Michigan Department of Natural Resources

Interoffice Communication

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To : Acetone File (CAS # 67-64-1)

From : Gary Butterfield

Subject : ITSL for Acetone

There is no RfC, from EPA, available for acetone. EPA does, however, have an RfD. A comparison of toxicity from oral and inhalation routes of exposure indicates a rather large difference (at least one order of magnitude) in the mg/kg dosage. This large difference places into question the appropriateness of basing the ITSL on an oral RfD. This difference is consistently found in acute, as well as, chronic exposures. In the case of acute exposures, the LD50 for acetone is about 10 g/kg while the LC50 of 132 g/m3 converts to 120 g/kg (by 132 g/m3 x 0.9 m3/kg for rats = 120 g/kg), one order of magnitude difference. Possible reasons for this large difference include : there is a difference in absorption that is dependent on exposure route; tissue distribution is affected by route of exposure; there is a 'bolus effect' from oral doses. (The bolus effect should not be as noticeable with drinking water studies as it is with gavage studies. However, available data indicates there is still a large difference in mg/kg dose between inhalation and drinking water studies.)

No available data (on absorption, metabolism, excretion, etc.) was located that could provide an adequate explanation for this difference. Some of the information looked at during an evaluation of acetone's absorption, distribution, metabolism and excretion included :

1) Acetone is readily absorbed via inhalation, ingestion and through the skin (Rowe & Wolf (1963), Krasavage et al (1982)). Estimates for respiratory retention vary between 45 and 80 %. Wigaeus et al (1981) determined human respiratory retention to be 45 %.

2) Acetone, a highly water soluble compound, is distributed to tissues according to their water content, Haggard et al (1944), Rowe & Wolf (1963), Krasavage et al (1982), Wigaeus et al (1982).

3) Acetone is an endogenous material with typical concentrations of 7 umol/L blood, Rowe & Wolf (1963), Krasavage et al (1982), Wigaeus et al (1982), Pezzagno et al (1986). For exogenous acetone, metabolism plays a more important role in acetone elimination when the dose is smaller. Large doses of acetone result in excretion of unmetabolized acetone, Haggard et al (1944). Rats and mice metabolize acetone via three glucogenic pathways to glucose and finally ATP and CO2, Price & Rittenberg (1950), Sakami (1950),

Mourkides et al (1959), Casazza et al (1984), Kosugi et al (1986). 4) Excretion of endogenous acetone results in typical concentrations of 20 umol of acetone/L urine. Excretion of acetone has been described to take place via the following routes : exhalation of unmetabolized acetone 40-70% of the absorbed dose, 15-30% excreted in urine, and 10% through the skin, Rowe & Wolf (1963).

Given the large, unexplained difference between oral and inhaled dose, it does not appear to be appropriate to utilize oral toxicity data for obtaining the ITSL. Attempts for identification of NOAEL from a good quality inhalation study lead to the review of several animal and human studies. Of the animal studies, EPA (1988) discusses the study by Bruckner and Peterson (1981a), where rats showed narcotic signs after being exposed for a single 3 hr period to acetone at 19000 ppm. A three hour LC50 of 55700 ppm was identified in this study. In an eight week study, exposure for 3 hour per day, with a two week recovery period for a total of 10 weeks (Bruckner and Peterson (1981b)), male rats exposed to 19000 ppm had significantly decreased organ weights (kidney and brain) and insignificantly decreased body weight at the end of eight weeks. Organ weights returned to normal within two weeks of cessation of exposure. No histological changes of liver, heart, brain or kidneys was observed. There was no alteration of liver triglycerides, or signs of liver lipid vacuolation. In their review, EPA (1988) has pointed out some problems associated with the use of this study in developing an RfC. Other pharmacokinetics studies indicate that a 3 hour exposure is of inadequate length to achieve a body burden plateau (Wigaeus et al 1981), and that acetone is rapidly cleared from the blood. Therefore extrapolation to continuous exposure isn't possible from the short three hour per day study. Additional inhalation studies found exposures at 150 ppm to rats (Geller et al 1979a) or 500 ppm to baboons (Geller et al 1979b) caused some behavioral effects.

Human exposure data was found in the documentation provided by the ACGIH TLV and OSHA's PEL. Both list an occupational exposure limit for acetone as 750 ppm (or 1780 mg/m3). The documentation for OSHA's 1989 PEL (54FR2446-2448) has a lengthy discussion of the various articles on human effects from acetone exposure, either in controlled experiments or industrial situations. OSHA concluded that an eight hour TWA of 750 ppm for the PEL was appropriate. However, some authors have reported effects on humans at concentrations below the TLV or PEL. Dick et al (1989) exposed 137 volunteers to 250 ppm acetone for 4 hours while testing neurobehavioral performance via six tests before, during and after the exposure. Acetone exposure significantly changed responses to two of the tests (auditory tone discrimination and the profile of mood stages) and borderline non-significant changes in two other tests (visual vigilance, $p<0.06$ and postural sway, $p<0.09$). In addition, reports written in foreign journals (not available for review but cited in other articles) have provided evidence of lower exposures having effects. Matsushita et al (1979) found 3 hour exposure to 500 and 1000 ppm, but not less, initially caused

respiratory tract irritation, tolerance was observed to develop after 90 minutes of exposure. Nakaaki (1974), also reported irritation being observed at concentrations of 450 ppm or greater. Nelson et al (1943) exposed a group of volunteers to acetone vapors for a short period and asked the volunteers to estimate which concentration they would be satisfied being exposed to for 8 hours. The highest concentration agreed upon by the volunteers was 200 ppm.

NIOSH has established an REL of 250 ppm for acetone. It would be more appropriate to base the ITSL on NIOSH's REL of 250 ppm because of the reported irritant and neurobehavioral effects observed at doses lower than the TLV and PEL. Additionally, Rule 232(c) states that the lower value of the NIOSH REL and the ACGIH TLV should be used to determine the ITSL. The ITSL can then be calculated as follows.

NIOSH REL is 250 ppm (or 590 mg/m3)
ITSL = 0.01 x 590 mg/m3 = 5.9 mg/m3 with 8 hr averaging time.

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