MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

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INTEROFFICE COMMUNICATION

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January 7, 2015

To: Files for Sulfur Trioxide (SO3) [CAS # 7446-11-9],
Sulfuric Acid (H2SO4) [CAS # 7664-93-9], and Oleum [CAS # 8014-95-7]

From: Michael Depa, Air Quality Division, Toxics Unit

Subject: Screening Level Update

There are two sets of Initial Threshold Screening Levels (ITSLs) for the compounds Sulfur Trioxide (SO_3), Sulfuric Acid (H_2SO_4), and Oleum:

1. The chronic ITSL for sulfuric acid, sulfur trioxide, and for oleum is 1 µg/m^3 based on annual averaging time.

2. The acute ITSL for sulfuric acid, sulfur trioxide, and for oleum is 120 µg/m^3 based on a 1-hour averaging time.

Previously (Lehner, 2011) only one ITSL for these three compounds was set at 1 µg/m^3 with a 24-hr averaging time. The previous ITSL was based on a California Office of Environmental Health Hazard Assessment (OEHHA) chronic Reference Exposure Limit (REL) of 1 µg/m^3. California OEHHA uses an annual averaging time for their chronic RELs (OEHHA, 2015).

> Chronic RELs are designed to address continuous exposures for up to a lifetime: the exposure metric used is the annual average exposure.

If an ITSL is derived according to Rule 232, then the averaging time for an RfC derived ITSL is 24-hrs, see Rule 232(2)(b). However, if an ITSL is derived pursuant to Rule 229(2)(b), the averaging time associated with the ITSL is not designated. Because California OEHHA used a subchronic-to-chronic uncertainty factor of 3, it was determined that the REL specifically protects for long-term effects, and therefore an annual averaging time is appropriate and will be used for the ITSL.

A second ITSL of 120 µg/m³ with a 1-hr averaging time is being established at this time. This ITSL is also based on a California OEHHA acute REL. OEHHA designates that the acute ITSL is to be used with a 1-hr averaging time (see Table 1 for derivation).

In human asthmatic subjects, exposure to 450 µg/m³ sulfuric acid for 16 minutes decreased airway conductance but the magnitude of the decrease was not clinically significant (Utell et al., 1984). The lowest observed effect level (considered a NOAEL) for a 16-minute exposure resulting in decreased airway conductance in human

asthmatic subjects was 450 µg/m³ (112 ppb) sulfuric acid. The REL of 120 µg/m³ for a 1-hour exposure was derived using the formula $C^n \times T = K$, where n = 1.

Table 1. Derivation of the California Acute REL

Study	Utell et al., 1984
Study population	17 human asthmatics
Exposure method	inhalation
Critical effects	small changes in airway function, especially in asthmatics
LOAEL*	1,000 µg/m³
NOAEL**	450 µg/m³ (112 ppb)
Exposure duration	16 minutes
Extrapolated 1 hour concentration	120 µg/m³ ($C^1 \times 1$ hr = 450^1 µg/m³ x 16/60 hr)
LOAEL uncertainty factor	1
Interspecies uncertainty factor	1
Intraspecies uncertainty factor	1
Cumulative uncertainty factor	1
Reference Exposure Level	120 µg/m³ (30 ppb)

* LOAEL = lowest observed adverse effect level
** NOAEL = no observed adverse effect level

References

Lehner. 2011. Memo to the Files for Sulfur Trioxide (SO3) [CAS # 7446-11-9], Sulfuric Acid (H2SO4) [CAS # 7664-93-3], and Oleum [CAS # 8014-95-7]; FROM: Doreen Lehner, Toxics Unit, Air Quality Division; DATED: September 9, 2011

OEHHA. 2008. Individual Acute, 8-Hour and Chronic Reference Exposure Level Summaries APPENDIX D. Office of Environmental Health Hazard Assessment (OEHHA). Air Toxicology and Epidemiology, Air Toxics Hot Spots Program, Revisions to the Technical Support Document for Noncancer Risk Assessment. [07/18/08]. TSD for Noncancer RELs. June 2008. http://www.oehha.ca.gov/air/hot_spots/pdf/AppendixD_int071808.pdf

OEHHA, 2015. Office of Environmental Health Hazard Assessment (OEHHA). Air Toxicology and Epidemiology. OEHHA Acute, 8-hour and Chronic Reference Exposure Level (REL)s. Footnote 1. http://www.oehha.ca.gov/air/allrels.html

Utell MJ, Morrow PE, Hyde RW. Latent development of airway hyperreactivity in human subjects after sulfuric acid aerosol exposure. J Aerosol Sci 1983;14:202-205.

Utell MJ, Morrow PE, Hyde RW. Airway reactivity to sulfate and sulfuric acid aerosols in normal and asthmatic subjects. J Air Pollut Control Assoc 1984;34:931-935.

MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

TO: Files for Sulfur Trioxide (SO_3) [CAS # 7446-11-9],
Sulfuric Acid (H_2SO_4) [CAS # 7664-93-3], and Oleum [CAS # 8014-95-7]

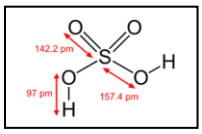
FROM: Doreen Lehner, Toxics Unit, Air Quality Division

DATE: September 9, 2011

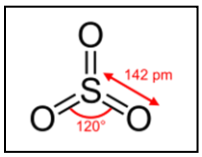
SUBJECT: Re-examination of the Initial Threshold Screening Level for Sulfuric Acid [CAS # 7664-93-3]
Sulfur Trioxide [CAS # 7446-11-9]
& Oleum [CAS # 8014-95-7]

The initial threshold screening level (ITSL) for sulfuric acid, sulfur trioxide, and for oleum is 1 $\mu g/m^3$ based on a 24-hour averaging time.

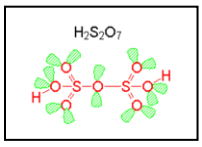
A literature review was conducted to identify if any new data are available since the 1996 chemical memo to the file for sulfuric acid, sulfur trioxide, and oleum. The following references and databases were searched to derive the above screening level: United States Environmental Protection Agency (US EPA) Integrated Risk Information System (IRIS), American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Values and Biological Exposure Indices (TLV/BEI) 2010 guide, National Toxicology Program (NTP) Study Database, EPA Aggregated Computational Toxicology Resource (ACToR) Database, and the Agency for Toxic Substances and Disease Registry Toxic Substances Database.



Sulfuric acid



Sulfur trioxide



Oleum

Sulfuric acid is a strong acid used as an intermediate in the synthesis of linear alkylbenzene sulfonation surfactants used in dyes, in petroleum refining, for the nitration of explosives, in the manufacture of nitrocellulose, in caprolactam manufacturing, as the electrolyte in lead-acid batteries, and as a drying agent for chlorine and nitric acid. Sulfuric acid is formed in the atmosphere from sulfur dioxide, from sulfur trioxide, and from oleum (a combination of sulfur trioxide and sulfuric acid used industrially) (Wikipedia, 2011). Sulfur trioxide is the anhydride of sulfuric acid and can exist as a colorless or white crystalline solid which will fume in air. In the gaseous form, it reacts violently with water to form sulfuric acid with the release of heat and is the primary agent in acid rain. It is used in combustion to charge the ash before flowing through electrostatic precipitators, which will trap the ash and allow for cleaner emissions (Wikipedia, 2011).

An extensive review of sulfur trioxide, sulfuric acid, and oleum was performed by Dan O'Brien in 1996 to determine an ITSL for these compounds and therefore, this memo to the file will only discuss the reasoning behind the change in the ITSL. This chemical meets the definition of a

carcinogen per Rule 336.1103(c) (APCR, 2011), but risk assessment and risk management considerations indicate that no IRSL should be derived. Sulfur trioxide, sulfuric acid and oleum are expected to act as threshold carcinogens. Explanation of the mechanism of a threshold carcinogen, is discussed in O'Brien's 1996 chemical memo to the file.

EPA has no established reference concentrations or reference doses for sulfuric acid, sulfur trioxide, or oleum and the IRIS database did not have any information on these compounds. ATSDR has a toxicological profile for sulfur trioxide and sulfuric acid, but did not derive any Minimal Risk Levels. AGCIH has developed a threshold limit value- time-weighted average (TLV-TWA) of 0.2 mg/m^3 for occupational exposure to sulfuric acid. The TLV is partially based on work by Alarie et al., 1973, which demonstrated that slight histologic and functional changes can occur in the lungs of non-human primates chronically exposed at 0.5 to 2.4 mg/m^3 sulfuric acid. AGCIH also looked at clearance studies in rabbits, donkey, and human subjects, which demonstrated that acute exposure to sulfuric acid aerosols can alter the tracheobronchial clearance mechanisms of inhaled particles. It appears that most of the effects of exposure to sulfuric acid aerosols and the potential for development of mucociliary clearance changes can be reduced and eliminated in many of the exposed persons if the exposure is kept below 0.25 mg/m^3 (AGCIH, 2004). AGCIH TLVs are for workplace exposure (for periods of 8 hours), unless specified otherwise.

California EPA has determined a noncancer chronic inhalation reference exposure level (REL) of 1 $\mu g/m^3$ for sulfuric acid using the Alarie et al., 1973, study. Alarie et al., 1973, exposured of 9 cynomolgus monkeys (5 males and 4 females per group or vice versa) to sulfuric acid concentrations of 0, 0.38, 0.48, 2.43, and 4.79 mg/m^3 continuously for 78 weeks resulted in dose-dependent adverse histological changes in lung and bronchiolar epithelial and parenchymal tissue in addition to a dose-dependent decrease in blood oxygenation. "In the animals exposed to 0.38 mg/m^3, significant bronchiolar epithelial hyperplasia was observed in 5 of 9 animals; thickening of the bronchiolar walls was observed in 3 of 9 animals. A slight focal bronchial epithelial hyperplasia was present in 4 of the 9 animals. One animal died after 4 weeks exposure to 0.38 mg/m^3. Although signs of pulmonary edema and cardiac hypertrophy were found, the cause of death was not determined." (Cal EPA, 2001) The LOAEL for this study is 380 $\mu g/m^3$ and no NOAEL was observed. Cal EPA used the following uncertainty factors: a LOAEL to NOAEL uncertainty factor of 3; a subchronic to chronic uncertainty factor of 3; an interspecies uncertainty factor of 3 for non-human primates; and an intraspecies uncertainty factor of 10 for sensitive individuals. Cal EPA also noted studies on sulfate and hydrogen ions and stated that these effects are difficult to disentangle from each other and from the effects of other particulate matter constituents. The 1 $\mu g/m^3$ REL appears to be protective for sensitive populations (Cal EPA, 2001).

As the Cal chronic inhalation REL is an exposure that is not likely to cause adverse effects in a human population, including sensitive subgroups, exposed to that concentration for extended periods of time, and since Cal RELs are peer-reviewed, the value of 1 $\mu g/m^3$ will be adopted as the initial threshold screening level (ITSL) for sulfuric acid, sulfur trioxide, and for oleum (based on a 24-hour averaging time). Also, the combined ambient impacts of sulfuric acid, sulfur trioxide and oleum cannot exceed the ITSL of 1 $\mu g/m^3$ (24-hour average).

References:

APCR. 2011. Air Pollution Control Rules, Promulgated pursuant to Part 55, Air Pollution Control, of the Natural Resources and Environmental Protection Act, Michigan Department of Environmental Quality. 1994. Act 451, as amended (NREPA).

CAL EPA. 2001. Determination of Noncancer Chronic Reference Exposure Levels Batch 2B December 2001. Chronic Toxicity Summary. Sulfuric Acid. http://oehha.ca.gov/air/chronic_rels/pdf/sulfuric.pdf

Wikipedia. 2011. Sulfuric Acid. Retrieved data on 9/8/11.

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MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

October 25, 1996

TO: Files for Sulfur Trioxide (SO_3) [CAS # 7446-11-9], Sulfuric Acid (H_2SO_4) [CAS # 7664-93-9] and Oleum [CAS # 8014-95-7]

FROM: Dan O'Brien, Toxics Unit, Air Quality Division

SUBJECT: Initial Threshold Screening Levels for Sulfur Trioxide & Oleum, & Re-examination of the Screening Level for Sulfuric Acid

The initial threshold screening level (ITSL) for sulfur trioxide and for oleum is 10 µg/m^3 based on an 8 hour averaging time.

The following references or databases were searched to identify data to determine the ITSL: AQD chemical files, IRIS, HEAST, ACGIH TLV Booklet, NIOSH Pocket Guide to Chemical Hazards, RTECS, NTP Management Status Report, EPB Library, IARC Monographs, CAS On-line and NLM/Toxline (1967 - January 3, 1996), CESARS, Handbook of Environmental Data on Organic Chemicals, Patty's Industrial Hygiene and Toxicology, Merck Index and Condensed Chemical Dictionary.

Sulfur trioxide is the anhydride of sulfuric acid, and can exist as a crystalline solid (α, β, and γ forms), a fuming liquid or as a gas (IARC, 1992; Grint and Purdy, 1990; Merck, 1983). Oleum, or fuming sulfuric acid, is a mixture of sulfuric acid with sulfur trioxide. SO_3 is used primarily as a sulfating or sulfonating agent in many industrial processes, including soap and detergent manufacture; the making of polystyrene dispersing agents; synthesis of chemical intermediates for dyestuffs, drugs, insecticides and lubricant additives; surface treatment of polymers; and to increase the efficiency of electrostatic fume precipitators (IARC, 1992; Grint and Purdy, 1990) .

SO_3 is highly toxic (Hawley, 1981), and a corrosive oxidizing agent to all mucous surfaces (Beliles and Beliles, 1994). It reacts immediately [on the order of "a few hundred microseconds" (Keesee et al., 1986)] completely, and violently in the presence of water or water vapor to form sulfuric acid or sulfuric acid mist, respectively (Beliles and Beliles, 1994; Grint and Purdy, 1990; Soskolne et al. 1989; Hofmann-Sievert and Castleman, 1984; Merck, 1983; Hawley, 1981). Sulfur trioxide and sulfuric acid mists are strongly irritant, and inhaling concentrations of approximately 3 mg/m^3 causes a choking sensation. Persons accustomed to the exposure are unable to notice concentrations of that magnitude (Beliles and Beliles, 1994). These agents also attack the enamel of teeth.

Data concerning exposure of laboratory animals to SO_3 are quite limited, a single article (Cameron, 1954) being the only one located. In that report a variety of species were

exposed to “chlorsulphonic acid-sulphur trioxide mixture smoke clouds” consisting of “particulate sulphuric acid with varying amounts of HCl [hydrochloric acid] in the gaseous state”. Two experiments were completed in a 100 m^3 exposure chamber. In the first, 2 goats, 12 rabbits, 12 guinea pigs and 20 rats were exposed to a concentration of 60 mg/m^3 SO_3 6 hours daily for 9 days and to a preliminary concentration of 30 mg/m^3 SO_3 for 6 hours on the first day. A monkey and 20 mice were exposed to 60 mg/m^3 for 7 days. For the second experiment, one monkey, 2 goats, 12 rabbits, 20 guinea pigs, 20 rats and 20 mice were exposed 6 hours per day for 14 days to a concentration of 30 mg/m^3 SO_3. The only health endpoints monitored were clinical signs, body weights (before exposure and subsequently at three day intervals) in all animals but the monkeys. At the end of each experiment, survivors were weighed, killed and necropsied. The clouds dispersed were “checked by analysis” as to chamber concentration, but the method is not stated. No statistical analyses were reported. Interestingly, the investigator(s) apparently also exposed themselves. For experiment one, the mean ± S.D. chamber concentrations for SO_3 and HCl are listed as 52.8 ± 7.5 mg/m^3 and 2.8 ± 0.3 mg/m^3, respectively, while for experiment two, they were 30 ± 3 mg/m^3 and 1.8 mg/m^3 (no S.D. given) . The investigator’s descriptions of the cloud at a concentration of ~ 30 mg/m^3 were “no immediate symptoms beyond a very slight tingling in the nose”. This was described as becoming “more pronounced, developing into a soreness” which dissipated after about 5 minutes. “Breathing through the mouth led to coughing and a feeling of constriction in the chest, so that the observer had to leave the chamber.” At 60 mg/m^3, “two observers found that tightness in the chest and coughing soon became unbearable. The cloud was much more dense than that at 30 mg/m^3, and cages on the floor could not easily be distinguished”. The only animals that showed clinical signs during exposure were the goats, for which “some coughing” was reported, and the guinea pigs, some of which showed signs of bronchial spasm, and some of which died after only 6 hours exposure in both experiments. No eye irritation was reported (although considering the author’s reported difficulty of seeing even the cages on the floor at the higher concentration, good clinical observations may have been impossible). The authors state that none of the animals lost weight, although the tabulated data suggest that there were slight weight losses in the goats and mice at both SO_3 concentrations. The rats showed slight weight gains in both trials. The other species approximately maintained their original weights. No deaths occurred amongst the monkeys, goats or rabbits exposed for 42-84 hours to either concentration of SO^3. No rats or mice died during 7-9 six-hourly exposures of 60 mg/m^3, but two animals of each species succumbed to 30 mg/m^3, after 7 and 8 six hour exposures in the two rats, and after 6 six hour exposures in the mice. The authors felt that the rats had a “high incidence of natural lung disease, whilst S. ærtrycke infection was found in some of the mice”, and consequently, that the mortalities were not attributable to exposure. The guinea pigs were markedly the most sensitive species, with 11/12 animals dying after less than two days exposure to 60 mg/m^3, and 9/20 failing to survive beyond 2 days of exposure to 30 mg/m^3. With respect to pathology, among animals exposed to 60 mg/m^3, the single monkey and all of the guinea pigs were reported as “showing lung damage”, while in the 30 mg/m^3 groups, 1/2 goats, 2/20 mice, 8/20 rats and 16/20 guinea pigs showed such damage. The chief pathological lesions reported in the deceased animals were renal, hepatic and adrenal congestion, and prominent pulmonary edema and emphysema, surrounding areas of consolidation and acute bronchitis. This picture was consistent regardless of species. Notably, “no evidence of nasal or eye irritation was obtained”. Survivors showed similar though less severe lung pathology, with bronchopneumonia the most prevalent lesion. Their other organs remained normal. In

summary, the authors concluded that “it is necessary to have some predisposing factor in most animals to induce lung damage by means of chlorsulphonic acid fumes”, and that “persons not subject to pulmonary disturbance should prove resistant to chlorsulphonic acid smokes in relatively low concentrations in the open air. A hazard may, however, exist in human beings who suffer from asthma or allied conditions.” While valuable because of the variety of species exposed, the fact that the exposure was mixed limits the usefulness of this study for derivation of a screening level. As has been noted by the International Agency for Research on Cancer [IARC] (l992b) and confirmed by our current searches, no long term studies of SO_3 exposures to experimental animals are currently available.

During review of a draft of this document by the Scientific Advisory Panel in April of 1996, interest was expressed in the comparative toxicity of H_2SO_4 to plants versus animals, and in the threshold concentrations for effects of the agent on plants versus animals. While a great deal of data concerning the effects of acid precipitation and environmental acidification on plants has been published recently, much of the literature addresses very specific research questions[1], while summary references seem to be few. Fewer still are data suggesting specific quantitative thresholds for adverse effects of H_2SO_4 on plants. Extended literature searches turned up only two older summary references (EPA, 1978; Air Pollution Control Association, 1970), and neither addresses H_2SO_4 threshold concentrations which might be incorporated into a quantitative risk assessment. However, both offer an extensive treatment of the toxicity of sulfur dioxide (SO_2) to plants, and threshold concentrations for the effects of that pollutant are available (EPA, 1978).

Reports are available which document several incidents of accidental inhalation exposures of humans to SO_3 or oleum. Grint and Purdy (1990) briefly recount five separate episodes in England, Sweden and India. In all cases, the circumstances involved accidental spillage of SO_3 or oleum from storage tanks, forming dense clouds of sulfuric acid mist which drifted from the site and exposed people in surrounding areas. The most severe occurred in Delhi, where 40 tons of oleum escaped from a collapsed tank, ran into a nearby sewer, and produced an acid cloud that spread up to 15 km from the leak, affecting several thousand people. Over 250 people were treated in hospital, with 77 requiring admission. Nine of these were in serious condition. Clinical signs in all cases were characterized by eye and upper respiratory irritation, coughing, and difficulty breathing. The authors note that people exposed to such a cloud would experience great difficulty breathing and seeing, making escape from a cloud very difficult. The SO_3/H_2SO_4 air concentrations which precipitated these health effects were not reported by these authors. A more detailed description of an accidental human exposure has also been published (Stueven et al., 1993; Stueven, 1992). In that account, eleven men and a woman working outdoors in a cattle yard next to a chemical plant reported a fog-like emission from the plant that supposedly persisted for two hours. Nine of the twelve were taken by ambulance to a hospital emergency service,

[1] An individual with specific training in botany and plant pathology or ecotoxicology would seem sufficiently qualified to evaluate the relevance of these focused studies within the context of the larger issue of H_2SO_4 toxicity. However, such an evaluation is beyond the reach of this author and the scope of this risk assessment. Moreover, some of the potentially useful citations are in languages other than English. Citations from focused searches of the phytotoxicity of H_2SO_4 are available in the AQD chemical File for SO_3, and the interested reader is referred to that reference for further information.

where they variously complained of pleuritic chest pain/tightness/discomfort, eye irritation, dizziness, light-headedness, cough and acidic taste in the mouth. The only clinical sign noted by staff was minimal conjunctival injection in a single patient. Clinical evaluations included respiratory rates, pulse, blood pressure, pulse oximetry, chest radiographs, electrocardiograms, conjunctival pH, and pulmonary function testing (at admission and between three and four hours thereafter). Five individuals were initially hypertensive, but all had normal blood pressures prior to discharge. A single patient had radiographically evident right atrial enlargement. At admission, forced expiratory volume (FEV) was >100% of predicted in five of the nine; among the others, FEV ranged from 77.4 to 96.7%. At the second evaluation, FEV had increased in three of these four; in the other, it declined from 96.7 to 89%. All patients were asymptomatic within six hours and were discharged. Seven of the nine had a follow-up exam within the next ten days. At that time, two reported no symptoms since discharge, two reported transient burning sensations in the nostrils, mouth and throat, one an exfoliative scalp lesion, one a transient headache the day after exposure, and two reported persistent pleuritic chest pain. Physical examinations were normal in all but one individual. That person had mild pain on chest palpation which had remained unchanged since the initial presentation. Repeat pulmonary function testing was 100% of predicted in 3/7; the other four ranged from 85.7% to 96.6%. Three of these four had decreased FEVs at their initial presentations as well. Under conditions of the report, sulfur trioxide caused only self-limiting irritant effects in humans. It should be noted, however, that the means by which it was determined that these individuals were exposed to SO_3 is not stated by the authors. As with the episodes reported by Grint and Purdy, no determinations of concentrations of SO_3 leading to these effects were included in the paper.

Four other references located in our searches associate human disease with exposure to SO_3, but the relationships claimed are not well documented. The first, an abstract (La Rosa et al., 1987), postulates that mixed exposure to chemical pollutants (including SO_3) decreases cell mediated immunity in children. Another abstract (Rogacheva, 1993) summarizes a retrospective analysis of pregnancies and birth outcomes in 987 Russian women who lived in an area of air contamination, the main components of which were “nitrogen oxides, sulfur anhydride [SO_3] and hydrochloric and sulfuric acids”. Contaminated atmospheric air was significantly associated with development of “hypotrophy of the fetus” (presumably, low birth weight), and with increased frequencies of “threatened abortion”, “late gestosis”, and “extragenital and genital diseases”. Air contamination showed the greatest negative influence in the second trimester. Unfortunately, published details of this study were insufficient to allow critical evaluation. The other two articles (Rosenhall and Stjernberg, 1982; Aviado and Salem, 1968) are essentially brief reviews that equate the effects of SO_3 exposure with those of sulfur dioxide (SO_2) exposure, namely, irritation, coughing, bronchoconstriction and chronic bronchitis.

IARC (1992b) has noted that “in the moist environment of the respiratory tract, sulfur trioxide reacts instantaneously with water to form sulfuric acid; therefore, the toxicology of sulfur trioxide would be expected to be the same as that of sulfuric acid”. Consequently, it seems reasonable that SO_3, H_2SO_4 and oleum should share a common screening level, and in situations where an individual is exposed to all three simultaneously, that their potential for additive toxicity be taken into account. Though it will not be discussed in detail here, a large body of data is available concerning sulfuric acid exposures, including some reports of controlled short term human exposures (Sim

and Pattle, 1957; Pattle and Culluinbine, 1956; Amdur et al.., 1952) and many occupational epidemiology studies (IARC, 1992b). The current screening level for H_2SO_4 was derived in July of 1992 according to the Interim Process for Developing Screening Levels. Based on the American Conference of Governmental Industrial Hygienists Threshold Limit Value (ACGIH-TLV) of 1 mg/m^3, for an eight hour time-weighted average (TWA), the ITSL was set at 10 µg/m^3 based on an 8 hour averaging time. Review of the TLV documentation (ACGIH, 1992) suggests that this concentration is based on the controlled human inhalation results of Amdur et al. (1952), which found 1 mg/m^3 to be the threshold below which the agent could not be detected by odor, taste or irritation. Those authors exposed unacclimated subjects to concentrations of H_2SO_4 ranging from 0.35 mg/m^3 to 5 mg/m^3 for durations of 5 to 15 minutes. It should be noted that Amdur and coworkers recorded "purely reflex" respiratory changes at a concentration of 0.35 mg/m^3, a level at which the subject was unable to even detect the presence of the acid in the inhaled air.

However, also in 1992, IARC published a comprehensive monograph of data concerning human and animal exposures to H_2SO_4 and other strong inorganic acids, and concluded that "Occupational exposure to strong-inorganic-acid mists containing sulfuric acid is carcinogenic to humans (Group 1)". This fact was noted by the TLV committee, which stated only that IARC's categorization "is undergoing review" (ACGIH, 1992). Amongst other data, the IARC Commission examined the more than twenty-five epidemiological studies of workers exposed to 1 H_2SO_4 in a variety of industrial processes. The decision of sufficient evidence of carcinogenicity was based primarily on the consistency of findings of increased incidences of upper respiratory cancers[2] in workers involved in isopropanol and synthetic ethanol manufacturing, soap and detergent manufacturing and steel pickling. In these settings, H_2SO_4 was the most common (and in some cases, the only) documented exposure. Available data suggest the particle size of these mists in an industrial setting averaged about 5 µm, with a geometric standard deviation (σ_g) of 4 µm (Jones and Gamble, 1984). Although workers exposed during manufacturing of phosphate fertilizer, lead batteries, and sulfuric and nitric acid were examined, those studies were considered to be "not informative" (IARC, l992a).

Some of the individual studies abstracted by IARC were examined in detail[3] by AQD in an attempt to gain a better understanding of the strengths and weaknesses of the epidemiologic evidence for carcinogenicity (Soskolne et al., 1992; Hagmar et al., 1991; Steenland and Beaumont, 1989; Steenland et al., 1988; Beaumont et al., 1987; Stayner et al., 1985; Soskolne et al., 1984; Lynch et al., 1979; Rencher et al., 1977; Hueper, 1966; Weil et al., 1952). In addition, the epidemiological literature was monitored through most of 1996 in order to remain current on recent publications; this yielded another study (Coggon et al., 1996) for review. Selection for examination was based on subjective impressions, gained from IARC's summaries, of studies which seemed most likely to: 1) be of substantial scientific quality; 2) provide critical support for the conclusion of sufficient evidence of human carcinogenicity; and 3) yield data which could be used in a quantitative risk assessment. Of these, a subset of studies

[2] The most convincing data were associated with cancer of the larynx, although positive findings were also noted for cancers of the pharynx, paranasal sinuses and lungs in some of the studies.

[3] Since the IARC commission which examined the entire body of data was composed of recognized experts from around the world, it was not considered necessary to review in detail all of the studies considered by IARC

considered to comprise the best evidence reviewed will be summarized briefly below in chronological order.

Soskolne et al. (1984) carried out a case-control study of refinery and chemical workers in Louisiana. Fifty incident, histologically-confirmed cases of primary upper respiratory cancer (34 laryngeal, 11 pharyngeal and 5 nose, nasal, middle ear or sinus) in male workers were matched with three to five controls each, randomly selected from a pool of all employees at the same plant. Cases were diagnosed between July 1944 and August 1980. Subjects were matched on duration of employment, year of first employment, age, sex and race. All data collection was based on medical records. Information on potential confounders included tobacco use (cigarette, cigar, pipe and chewing tobacco), history of alcoholism, history of previous ear, nose and throat disease, and exposures to other potential upper respiratory carcinogens (e.g., ethanol, isopropanol, asbestos, nickel and wood dust) . Exposures were assessed for likelihood of H_2SO_4 and confounding exposure using an ordinal scale, job/location/era industrial hygiene measurements, and detailed work histories. Primary analysis was via conditional logistic regression, for which the final best-fit model found significant effects for high and moderate H_2SO_4 exposure, history of alcoholism, history of ear, nose and throat disease, and high and moderate tobacco consumption on the likelihood of laryngeal cancer. There were no significant interactions. With all of these factors controlled for in the analysis, workers with high (≥90% strength) H_2SO_4 exposure were more than five times as likely (Odds ratio [OR] = 5.2, 95% confidence interval [C.I.] {l.23-22.09}), and those with moderate (75-89% strength) H_2SO_4 exposure about three times as likely (OR = 2.9 {0.74-11.26}) to develop laryngeal cancer as controls. The numbers of cases of other upper respiratory cancers were too small to assess using logistic regression, but stratified analyses for all upper respiratory cancers taken as a group yielded ORs in the same general range.

Beaumont et al. (1987) conducted a retrospective cohort study of mortality in 1,165 steel pickling workers in three midwestern U.S. mills between 1940 and 1981. Exposure assessments were based on jobs categorized according to whether the acid used was sulfuric or another, and by the likelihood of daily exposure to acid mist. Area and personal sampling data from National Institute for Occupational Safety and Health (NIOSH) walkthrough surveys and health hazard evaluations of two of the facilities conducted in 1979 and 1977, as well as a company survey conducted at the third facility in 1975 were used to quantify the likely acid exposures for each job category. The mean H_2SO_4 concentration of 34 area samples was 0.29 mg/m^3, with a range from 0.00 to 1.20 mg/m^3, while the mean H_2SO_4 concentration of personal samples was 0.19 mg/m^3, with a range from <0.03-0.29 mg/m^3. The investigators considered a reasonable average daily worker exposure to be 0.2 mg/m^3 (based on the mean of personal samples). NIOSH also sampled for a variety of likely confounding chemical exposures, and the only ones detected were iron oxide and lead. Of these, only iron oxide was found in “appreciable quantities”. Vital status was ascertained through company, Internal Revenue Service (IRS) and Social Security (SS) records; cause of death was obtained from death certificates. Losses to follow-up ranged from 0.5-1.7% depending on exposure subgroup. Data were analyzed via life tables, stratified on calendar time, age, sex and race, length of employment and time since first employment. Standardized mortality ratios (SMRs) were compared both to the U.S. general population and a cohort of Pennsylvania steel workers. The confounding effect of smoking was controlled for indirectly by three separate methods. Statistically significant increases in deaths for all

respiratory cancers (SMR = 1.63, 95% C.I. {1.15-2.26}), and lung cancer (SMR 1.64 {1.14-2.28}) were found for workers exposed to any acid vs. the general U.S. population, and for lung cancers among workers exposed to H_2SO_4 only with probable daily exposure for ≥20 years vs. the general U.S. population (SMR = 1.93 {C.I excludes 1)). Control for smoking failed to account for all of the increased lung cancer risk.

Steenland and coworkers (1988) analyzed a subcohort of 879 pickling workers nested in the cohort of Beaumont et al. (1987) for incidence of laryngeal cancer[4]. The incident subcohort consisted of all men for whom it could be determined whether or not they had ever had laryngeal cancer. This was ascertained by interview with live workers, or by interviews with next of kin, or medical records, for decedents. A conservative case definition was used, wherein only laryngeal cancer cases confirmed by a physician or by medical records were included as cases for purposes of the study; laryngeal cancers reported only by death certificate or by interview were excluded. Interviews for the entire cohort inquired about incidence of cancer, smoking (including pipe and cigar) and alcohol consumption (including binge drinking) habits; cohort members still alive were also questioned about co-exposure to asbestos, nickel and wood dust and incidence of vocal cord polyps. Non-response rates were 21% for the living and 41% among the next of kin of decedents. Exposure assessment was identical to that described in Beaumont et al., with the exception that sample sizes were insufficient to separately analyze those exposed to H_2SO_4 alone versus other acids. For all members of the cohort, the predominant exposure was to H_2SO_4. Analysis was via life tables stratified on calendar time, age, sex, and duration of and time since first exposure; Standardized Incidence Ratios (SIRs) were the outcome measure. Comparisons were made with rates from the U.S. general population, and with rates from two states with laryngeal cancer registries (NY and CT). Nine cases were observed, five of whom were deceased. In addition, there were two workers with benign laryngeal growths and seven with vocal cord polyps. None of the four live cancer cases reported exposure to asbestos, nickel or wood dust. All nine cases were current or former smokers, and drinking habits varied. Even after adjustment for smoking and drinking habits, SIRs for laryngeal cancer were significantly elevated (2.30, 2.04 and 2.70 compared to the U.S. general population, CT and NY, respectively). Neither analysis by duration of employment or time since first exposure yielded statistically significant results (SIRs for exposure duration : ≤ 5 years, 1.70; > 5 years, 2.76; SIRs for time since first exposure: ≤ 20 years, 3.27; > 20 years, 2.03).

Steenland and Beaumont (1989) performed a further follow-up of the retrospective cohort of Beaumont et al. (1987) through the period 1981- 1986, primarily in an attempt to better control for the confounding effects of smoking on lung cancer. These authors were able to contact 73% of the cohort (either the workers themselves or next of kin). Exposure assessment and comparison populations were identical to those reported above for Beaumont et al., while details of the interview methods/response/follow-up and of control for smoking were the same as those reported above for Steenland et al. (1988). Analysis was once again via life table analysis, with SMR as the outcome

[4] Because Beaumont et al. studied mortality as the endpoint, that study was by design relatively insensitive for assessment of laryngeal cancer occurrence. Both Steenland et al. and Beaumont et al. point out that because over half of patients diagnosed with laryngeal cancer are treated and subsequently survive for five years or more, their deaths are frequently caused by diseases other than that cancer. Consequently, a cohort mortality study with vital status ascertained by death certificates (like Beaumont et al.) could have missed cases of laryngeal cancer among the studied workers.

measure. One hundred sixty two men (14% of the cohort) alive in 1981 were lost to follow-up by 1986. Six additional workers died from lung cancer during that period. Taking into account the five additional years of follow-up and adjustment for smoking, for all cohort lung cancer deaths, the SMR = 1.36 (0.97-1.84); for those with 20 years since first exposure, the SMR = 1.50 (1.05-2.27). A test for trend with increasing duration of employment on the data unadjusted for smoking was not significant. This led the authors to speculate that perhaps duration of exposure may be a poor surrogate of dose, since the data adjusted for smoking indicated a significantly increased risk of lung cancer, given sufficient latency.

Soskolne et al. (1992) carried out a population-based, matched case-control study of 183 histologically confirmed incident cases of laryngeal cancer in Southern Ontario diagnosed between March 1977 and July 1979. Cases were restricted to men, and matched one to one with controls for age and neighborhood of residence. These authors used interviewer-administered questionnaires to assess tobacco and alcohol consumption histories, job histories, and workplace exposures to asbestos, nickel and sulfuric acid. Exposure assessment was retrospective, and based on bibliographic information, and one author's knowledge of occupation, industry and era. Nickel, asbestos, tobacco and alcohol exposure information was available from a previous study (Burch et al., 1981); jobs were categorized as exposed or unexposed to H_2SO_4. For those considered exposed, three ordinal four-point scales were developed to describe the concentration, frequency, and certainty of exposure[5]. No actual measurements of H_2SO_4 were conducted in this study. A five point ordinal factor for duration of exposure was also developed, and interactions between the various factors were tested for during analysis. A rather complex system of conditional logistic regression models was used to assess the effects of these variables on the likelihood that a study subject had laryngeal cancer[6]. An association between exposure to sulfuric acid in the workplace (particularly at higher concentration and over longer periods) and the development of laryngeal cancer was demonstrated with the effects of both tobacco and alcohol consumption controlled for. Interactions between these factors, and with asbestos exposures, were insignificant. Depending on the model used, ORs ranged from 1.04 (0.34-3.21) to 6.90 (2.20-21.74).

While the consistency of the findings of increases in upper respiratory cancer across well-conducted epidemiological studies is compelling, a number of formidable difficulties arise when attempting to use these data for quantitative cancer risk assessment. Perhaps the most significant one relates to the assessment of H2S04 exposure. While authors such as Soskolne and colleagues have noted significant associations between H2S04 exposure in an occupational setting and increased risks of laryngeal cancer, because they assessed exposure based on job categories and did not actually measure H2S04 concentrations in the workplace, it is not possible to tell exactly what exposure concentrations are associated with the increased cancer risk. Soskolne et al. (1992) summarized this problem rather well when they noted that "it would not be meaningful to relate the average exposure level derived by the methods used in this study to exposure in the occupational setting. The exposure measure used is a synthetic composite.. .and it cannot be expressed on an interval scale". The exposure assessment of Beaumont et

[5] Concentration: Unexposed, low, medium, high; Frequency: Unexposed, low [1-5% workday], medium [5-30% of workday], high [>30% of workday]; Certainty: unexposed, possible but not probable, probable, certain.

[6] As the mechanics of the modeling were beyond the scope of this risk assessment document, only a summary of the results are presented. Details of the analysis can be obtained from the original publication.

al. (1987), while based on actual workplace air samples and presumably characterizing worker exposures accurately, was not conducted concurrent with the follow-up. Beaumont and coworkers noted that “while available process evidence regarding process engineering suggests that air concentrations in past years were likely to have been similar to those reported”, “the possibility that sulfuric acid mist exposures may have been higher prior to 1975 cannot be excluded”. As a result, it is not possible to say with certainty that the exposure concentrations recorded by NIOSH in the 1970s were the actual exposure concentrations which caused the increases in cancer in the workers studied. On the other hand, if those concentrations did accurately reflect worker exposure, the results suggest that the current TLV of 1 mg/m^3, based on avoidance of upper respiratory and eye irritation, may not protect exposed individuals from an increased risk of respiratory cancers (recall that the average H_2SO_4 exposure of the exposed workers, based on the mean of NIOSH personal samples, was 0.19 mg/m^3, and that all of the personal samples, and nearly all of the area samples, were less than the TLV) . This suggests that one cannot be certain that concentrations which are free from sensory irritation will not increase the risk of respiratory cancers, although the most recent study reviewed (Coggon et al., 1996) suggested “...that any risk from exposures to sulphuric and hydrochloric acid below 1 mg/m^3 is small”.

Other concerns about the validity of the epidemiologic data could potentially be raised. Since the cancer endpoints being studied are respiratory cancers, control for the effects of tobacco use by the subjects is critical. While not all of studies considered by IARC controlled for the effect of smoking, the better studies abstracted above did. Granted, analytical techniques used for control varied from study to study, and because the data on tobacco consumption were based on interview and questionnaire data, the possibility of recall bias on the part of the subjects who smoked cannot be excluded. However, the fact that the better studies consistently found increased risks of cancer after adjusting for the confounding effects of smoking should not be ignored. As IARC (l992a) has pointed out, “Although tobacco smoking was not controlled for in most of the studies considered, the finding of increased risks of laryngeal cancer in the absence of increased risks for lung cancer meant that smoking could be ruled out as a major confounder”. It could also be argued that confounding exposures from other workplace carcinogens could have been responsible for all or part of the observed cancer increase. The workers studied were most commonly exposed to other acids, primarily hydrochloric acid (HCl). Yet IARC (1992a,b) considered worker exposures to HCl in their assessment, and noted that “the epidemiologic studies were considered to provide inadequate evidence for the carcinogenicity of hydrochloric acid to humans”. This conclusion tends to rule out HCl as a confounding causal exposure. Exposure to other known and unknown workplace carcinogens was possible, yet where known workplace carcinogens such as asbestos, nickel, chromium and wood dust were considered in the better studies, they were either not detected (Steenland and Beaumont, 1989; Steenland et al., 1988; Beaumont et al., 1987), or were controlled for in the analysis (Soskolne et al., 1992; Soskolne et al., 1984). Either way, none of the confounding exposures could completely account for the increased risks of respiratory cancer. While some unknown confounding exposures could conceivably have contributed, there is no data to suggest that that is the case. Again, since H_2SO_4 was the most common (and in some cases the only) exposure documented, it is reasonable to conclude that it is the most likely causal agent for the cancers (IARC 1992a).

Finally, the inconsistency of findings of increased respiratory cancer risk with increased duration of exposure to H_2SO_4 could be argued as evidence that sulfuric acid was not responsible. Yet, it is well-recognized that cohort studies are relatively insensitive for the study of rare diseases, and laryngeal cancers are relatively rare. Given the small number of cases to begin with, and the further decrease in sample size that resulted from stratification to assess duration of exposure, it is quite possible that the failure to find a statistically significant dose-response relation is due to a lack of power in the studies of Steenland and coworkers. Because Soskolne et al. (1984) matched on duration of exposure, they were not able to assess the effect it may have had on laryngeal cancer in their logistic models. However, when they stratified their matched case-control sets to reflect likely high or moderate summary work life exposure (as compared to low/no exposure), estimated odds ratios suggested those workers with high exposure had a greater tendency to develop upper respiratory cancers than did moderately exposed workers (though these tendencies were not always statistically significant). Their later study (Soskolne et al., 1992) did find a significant relationship between the duration and intensity of exposure to H_2SO_4 and the risk of developing laryngeal cancer via logistic modeling. Consequently, this argument seems unconvincing.

Presented with sufficiently sound scientific evidence of the human carcinogenicity of H_2SO_4, and the need to derive a screening level which will adequately protect the public, but also with somewhat uncertain exposure data and a complete lack of long-term animal cancer studies, which might be utilized for traditional cancer risk assessment, an alternative approach is indicated. Soskolne et al. (1989) have reviewed the available data concerning the possible mechanisms of chronic health effects induced in humans and animals by H_2SO_4 and other acids, with an emphasis on cancer induction. There is no clear consensus on the mechanism by which sulfuric acid exposure causes cancer; direct genotoxicity, modulation of mitotic activity and cell differentiation, chronic irritation/inflammation[7], and pH-induced impairment of DNA repair have all been suggested, as has some unknown combination of these mechanisms. Most of the evidence available in our review has suggested that the carcinogenicity is most likely due to decreases in pH, rather than the sulfur moiety itself[8]. To the extent that carcinogenicity is a function of low pH, a critical threshold of acidity might need to be reached in the respiratory tract to induce cancer. So, to the extent that the airways can buffer acid mist exposures, induction of cancer might be prevented. The mucus layer, or airway lining fluid (ALF) of the respiratory tract, has the capacity to buffer hydrogen ions to prevent their penetration to surrounding tissues (Hatch, 1992; Holma, 1989,1985) . Studies in mice and dogs *in vivo* and in cattle tracheal cells in vitro all suggest that the earliest obvious histopathological effects attributable to decreased ALF pH occur below an approximate pH of 6.5 (Holma, 1989). These changes start with intra- and intercellular edema and progress to loosening of epithelial cells from each other and from their basement membranes at about pH 6.

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[7] On review of the materials presented here, the Scientific Advisory Panel has suggested that a chronic irritation model of carcinogenicity may be the most plausible. Under such a model, direct exposure of cells to droplets of concentrated acid would cause cell death directly. In an attempt to replace the dead and damaged cells, cell replication in tissues immediately adjacent to the site of injury would increase. As this increased rate of cell replication is maintained over time, the possibility increases that a random genetic mutation may be amplified, overcoming the tissue's inherent capacity for genetic repair, and eventually progressing to clinical cancer.

[8] However, given the irritancy and toxicity of other organic sulfur species such as hydrogen sulfide, it may not be possible to solely implicate low pH at this time.

Holma (1985), conducted a study to investigate the buffering and rheological properties of airway mucus, to demonstrate their importance in the health effects of acid air pollutants. He obtained fresh samples of morning sputum from a variety of subjects including: a man (S) and a woman each smoking 20 cigarettes a day; a man smoking 10 cigarettes a day; a cigar smoking man with chronic bronchitis; three women and a man with allergic asthma, all non-smoking; three non-smoking men with intrinsic asthma; and a healthy non-smoking man. The sputum samples of S on eight different days were titrated with H_2SO_4 to develop a titration curve, and those of all the subjects were used to determine the absorption capacity of respiratory tract mucus for H^+ ions from 1 M H_2SO_4. The pH of the sputum samples, as well as their buffering capacity, was found to vary from day to day. The most acid samples were recorded among the smoking women; their sputum pHs were all 6.2. Male smokers' values ranged from 6.74-7.48; those of the allergic asthmatics, from 6.27-7.36; and those of the non smoking intrinsic asthmatics, from 6.33-6.98. The normal subject's sample pH was 7.41. The ALF buffering capacity of the subjects, ranked in increasing order, was intrinsic asthmatics < allergic asthmatics < smokers < non-smoker, with some overlap between some of the smokers and the normal non-smoker. This same general ranking was observed with respect to the ability of mucus to bind H^+ ions over time and prevent their contact with adjacent tissues. These results suggested that asthmatics are likely to be the most sensitive members of the population to the pH-induced effects of H_2SO_4 exposure, a point emphasized by Holma. He further noted that detrimental respiratory epithelial effects would be expected in asthmatics at low mucus pH values under even normal circumstances without acidic exposures (Holma, 1985), and that "for this group of people, it is unrealistic to establish a threshold level under which no adverse effects can occur" (Holma, 1989). While the adverse effects referred to by Holma were not specifically carcinogenic ones, to the extent that pH is the inducing factor, asthmatics may also be most at risk for upper respiratory cancers.

Holma (1985) then used his experimental results to calculate the concentration that an individual could be exposed to over a period of time without exceeding the buffering capacity of the mucus. The biochemical event associated with this threshold is the saturation of mucus proteins with H^+ ions until "optimum mucus viscosity is reached. Thereafter, the acidic exposure will be more pronounced for the surrounding tissues, with increased epithelial permeability facilitating a variety of reactions. A rough estimate indicates that this state can be expected to occur for smokers somewhere between 3000 to 6000 µg SO_2/m^3, or about 300 µg H_2SO_4/m^3 (30-min values[9]). . . . These levels of acidic pollutants are indicated to be the lowest levels also for nonsmokers and thus no effect is to be expected in normal adults below those demonstrated in experimental research" (Holma, 1989) . It is notable that Holma performed his buffering capacity work on samples from smokers and asthmatics, "hence, only values from abnormal sputum are available for judging the threshold values for acidic pollutants for normal people. On the other hand it might be of more concern to establish the levels acceptable for different risk groups." Consequently, some degree of conservatism is already incorporated into these threshold concentrations with respect to the protection of unusually sensitive members of the population.

[9] The 30 minute averaging times appears to be based on the approximate upper bound of nasal mucous transit time in humans (Holma, 1985, p. 116).

In referring to these buffering capacity concentrations, Holma also notes that "to these figures should be added the neutralization by NH_3 in the airways". Ammonia is present in the oral cavity during quiet breathing (Larson et al.., 1977), and the $(NH_4)_2SO_4$ formed through the neutralization of H_2SO_4 can reach a maximum of ~1500 µg/m^3 (Holma, 1985). He reports that no biological effect of this nearly neutral salt has been reported for concentrations up to 3000 µg/m^3 for a 10 minute human exposure; that concentration "can in theory be obtained as a result of 1500 µg H_2SO_4/m^3 in inhaled air". As cited by IARC (1992b), EPA (1989) has provided the only other estimate of buffering capacity for the human respiratory tract found in our searches. That reference estimates that exposure to H_2SO_4 at 1300 µg/m^3 for 30 minutes at a ventilation rate of 20 L/min and 50% deposition would lower the pH of tracheobronchial mucus one unit (assuming uniform distribution of 2 µ particles). Assuming the maximum pre-exposure mucus pH of 7.4 as reported by Holma, such a concentration would drive mucous pH below the threshold for cytotoxicity. EPA's estimated buffering concentration, like Holma's, does not take into consideration neutralization of acid in the airways by ammonia.

It seems useful to compare the current ITSL for H_2SO_4 (10 µg/m^3, based on an 8 hour averaging time), with Holma's and EPA's thresholds for the avoidance of pH-induced respiratory cell damage (300 µg/m^3 and 1300 µg/m^3 respectively, based on a thirty minute averaging time). Using the approximate conversion equation taken from Turner (1970)[10] to convert Holma's concentration from a 30 minute averaging time to an eight hour averaging time:

$$x = x_t * \left[\frac{t_k}{t_x}\right]^p$$

$$= 300\ \mu g/m^3 * \left[\frac{0.5\ hour}{8\ hours}\right]^{0.2}$$

$$= 300\ \mu g/m^3 * 0.574$$

$$= 172.3\ \mu g/m^3$$

where x = Concentration of the chemical under the new averaging time
x_t= Concentration of the chemical under the current averaging time
t_k = The averaging time associated with the current concentration
t_x = The averaging time one wishes to convert the concentration to
p = A constant, = 0.2

Thus Holma's concentration would be approximately 172 µg/m^3 on an 8 hour average. Employing the same calculations, the EPA estimate of buffering capacity would be approximately 747 µg/m^3 on an 8 hour average. If one is willing to accept the assumptions made here and the uncertainty inherent in this methodological approach, it appears that the current ITSL, based on protection from irritation, should theoretically be protective of carcinogenic effects as well. Taking into consideration the additional

[10] This conversion equation was provided by AQD's Modeling and Meteorology Unit, and the averaging time conversions it provides are based solely on meteorological considerations. Whether an 8 hour human exposure to a lower concentration would have a biological impact in the airways comparable to a thirty minute exposure at the higher concentration is not clear based on the data available.

buffering capacity which could be contributed by ammonia in the airways, these concentrations may be conservative.

It is also of interest to compare Holma's threshold concentration with the average worker exposure concentration from the cohort studies of steel pickling workers (Steenland and Beaumont, 1989; Steenland et al., 1988; Beaumont et al., 1987). As was stated earlier, the results of those studies suggested that average worker H_2SO_4 exposure concentrations (0.19 mg/m^3) that were below the TLV concentration were associated with increased risks of respiratory cancers. Converted to equivalent units[11], that concentration (190 µg/m^3) is still higher than Holma's threshold value (172 µg/m^3) which should theoretically protect against pH-induced respiratory cancers. It is, on the other hand, considerably lower than the EPA threshold concentration (747 µg/m^3). Caution in interpretation is warranted, however. Given the substantial uncertainty associated with Beaumont's exposure assessment (and indeed with this entire alternative cancer risk assessment methodology) it may simply not be realistic or meaningful to make direct comparisons between these concentrations.

In conclusion then, while the available epidemiological data appear adequate to support the qualitative conclusion that sulfuric acid exposures are carcinogenic to humans under some conditions, it cannot be overemphasized that the data available for quantitative risk assessment are extremely limited and probably inadequate to derive an Initial Risk Screening Level (IRSL). Moreover, it should also be emphasized that the buffering capacity-based approach outlined here entails a substantial amount of uncertainty, and is employed solely for lack of sufficient data and a viable alternative method. However, considering all of the data limitations and uncertainties discussed, it appears that the current ITSL of 10 µg/m^3 based on an 8 hour averaging time may reasonably be expected to afford protection from the risk of upper respiratory cancers due to exposure to sulfuric acid mists. Consequently, the **ITSLs for SO_3 and oleum assume ITSLs identical to that for sulfuric acid, 10 µg/m^3 based on an 8 hour averaging time.**

REFERENCES

ACGIH (1991) . Sulfuric Acid (7664-93-9). *In:* Documentation of Threshold Limit Values and Biological Exposure Indices, American Conference of Governmental Industrial Hygienists, Cincinnati, pp. 1461-1463.

Air Pollution Control Association (1970). Recognition of Aix Pollution Injury to Vegetation: A Pictorial Atlas (Jacobson, J.S. and Hill, A.C., Eds.). Air Pollution Control Association, Pittsburgh, PA.

Amdur, M.O., Silverman, L. and Drinker, P. (1952). Inhalation of sulfuric acid mist by human subjects. *AMA Arch Indust Hyg Occup Med* **6**(4) :305-313.

Aviado, D.M. and Salem, H. (1968). Acute effects of air pollutants on the lungs. *Arch Environ Health* **16**(6) :903-907

[11] Beaumont et al. do not list an averaging time associated with their estimated average exposure concentration. It is assumed here that this concentration represents a TWA over a workday, and so the concentration will be considered as representing an 8 hour average.

Beaumont, J.J., Leveton, J., Knox, K., Bloom, T. McQuiston, T., Young, M., Goldsmith, R., Steenland N.K., Brown, D.P. and Halperin, W.E. (1987). Lung cancer mortality in workers exposed to sulfuric acid mist and other acid mists. *J Nat Cancer Instit USA* **79**(5) :911-921.

Beliles, R.P. and Beliles, ELM. (1994). 8. Sulfur oxides. *In:* Patty's Industrial Hygiene and Toxicology, 4th Ed. (Clayton, G.D and Clayton F. E., Eds.), Volume I, Chapter Fourteen: Phosphorus, Selenium, Tellurium and Sulfur. John Wiley and Sons, Inc., New York, pp. 807-811.

Burch, J.D., Howe, G.R., Miller, A.B. and Semenciw, R. (1981). Tobacco, alcohol, asbestos, and nickel in the etiology of cancer of the larynx. *J Nat Cancer Instit USA* **67**:1219-1224.

Cameron, G.R. (1954). Toxicity of chlorsulphonic acid-sulphur trioxide mixture smoke clouds. *J Pathol Bacteriol* **68**(1) :197-204.

Coggon, D., Pannett, B. and Wield, G. (1996). Upper aerodigestive cancer in battery manufacturers and steel workers exposed to mineral acid mists. *Occup Environ Med* **53**(7): 445-449

EPA (1989). An Acid Aerosols Issue Paper: Health Effects and Aerometrics. Office of Health and Environmental Assessment, U.S. Environmental Protection Agency, Washington, DC(Document # EPA-600/8-88005F) [cited in IARC, 1992b] .

EPA (1978). Diagnosing Vegetation Injury Caused By Air Pollution (Lacasse, N.L. and Treshow, M., Eds). Prepared by Applied Science Associates, Inc., Valencia, PA, for Air Pollution Training Institute, Control Programs Development Division, Office of Air Quality Planning and Standards, Office of Air and Waste Management, U.S. Environmental Protection Agency, Research Triangle Park, NC. Document # EPA-450/3-78-005 (2/1978).

Grint, G. and Purdy, G. (1990). Sulphur trioxide and oleum hazard assessment. *J Loss Prey Process Ind* **3**(1): 177-184.

Hagmar, L., Bellander, T., .Andersson, C., Lindén, K., Attewell, R. and Möller, T. (1991). Cancer morbidity in nitrate fertilizer workers. *Int Arch Occup Environ Health* 63:63-67.

Hatch, G.E. (1992). Comparative biochemistry of airway lining fluid. *In*: Treatise Pulmonary Toxicology, Vol. I: Comparative Biology of the Normal Lung (Parent, R.A., Ed.), Sec. IV: Comparative Defense Capabilities of the Respiratory Tract (Schlesinger, R.B., Sect. Ed.), pp. 617-632. CRC Press, Boca Raton, FL, 830 pp.

Hawley, G.G. (1981). The Condensed Chemical Dictionary. Tenth Ed. Van Nostrand Reinhold Company, New York, p. 347.

Hofmann-Sievert, R. and Castleman, A.W., Jr. (1984). Reaction of sulfur trioxide with water clusters and the formation of sulfuric acid. *J Phys Chem* **88**:3329-.

Holma, B. (1989). Effects of inhaled acids on airway mucus and its consequences for health. *Environ Health Persp* **79**:109-113.

Holma, B. (1985). Influence of buffer capacity and pH-dependent rheological properties of respiratory mucus on health effects due to acidic pollution. *Sci Tot Environ* **41**:101-123.

Hueper (1966) . Occupational and environmental cancers of the respiratory system. *Recent Results Cancer Res* **3**:105-107, 183.

IARC (1992a). Meeting of the IARC working group on the evaluation of carcinogenic risks to humans from occupational exposures to mists and vapors from strong inorganic acids and other industrial chemicals. *Scan J Work Environ Health* **18**(5): 329-332.

IARC (1992b). *Occupational Exposures to Mists and Vapours from Strong Inorganic Acids; and Other Industrial Chemicals.* Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans, Vol. 54, pp.41-130. International Agency for Research on Cancer, Lyon.

Jones, W. and Gamble, J. (1984). Epidemiological-environmental study of lead acid battery workers. I. Environmental study. *Environ Res* **35**:1-10.

Keesee, R.G., Hofmann-Sievert, R. and Castleman, A.W., Jr. (1986). The interaction of sulfur trioxide with water clusters. *In*: Chemistry 0f Multiphase Atmospheric Systems. NATO Advanced Science Institute Series, Series G: Ecological Sciences, Vol. 6. (Jaeschke, W., Ed.). Springer-Verlag, Berlin, pp. 501-506.

La Rosa, M., Greco, D., Crea, G.F., Di Paola, M., Schilliro, G. and Bagnato, G.F. (1987). Cell mediated immunity in children exposed to chemical pollution. *Ann Allergy* **58**(4): 307 (Abstract).

Larson, T.V., Covert, 0.5., Frank, R. and Charlson, R.J. (1977). Ammonia in the human airways: Neutralization of inspired acid sulfate aerosols. *Science* **197**:161-163.

Lynch, J., Ranis, N.M., Bird, M.0., Murray, K.J. and Walsh, J.P. (1979). An association of upper respiratory cancer with exposure to diethyl sulfate. *J Occup Med* **21**:333-341.

Merck (1983). The Merck Index: An Encyclopedia of Chemicals. Drugs and Biologicals, (Windholz, M., Ed.) Tenth Ed. Merck and Company, Rahway, N.J., p. 1289.

Pattle, R.E. and Cullumbine, H. (1956). Toxicity of some atmospheric pollutants. *Brit Med J* **2**:913-916 [cited in Aviado and Salem, 1968].

Rencher, A.C., Carter, M.W. and McKee, D.W. (1977). A retrospective epidemiological study of mortality at a large Western copper smelter. *J Occup Med* **19**:754-758.

Rogacheva, V.S. (1993). Effect of contaminated air on the course of pregnancy and the health of the fetus and the newborn. *Reprod Toxicol* **7**(5) :515-516.

Rosenhall, L. and Stjernberg, N. (1982). Sulphur dioxide and bronchitis. *Eur J Respir Dis* **63**(118) :91-94.

Sim, V.M. and Pattle, R.E. (1957). Effect of possible smog irritants on human subjects. *J Amer Med Assoc* **165** (15): 1908-1913.

Soskolne, C.L., Jhangri, 0.5., Siemiatycki, J., Lakhani, K.R., Dewar, R., Burch, J.D., Howe, G.R. and Miller, A.B. (1992). Occupational exposure to sulfuric acid in southern Ontario, Canada, in association with laryngeal cancer. *Scan J Work Environ Health* **18**(4) :225-232.

Soskolne, C.L., Pagano, G., Cipollaro, M., Beaumont, J.J. and Giordano, G.G. (1989). Epidemiologic and toxicologic evidence for chronic health effects and the underlying biologic mechanisms involved in sub-lethal exposures to acidic pollutants. *Arch Environ Health* **44**(3): 180-191.

Soskolne, C.L., Zeighami, E.A., Hanis, N.M., Kupper, L.L., Herrmann, N., Amsel, J., P4ausner, J.S. and Stellman, J.M. (1984). Laryngeal cancer and occupational exposure to sulfuric acid. *Am J Epidemiol* **120**(3) :358-369.

Stayner, L.T., Meinhardt, T., Lemen, R., Bayliss, D., Herrick, R., Reeve, G.R., Smith, A.B. and Halperin, W. (1985) A retrospective cohort mortality study of a phosphate fertilizer production facility. *Arch Environ Health* **40**:133-138.

Steenland, K. and Beaumont, J. (1989). Further follow-up and adjustment for smoking in a study of lung cancer and acid mists. *Am J Indus Med* **16**:347-354.

Steenland, K., Schnorr, T., Beaumont, J., Halperin, W. and Bloom, T. (1988). Incidence of laryngeal cancer and exposure to acid mists. *Brit J Indus Med* **45** :766-776.

Stueven, H. (1992). A hazardous material episode: Sulfur trioxide. *Vet Hum Toxicol* **34**(4): 357 (Abstract).

Stueven, H.A., Coogan, P. and Valley, V. (1992). A hazardous material episode: Sulfur trioxide. *Vet Hum Toxicol* **35**(1): 37-38.

Turner, D.B. (1970). Workbook at Atmospheric Dispersion Estimates. Air Resources Field Research Office, Office of Air Programs, Environmental Science Services Administration, U.S. Environmental Protection Agency, Research Triangle Park, NC.

Verschueren, K. (1983). Handbook of Environmental Data on Organic Chemicals, 2nd Ed. Van Nostrand Reinhold Company, New York, p. 526.

Weil, C.S., Smyth, H.G., Jr. and Male, T.W. (1952). Quest for a suspected industrial carcinogen. *AMA Arch Induct Hyg Occup Med* **5**:535-547.

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