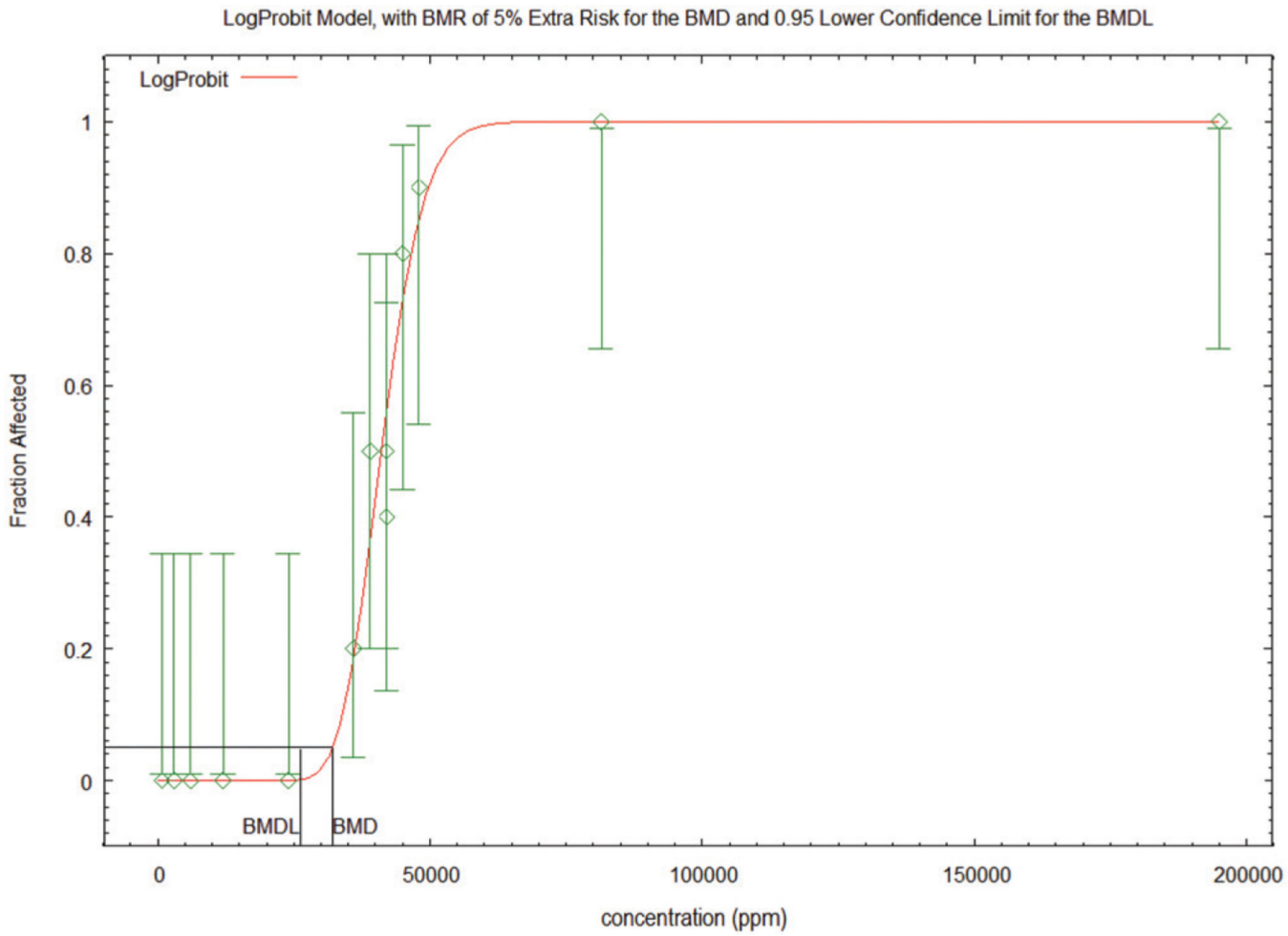

Figure 3.

A probit model fitted to pooled 4h mortality incidence data shown in Table 1. An estimate of the probit slope on the natural semi-logarithmical scale was $\hat{\beta} = 1$, 95% Wald CI 2.82–10.66, which identifies the curve as steep (Ruijten et al.2015). The error bars indicate 95% confidence intervals for the fraction affected.

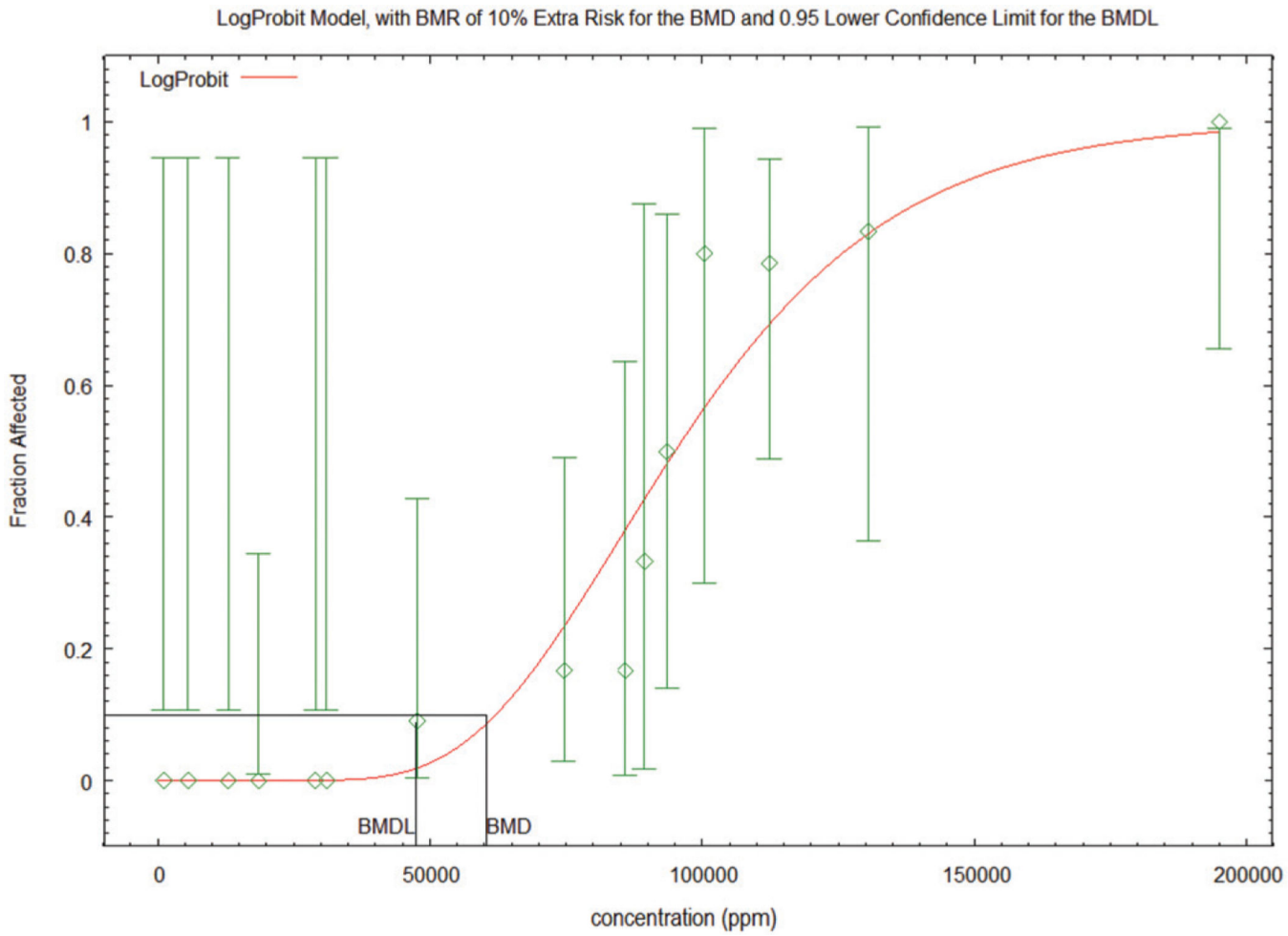

Figure 4.

A probit model fitted to pooled 15 min coma incidence data of Ljunggren and Norberg (1943), Schoenig (1967b) and Zieve et al. (1974). An estimate of the probit slope on the natural semi-logarithmic scale was $\hat{\beta} = 1$, 95% Wald CI 1.70–4.32. The error bars indicate 95% confidence intervals for the fraction affected.

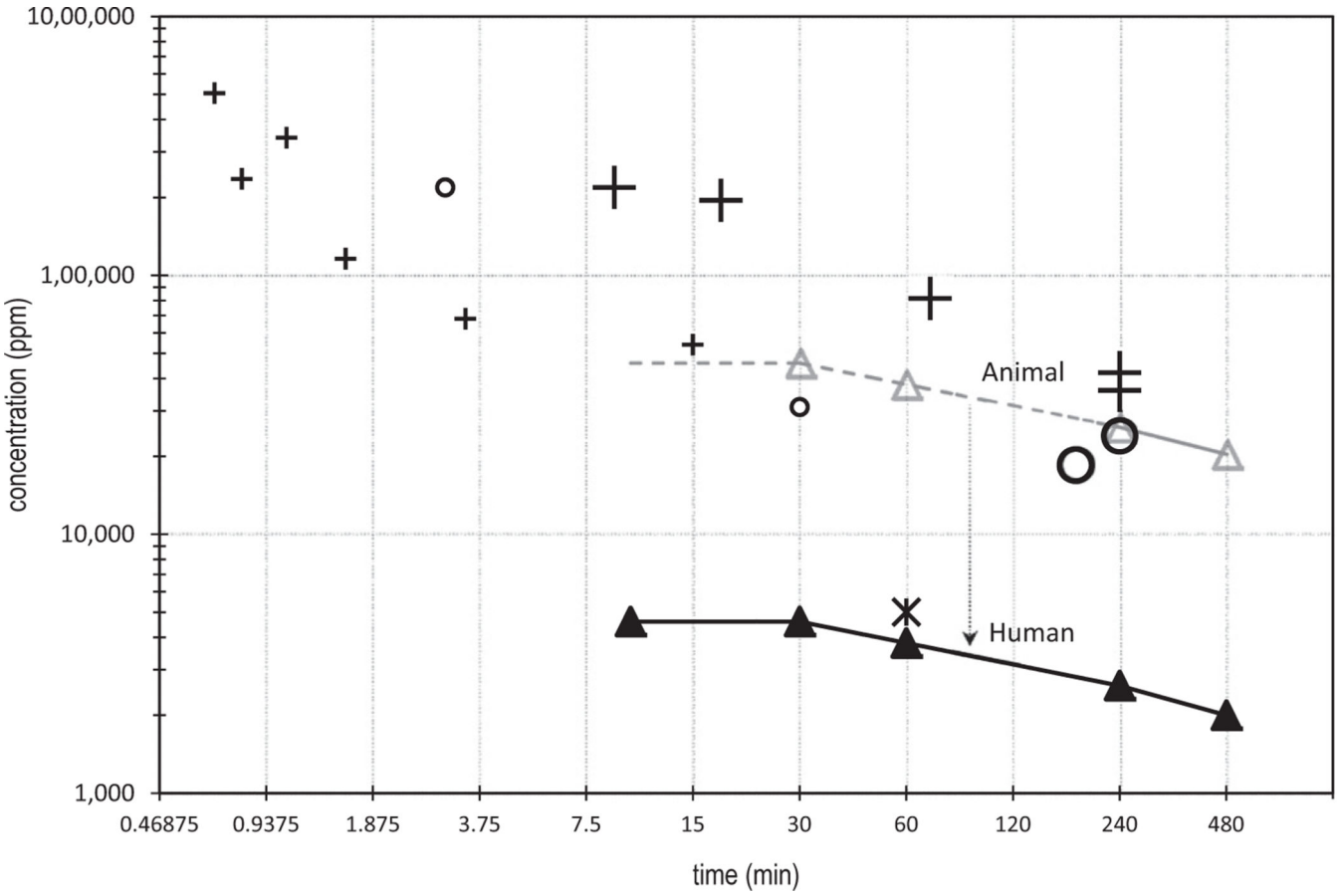

Figure 5.

Levels of tested exposure for tier-3 effects caused by DMS exposures (Supplementary material S13). Animal "effect" (+) and "no effect" (○) groups are shown, in which the "effect" is mortality. Petit symbols denote low-confidence subgroups. Animal PODs are shown in gray with empty triangles (Δ) and a dashed line. Human short-term inhalation exposure levels are shown with filled triangles and a solid line. The ERPG-3 is mapped with an asterisk (*).

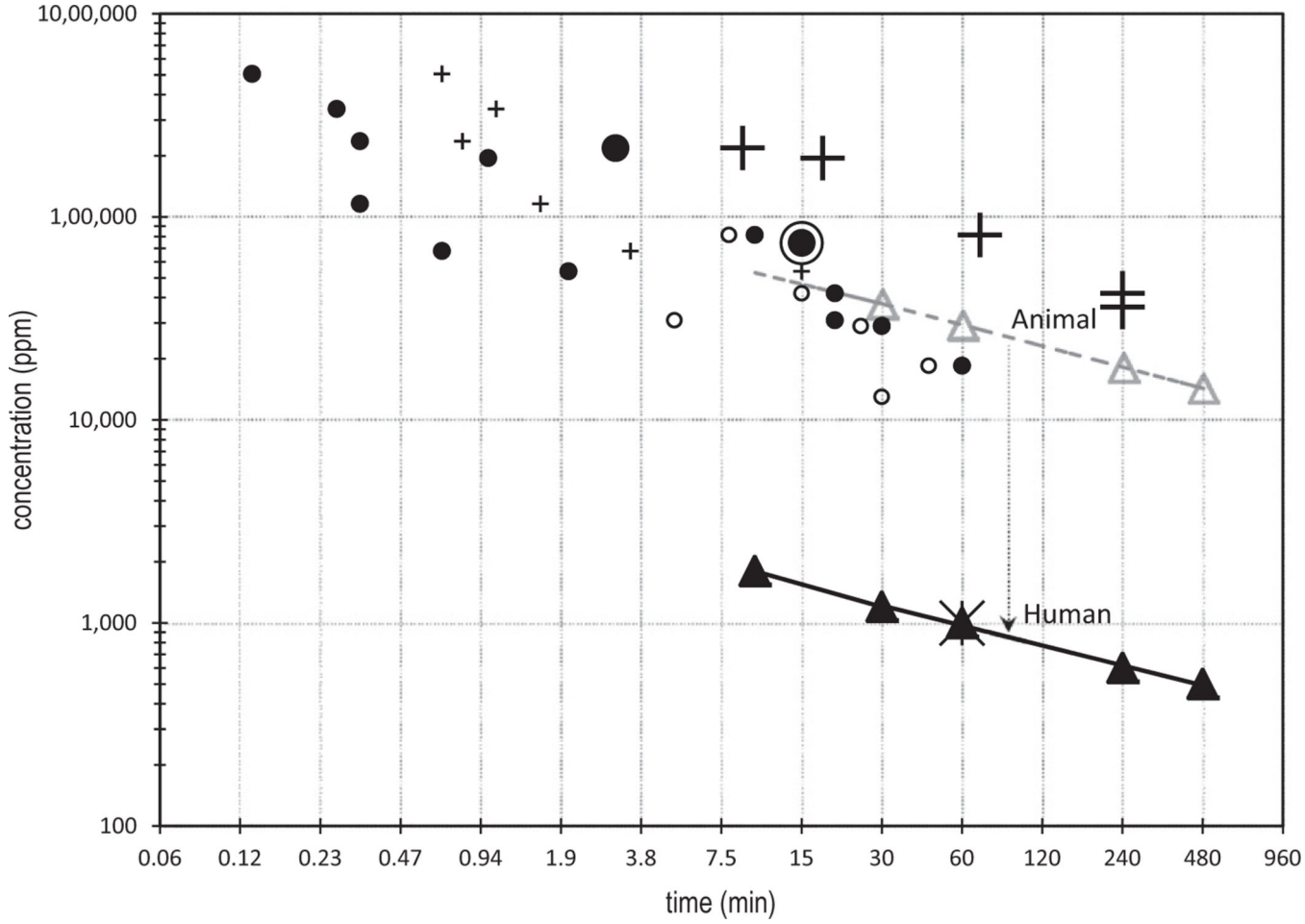

Figure 6.

Levels of tested exposure for tier-2 effects caused by DMS exposures (Supplementary material S14). The shown effect categories are: mortality (+), unconsciousness or a similar effect (●), and lack of unconsciousness (o). Petit symbols denote low-confidence subgroups. Animal PODs are shown in gray with empty triangles (Δ) and a dashed line. Human short-term inhalation exposure levels are shown with filled triangles and a solid line. The ERPG-2 is mapped with an asterisk (*).

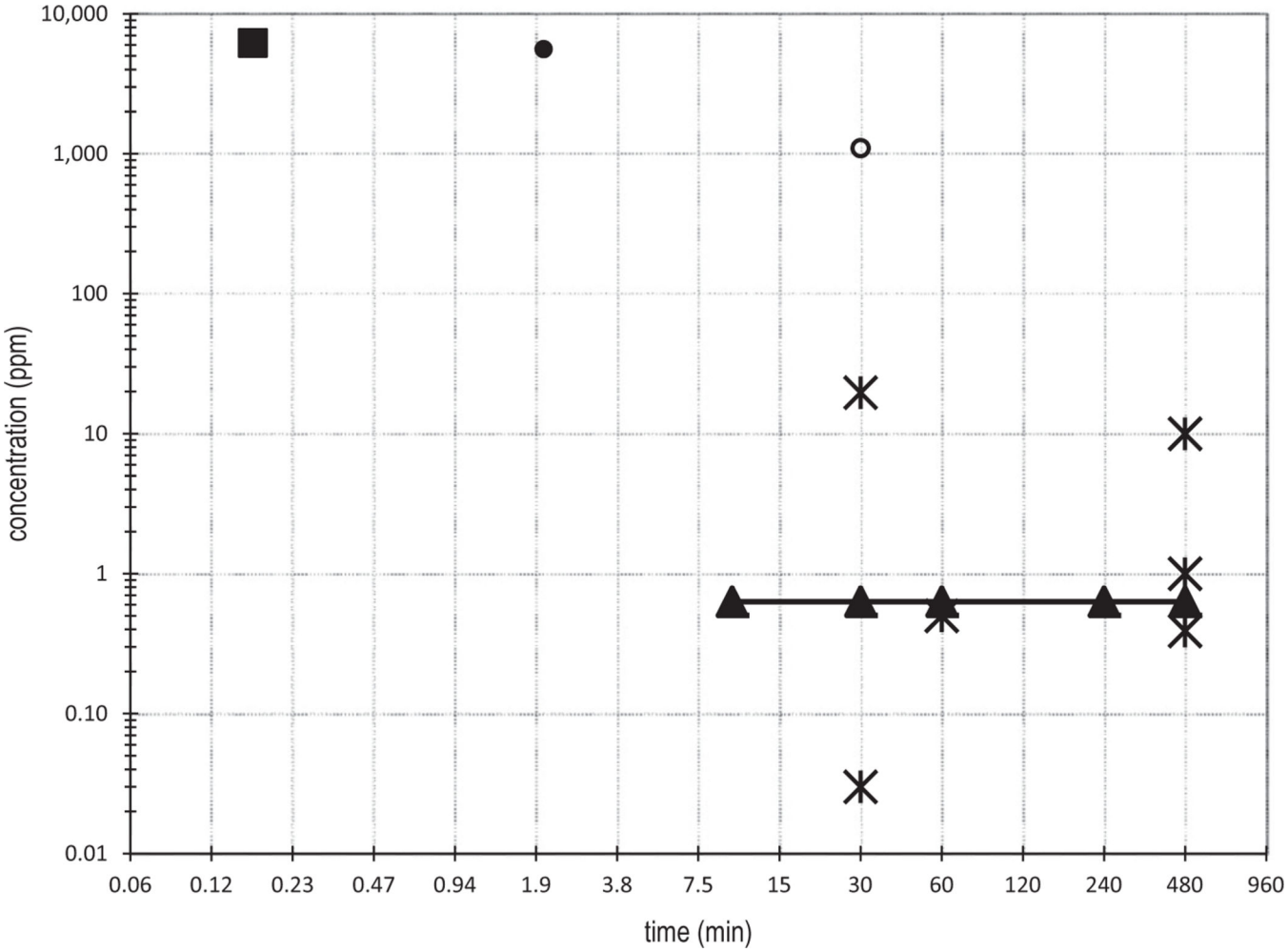

Figure 7.

Levels of tested exposure for tier-1 effects caused by DMS exposures (Supplementary material S15). The shown effect categories are: human eye irritation (■), animal eye irritation (●) and lack of it (○). Petit symbols denote low-confidence subgroups. Human short-term inhalation exposure levels are shown with filled triangles and a solid line. The ERPG-1 and other known health guidance values (Supplementary material S15) are mapped with asterisks (*).

Table 1.

Rat mortality caused by exposures to DMS in 4 h inhalation experiments.

Study	Average concentration (ppm)	Mortality incidence
Tansy et al. (1981)	800	0/10
	3000	0/10
	6000	0/10
	12,000	0/10
	24,000	0/10
	36,000	2/10
	39,000	5/10
	42,000	5/10
	45,000	8/10
	48,000	9/10
Schoenig (1967b)	42,100	4/10
	81,500	10/10
	195,000	10/10

Source: adapted from Tansy et al. (1981) and Schoenig (1967b).

Table 2.

Incidence of coma in rats after a 15 min exposure to DMS.

Study	Average concentration (ppm)	Coma incidence
Ljunggren and Norberg (1943)	1100	0/1
	5600	0/1
	13,000	0/1
	29,000	0/1
	31,000	0/1
	54,000	1/1
Schoenig (1967b)	18,500	0/10
	42,100	0/10
	195,000	10/10
Zieve et al. (1974)	74,643	2/12
	85,898	1/6
	89,445	1/3
	93,527	3/6
	100,425	4/5
	112,361	11/14
	130,468	5/6

Source: adapted from Ljunggren and Norberg (1943) and Schoenig (1967b); digitalized from Zieve et al. (1974).

Table 3.

Synopsis of short-term inhalation exposure levels[a]

	Short-term inhalation exposure levels			ERPG[b]	
Severity Tier	**1**	**2**	**3**	**2**	**3**
Key Study	Katz and Talbert (1930)	Zieve et al. (1974)[c]	Tansy et al. (1981)		
Species	man	rat	rat		
Adverse Effect	risk of nausea	coma	survival		
POD Type	olfactory	$BMCL_{10}$	$BMCL_{05}$		
POD Duration	none	15 min	4 h		
POD (ppm)	1.9	47,409	25,895		
Uncertainty Factor					
LOAEL	N/A	N/A	N/A		
interspecies	N/A	10	3		
intraspecies	3	3	3		
Modifying Factor	none	none	none		
Total Factor	3	30	10		
POD/TF (ppm)	0.6	1580	2590		
Time Scaling	none	$C_{POD} \times (t_{POD} / t)^{1/n}$			
		$n_{S\rightarrow L}$=**2.89**, $n_{L\rightarrow S}$=3.64		$n_{S\rightarrow L}$=1 $n_{L\rightarrow S}$=3	
10 min	0.6	1800	4600[d]	*1800*	*9100*
30 min	0.6	**1200**[e]	4600	*1300*	*6300*
1 h	0.6	**1000**	3800	1000	5000
4 h	0.6	**600**	2600	*250*	*1250*
8 h	0.6	**500**	**2000**	*125*	*625*

[a] Concentrations in ppm. Tier-2 and −3 levels were rounded to two significant figures.

[b] Shown for the purpose of comparison. ERPG is the maximum airborne concentration below which it is believed that nearly all individuals could be exposed for up to 1 h without experiencing or developing adverse health effects of specified severity (AIHA2014). These health effects are: for ERPG-1: mild, transient health effects or perception of a clearly defined objectionable odor; for ERPG-2:

irreversible or other serious health effect or symptoms that could impair an individual's ability to take protective actions; for ERPG-3: life-threatening health effects. Concentrations at exposure durations other than 1 h were extrapolated from the ERPGs using default UFs (NRC 2001). The extrapolated values are *italicized*.

[c] Supplemented with data from Ljunggren and Norberg (1943) and Schoenig (1967b) studies.

[d] Assigned at the level of 30 min exposure, following NAS recommendations (NRC 2001).

[e] Levels derived by concentration-time extrapolation from shorter to longer durations are shown in bold

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Table 4.

Comparison of tier-2 short-term inhalation exposure levels for DMS and the alternative values (ppm).

	Exposure duration						
Category	**10 min**	**30 min**	**1 h**	**4 h**	**8 h**	**Point of departure**	**Effect**
Tier-2 level	1800	1200	1000	600	500	47,409 ppm @ 15 min	Unconsciousness
Alternative	1500	1500	1300	900	700	Tier-3 levels (derived from POD @ 4 h)	N/A