MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

November 7, 1996

TO: File for Isobutanol (CAS # 78-83-1)

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

SUBJECT: Initial Threshold Screening Level (ITSL) for isobutanol

The initial threshold screening level for isobutanol is 1500 $\mu g/m^3$ 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 24, 1996), CESARS, Patty's Industrial Hygiene and Toxicology, Merck Index and Condensed Chemical Dictionary.

Isobutanol (IBOH) is a colorless, flammable liquid with a sweet, musty odor used in the manufacture of fruit flavoring and fragrance essences, as a latent solvent in paints and lacquers, and in varnish removers (Lington and Bevan, 1994, Merck, 1983; Verschueren, 1983; Hawley, 1981). It is also used as an intermediate in organic synthesis in the pharmaceutical and pesticide industries and for amino coating resins, and in fluorometric determinations and liquid chromatography. IBOH occurs naturally in a variety of fruits, and is added to foods and beverages as a flavoring agent (IPCS, 1987).

With respect to acute toxicity, IBOH is noted to be irritating to the skin and mucous membranes but only mildly so at low concentrations (Merck, 1983; Hawley, 1981). It is, however, severely irritating to the eyes (Lington and Bevan, 1994; IPCS, 1987). Acute oral LD_{50}s have been reported for rats (2.46 and 3.1 g/kg), mice (3.5 g/kg) and rabbits (3.4 g/kg); the dermal LD_{50} in rabbits is also listed as 3.4 g/kg (Lington and Bevan, 1994). Lethal inhalation concentrations were summarized by IPCS (1987) for rats (8000 mg/m^3 [for a four hour exposure]), guinea pigs (19,900 mg/m^3), mice (15,500 mg/m^3) and rabbits (26,250 mg/m^3). Smyth *et al.* (1954) recorded no mortality in rats exposed to atmospheres saturated with IBOH vapor ($\cong$ 49,248 mg/m^3) for two hours, but when exposure durations were extended to four hours, 2 of 6 rats exposed to half that concentration (24,624 mg/m^3) failed to survive. Signs of acute IBOH toxicity consist primarily of narcosis and alcoholic intoxication; these are consistent with the neurotoxicity of alcohols as a class (Shoemaker, 1981). Hillbom *et al.* (1974), studying the comparative toxicity of IBOH, ethanol and *n*-propanol, found no cases of inflammatory liver disease in four month old male Wistar rats given 1 M solutions of IBOH as their sole source of drinking fluid for a period of 4 months. IPCS (1987) has concluded that "on the basis of

available data, the Task Group considered it unlikely that isobutanol would pose a serious acute health risk to the general population under normal exposure conditions".

The metabolism and disposition of IBOH appear to have received substantial attention. It can be readily absorbed *via* the lungs and gastrointestinal tract (and in laboratory animals, the skin), and is rapidly oxidized following systemic absorption to isobutyraldehyde and then to isobutyric acid *via* the alcohol dehydrogenase pathway. Isobutyric acid is catalyzed to a succinate by reaction with coenzyme A, and subsequently enters the Krebs cycle (Lington and Bevan, 1994). Small amounts (< 0.5% of the dose) are excreted *via* the urine unchanged, or as the glucuronide, (IPCS, 1987). Shoemaker (1981) has hypothesized that the alcohols as a class exert at least their neurotoxic effects by decreasing the viscosity of biological membranes, resulting in alteration of transmitter-mediated interactions between neurons in the CNS. That author cites the close correlation between the neurotoxic potency of various alcohols and their lipid/water partition coefficients as the basis for the hypothesis. A brief review of the toxic interaction of IBOH with *m*-xylene is given by Krishnan and Brodeur (1994). They reported that the two chemicals show inhibitory metabolic reactions, which can be "expected to result in supraadditivity in humans". This conclusion appears to be based in part on the finding that the presence of IBOH decreased the dermal absorption of *m*-xylene. Additional pharmacokinetic/metabolic literature found for IBOH include consideration of partition coefficients (Poulin and Krishnan, 1995*a*,*b*; Kaneko *et al.*, 1994; Paterson and Mackay, 1989), and cytochrome P450 metabolism (Aarstad *et al.*, 1985).

Although IBOH exposure has been reported to cause cancer in laboratory animals, carcinogenicity data are quite limited and have not been replicated. Gibel and coworkers (1975) exposed groups of 19 ten week old Wistar rats to twice weekly oral IBOH doses of 0.2 ml/kg body weight[1]. Twenty-five control rats received 1 ml 0.9% sodium chloride twice weekly orally. All rats were dosed until spontaneous death. No statistical analysis was presented. Average survival was 495 and 643 days in the exposed and control groups, respectively. Tumor incidences (malignant:benign/total in group) were 3:9/19 in the exposed rats and 0:3/25 in the controls. The malignant tumors present in the three exposed animals were proventriculus carcinomas, liver carcinomas and sarcomas, splenic sarcomas and myeloid leukaemia. Non-carcinogenic effects in the exposed were primarily hepatic, with the majority of animals exhibiting hepatic cell necrosis, steatosis, cirrhosis and/or fibrosis. Hyperplasia of the blood-forming tissues was reported in most of the exposed animals as well. While the authors attributed the cancers to IBOH exposure, IPCS (1987) stated that "because of methodological inadequacies and the manner of reporting the data, it was not possible to determine whether isobutanol should be regarded as an animal carcinogen. Thus it is not possible to extrapolate from this study to possible long-term effects in man". Only a single mutagenicity study was located in our searches (Hillscher *et al.*, 1969). That study demonstrated an increased rate of reverse mutation in *E. coli* CA274 when exposed to 25,000 ppm IBOH without metabolic activation.

[1] While the group was composed of both sexes, the proportional breakdown was not given.

This study was judged inadequate by IPCS as well. Thus, in light of the lack of adequate data, there is insufficient evidence to treat IBOH as a carcinogen for purposes of quantitative risk assessment.

The developmental toxicity of IBOH was studied by Klimisch and Hellwig (1995). They exposed groups of 25 female Wistar SPF rats (mean body weight = 216 g, 10-11 weeks of age at initiation of experiments) per exposure group to IBOH concentrations of 0 (clean air), 0.5, 2.5 and 10 mg/L (500,000, 2,500,000 and 10,000,000 $\mu g/m^3$, respectively) 6 hours/day over days 6-15 post-coitum (pc). In addition, groups of 15 female Himalayan rabbits (body weight range 2.5-2.7 kg, 24-29 weeks of age at initiation) per exposure group were exposed to the same concentrations over days 7-19 post-insemination. Exposure levels were established as a result of range-finding toxicity tests; purity of the IBOH was 99.8%. Both species were acclimatized for at least 5 days prior to mating/insemination; rats were observed up to day 20 pc and rabbits up to day 29 pi. Animals were exposed in individual cages in exposure chambers with hourly chamber gas concentrations analyzed by gas chromatography. While not being exposed, animals had free choice access to pelleted rations and tap water. All animals were observed daily for behavior and state of health. Rats were weighed on days 0, 3 and 6 and rabbits on days 0,3 and 7 and from then on at 3 day intervals until the end of their observation periods. Rats were killed on day 20 pc by cervical dislocation and rabbits on day 29 pi by intravenous pentobarbitone. All animals were necropsied and gross pathology assessed. Uterus and ovaries were removed for the following determinations: intact uterine weight, number of *corpora lutea* (CL), number of implants (divided into live fetuses, early and late resorptions and dead fetuses). Fetuses were weighed, sexed and examined for external malformations. Soft tissue examinations were performed on fresh specimens of all the rabbit fetuses and on about half of the rat fetuses after Bouin's fixation. All rabbit fetuses and half of the rat fetuses were fixed in ethanol and stained for skeletal examinations. Results were analyzed *via* Dunnett's test (weight data, number of CLs, implants resorptions, live fetuses and implantation losses) and *via* Fisher's Exact Test (conception rate, maternal mortality and all fetal findings).

Mean (± S.D.) IBOH chamber concentrations in the three exposed groups were 0.49 (0.012), 2.5 (0.084) and 10.1 (0.33) mg/L for the rats and 0.5 (0.01), 2.51 (0.091) and 10.0 (0.37) mg/L for the rabbits. IBOH exposure did not have any significant adverse effects on maternal weights, uterine weights or behavior, and produced no clinical signs at any exposure level in either species. One rabbit exposed at 0.5 mg/L was killed on day 21 pi due to abortion, and one in the 2.5 mg/L group was found dead on day 24 pi; neither outcome was considered to be a result of exposure. Necropsy findings did not reveal any lesions attributable to IBOH exposure in either species at any exposure level. Similarly, there was little evidence, statistically significant or otherwise, that IBOH exposure had an adverse effect on fetal development at any exposure level in either species. The single statistically significant difference of note was an highly significant ($p < 0.01$) increase in the fetal incidence of a single soft tissue variation (traces of interventricular foramen) in the rabbits exposed to 10 mg/L (10,000,000 $\mu g/m^3$). The remaining statistically significant differences from control values seemed to suggest a protective

effect of IBOH exposure, rather than a detrimental one[2]. Based on these results, the authors determined a NOAEL for maternal toxicity of IBOH of 2.5 mg/L (2,500,000 $\mu g/m^3$) in the rabbit and 10 mg/L (10,000,000 $\mu g/m^3$) in the rat. They also concluded that "compound-induced embryotoxic or fetotoxic effects could not be detected in either species up to and including the highest concentration of 10 mg/L MEP [2-methyl-1-propanol, IBOH]. Furthermore, teratogenic effects were also not induced by these substances". Thus, there is no evidence found in our searches to suggest that developmental effects should be considered a critical endpoint upon which to base human health risk assessment.

As a result of IBOH's widespread use a coating solvent, there is considerable literature on human exposures. However, the available studies generally considered IBOH only as one component of a mixture of solvents rather than as a solitary exposure. Consequently, it is not possible to dissect any effects that are due solely to IBOH exposure, limiting the usefulness of the available epidemiologic literature for purposes of quantitative risk assessment. Nonetheless, synopses of the studies found in our searches are included here for reference, and in the interest of completeness. A method for estimating the health-related hazard resulting from exposure to a mixture of organic solvents (one of which was IBOH) has been reported by Scheffers *et al.* (1985). Williamson and Winder (1993) gave an interim report of an on-going prospective cohort study of men enrolled as apprentices in Australian Technical Colleges. Neurobehavioral performance testing, a comprehensive demographic questionnaire, medical examination and biological sampling were performed to assess the neurotoxicological effects of exposure to various solvents over a three year period. Although no decrement in neurobehavioral function was noted in comparing more highly exposed apprentice spray painters with less exposed apprentice electricians, massive losses to follow-up (70% of electricians and 56% of painters from Year 1 to Year 3) from what was a small sample size at the outset (total n = 100), and a short duration of exposure (3 years) seem likely to have severely reduced the power of the study, possibly accounting for the negative findings. Neurobehavioral tests and questionnaires were also used in a case-control design to assess effects of exposure to multiple solvents in 110 paintmakers and 110 age-matched controls (Spurgeon *et al.*, 1994). Exposure concentrations, including those of IBOH, were generally below occupational exposure limits (OELs). The study did not find significant detrimental effects on cognitive function or mental health in the exposed; actually, exposed individuals generally scored higher in the neurobehavioral assessments than did the less exposed controls. Hepatic effects of solvent exposure were studied *via* enzyme concentrations in group of 47 paint industry workers matched to controls on age, sex and place of residence (Lundberg and Hakansson, 1985). Alanine transaminase (ALT), aspartate transaminase (AST), ornithine carbamyl transferase and γ-glutamyl transferase (γGT) concentrations were not significantly different between the two groups after controlling for the effects of alcohol and drug consumption and

[2] For example, a significant *decrease* in the total number of retardations and % post-implantation loss was noted among rats exposed at the highest dose level compared to controls. Further, IBOH exposed rats had lower incidences of some soft tissue variations (dilated renal pelvises, total variations) than did the control rats.

history of liver disease, even among the most highly exposed workers; analysis was by Wilcoxon Rank Sum tests and multiple regression analysis. The median of breathing zone measurements of IBOH was 4 mg/m^3 (range 1-1040 mg/m^3). Asthmatic symptoms that might be related to solvent exposure were the endpoints examined in a pair of Swedish studies, one in a population of lacquer workers in a woodworking factory (Alexandersson and Hedenstierna, 1988), and one in a residential population (Norbaeck *et al.*, 1995). In the former, 38 exposed workers and 18 controls were interviewed for subjective respiratory symptoms and assessed *via* spirometry, N_2 washout and blood concentrations of total IgE and IgG. Breathing zone concentrations of formaldehyde, *n*-butanol, IBOH, butyl acetate, ethanol, ethyl acetate, toluene and xylene were measured. The mean IBOH concentration was 10 mg/m^3 as an 8 hour average (n = 132). The authors found significant (*via* Student's t) increases in the incidence of eye and nose/throat work-related symptoms, and decreases in Forced Vital Capacity (FVC) and Forced Expiratory Volume in 1 second ($FEV_{1.0}$) among the exposed, but these were attributed to exposure to formaldehyde rather than the other solvents studied. The second study investigated 88 subjects aged 20-45 and solvent exposures they experienced in their dwellings. Volatile organic compounds (VOCs) and formaldehyde were measured *via* gas chromatography (GC) in the subjects' living and bedroooms. Structured interviews, spirometry, PEF, methacholine challenge, skin prick tests and total serum IgE were used to assess respiratory and immunologic effects. The authors reported a significant ($p < 0.05$ *via* Mann-Whitney U) relation between the presence of nocturnal breathlessness/chest tightness and concentrations of total butanols (Σ of *n*- and iso- butanols). Mean butanol (range) exposure for those complaining of this symptom were 18.5 µg/m^3 (1-90 µg/m^3) vs. 10 µg/m^3 (1-43 µg/m^3) in those not reporting it. It should be noted that there was a significant association for every VOC measured with the presence of at least one symptom. Norbaeck and co-workers then calculated Odds Ratios (ORs) for the presence of symptoms in more exposed vs. less exposed subjects for those chemicals with the most highly significant relationships (of which total butanols was not one). The highest ORs were associated with carbon dioxide and formaldehyde exposures, and the authors attributed most of the observed effects to them.

In a study utilizing male Swiss OF_1 mice, De Ceaurriz and coworkers (1981) used an animal model for sensory irritation to validate the protectiveness of the OELs for IBOH[3]. Using body plethysmographs, groups of six mice were exposed in chambers to room air for 10 minutes (to establish control respiratory rates) and then to one of at least four different concentrations of IBOH for about 5 minutes. During the exposure, the respiratory rates of the animals decreased, and the maximum percent decrease from the control values was calculated. This maximum percent decrease was then plotted against the logarithm of the exposure concentration, and curves were fitted to these data by linear regression. From this relation, the concentration of IBOH associated with a 50%

[3] The basis for the work was the previously reported finding of a reflex pause in the expiratory phase of respiration, resulting in a marked decrease in respiratory rate in animals on exposure to irritants of the upper respiratory tract (Alarie, 1966). That same author went on to verify that a qualitative correlation existed between this reflex decrease in mice and the complaints of eye, nose and throat irritation reported by exposed human subjects (Kane *et al.*, 1979; Alarie, 1973).

decrease in respiratory rate (RD_{50}) was calculated. This was then compared with the work of Kane *et al.* (1979) which demonstrated that the American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Value (TLV) should fall between 0.1 and 0.01 of the RD_{50} [4]. In the case of IBOH, the resulting values for the RD_{50}, $0.1 \times RD_{50}$ and $0.01 \times RD_{50}$ in ppm were 1818, 182 and 18, respectively. Comparing these boundaries with the TLV concentration of 50 ppm (152 mg/m^3), the authors validated that the TLV fell within the intended limits, and that it was considerably closer to the concentration associated with minimal or no human effects than to the concentration associated with an uncomfortable but tolerable level of sensory irritation.

Both the ACGIH TLV and the National Institute for Occupational Safety and Health (NIOSH) have established OELs for IBOH (NIOSH, 1994; ACGIH, 1992). The ACGIH TLV and the NIOSH Recommended Exposure Limit (REL) take on the identical value of 50 ppm ($\cong$ 152 mg/m^3), although neither concentration is well documented. The TLV is noted to have been set at its current value "based on the slightly greater acute toxic potential of isobutyl alcohol versus *n*-butanol" (ACGIH, 1992). ACGIH's basis for this conclusion appears to have been the 4 hour inhalation studies of Smyth *et al.* in rats (Smyth *et al.*, 1954). Thus, the TLV for IBOH is set at the same numeric value as that for *n*-butanol (*n*-BOH) though the TLV for *n*-BOH itself does not appear to be based on acute animal toxicity data. Rather, the TLV for n-butanol appears based on avoidance of sensory irritation, and on hearing/vestibular impairment in occupationally exposed humans (ACGIH, 1991). Conversely, the TLV documentation for IBOH does not mention sensory irritation in humans as even a partial basis for that TLV. Adding to the uncertainty, at the time of this writing, the TLV for *n*-BOH appears on ACGIH's Notice of Intended Changes (ACGIH, 1996). How a change in the TLV for *n*-BOH might effect the TLV for IBOH remains to be seen. With respect to the NIOSH REL, the critical health hazard symptoms and target organs listed for IBOH involve irritation of the eyes, skin and respiratory system, yet no documentation is provided. IPCS (1987) summarizes two case series (Seitz, 1972; Büsing, 1952) of occupational exposures to mixtures of IBOH/*n*-BOH and IBOH/butyl acetate, one of which reported eye irritation as an effect (Büsing, 1952). Though exposures were characterized as "excessive", no quantification was reported. In summary then, though the OELs appear to be loosely based on the avoidance of sensory irritation, and there is evidence from animal models to support that IBOH does cause sensory irritation, definitive human data are apparently lacking.

IRIS (1992) lists a Reference Dose (RfD) for IBOH of 0.3 mg/kg-day, which appears to be based on an unpublished 13-week gavage study in rats (EPA/OTS, 1986). In that study, 30 rats/sex/group received daily oral IBOH doses of 0, 100, 316 or 1000 mg/kg-day. Of the endpoints measured, the only significant effects attributed to exposure were: 1) hypoactivity in all rats at the 1000 mg/kg-day level in the first week of the study (which markedly decreased by the fourth week and occurred only sporadically afterwards); 2) decreased body weight gain during the second week; 3)

[4] The value associated with 0.1 of the RD_{50} (the concentration responsible for an uncomfortable but tolerable level of irritation) was considered the highest permissible level for humans, and the value associated with 0.01 of the RD_{50} was considered a value with minimal or no effect on humans.

decreased serum potassium concentrations; and 4) a low incidence of ataxia which occurred throughout the study. All of these effects were present only in the high dose group. All other measured parameters (body weight changes, food consumption, ophthalmologic exams, clinical and biochemical parameters and gross and histopathology) were within normal limits. EPA has expressed medium confidence in the study and low confidence in the RfD. While CNS effects such as hypoactivity and ataxia appear to occur with both oral and inhalation exposures for those alcohols that have been studied in animals (Shoemaker, 1981), the limited animal data available suggest that sensory irritation may occur at lower concentrations than those associated with CNS effects and/or precede CNS effects at the same level of exposure (IPCS, 1987; De Ceaurriz *et al.*, 1981). Thus, while little good human data on the sensory irritation effects of isobutanol was available to us, data from animal models of sensory irritation are available to supplement the inadequately documented REL. This affords a degree of confidence in the choice of irritation as a critical effect for risk assessment of inhalation exposures to humans as well as animals. Moreover, given that sensory irritation appears to be a more sensitive endpoint (at least in animals) than the one on which the RfD is based, the validity of using of the oral RfD to derive a screening level to protect against inhalation exposures to IBOH appears open to question.

Derivation of the ITSL: In choosing data for screening level development, preference is generally given to human epidemiologic data or chronic laboratory animal studies which can be used to derive a Reference Concentration (RfC). Such data were not found in our searches. When adequate data for RfC calculation are not available, next preference is given to oral data for calculation of a Reference Dose (RfD) if available data do not indicate that extrapolation from the oral to the inhalation route of exposure is inappropriate. In the case of IBOH, eye and upper airway irritation is a critical effect exhibited following inhalation exposure in animal studies (De Ceaurriz *et al.*, 1981), and is the basis for OELs in humans (NIOSH, 1994; Kane *et al.*, 1979; Alarie, 1973), though definitive data on sensory irritation in humans was not found. This suggests the presence of portal-of-entry effects that may not be accurately accounted for by the use of oral data. So, while the available data are far from ideal, the use of the oral RfD as the basis for calculating a screening level for IBOH seems, on weight of evidence, to be less defensible than the use of data involving inhalation exposures.

The next most appropriate alternative is an ITSL based upon an OEL. Given the unavailability of other inhalation data of sufficient quality for derivation of an RfC, and the questionable appropriateness of the use of oral data as noted above, the NIOSH REL is used here for the calculation of an ITSL for IBOH.

Per Rule 232(1)(c), part 55, of Act 451:

$$\textbf{ITSL} = \text{OEL} \times \frac{1}{100} = 150\ \text{mg/m}^3 \times \frac{1}{100} = 1.5\ \text{mg/m}^3 \times \frac{1000\ \mu\text{g}}{1\ \text{mg}} = \mathbf{1500\ \mu g/m^3}$$

where the factor of 1/100 is a safety factor to account for: 1) differences in susceptibility between the healthy, adult worker population as compared to the general population which may include individuals or subpopulations

more sensitive[5] to the effects of exposure to IBOH and 2) the difference in exposure duration for the worker population as opposed to the general population. The factor is derived as follows:

$$\text{Safety factor} = \frac{40 \text{ hours}}{168 \text{ hours}} \times \frac{30 \text{ years}}{70 \text{ years}} \times \frac{1}{10} = \frac{1}{100}$$

The first term adjusts for the difference between a 40 hour work week and the total hours in a week; the second factor adjusts for the difference between an assumed working life of 30 years and an assumed total lifespan of 70 years; and the third factor is a standard ten-fold uncertainty factor to extrapolate from the healthy worker to sensitive individuals in the general population[5].

Consistent with 232(2)(a), since the REL used here is based on a time-weighted average, an **8 hour averaging** time applies.

As a final comment, IPCS (1987) has concluded that it was "unable to make an assessment of the long-term health risk of isobutanol for the general population". Consequently, this ITSL should be revisited if better quality (particularly human) data become available in the future, especially if ACGIH's reconsideration of the TLV for *n*-BOH leads to a revision of the OELs for IBOH.

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[5] Dermal vascular sensitivity to IBOH and a number of other alcohols was described by Wilkin and Fortner (1985). These authors note that some individuals of Asian descent may be especially sensitive to some effects of alcohols. In that study, IBOH provoked a positive cutaneous vasomotor response in 2 of 12 subjects challenged in patch tests.

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