MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

February 8, 2000

TO: File for light alkylate naphtha (CAS No. 64741-66-8)

FROM: Marco Bianchi, Toxics Unit, Air Quality Division

SUBJECT: Initial Threshold Screening Level

The Initial Threshold Screening Level (ITSL) for light alkylate naphtha (also known as branched octanes and Isoparaffinic HC solvent) is 138 microgram per cubic meter (ug/m^3) based on an annual averaging time.

The following references or databases were searched to identify data to determine the ITSL: Integrated Risk Information System-online, Health Effects Assessment Summary Table, National Toxicology Program Management Status Report-online, Registry of Toxic Effects of Chemical Substances, Environmental Protection Bureau (EPB)-Chemical Criteria Database, EPB library, Chemical Abstract Service-online, National Library of Medicine-online, International Agency for Research on Cancer-online, National Institute for Occupational Safety and Health Pocket Guide, and American Council of Governmental Industrial Hygienists Guide.

Light alkylate naphtha (LAN) is a petroleum distillate obtained from a combination of atmospheric distillation and alkylation processes. It is comprised of components with carbon numbers predominately in the C_7-C_{10} range with a boiling range of 90-160^{0}C. LAN is the starting material for isoparaffinic solvents. It is blended with other refinery streams to produce gasoline. It can comprise up to 20% of automobile gasoline, and typically comprises about 80% of aviation gasoline.

In acute studies sponsored by the American Petroleum Institute (API, 1986, 1987), LAN was classified as nontoxic to rats by ingestion (Lethal Dose 50 [LD_{50}] >7.0 grams per kilograms [g/kg]), and by inhalation (LD_{50} >5.0 milligrams per liter, rats). This compound was also slightly toxic by dermal application (LD_{50} >2.0 g/kg, rabbits), and slightly irritating to the skin and eyes of rabbits. Results from an *in vitro* mouse lymphoma assay (API, 1985a) and *in vivo* bone marrow cytogenetics assay in rats (API, 1985b) did not indicate that LAN was a mutagen. No tumorigenic activity was apparent from a chronic dermal carcinogenicity study in mice (API, 1989).

During the course of this literature search, a Toxic Substance Control Act (TSCA) 8(e) submittal was found that characterized the long-term toxicity of LAN. This TSCA 8(e) submittal was a subchronic rat inhalation study conducted by Bio/dynamics, Inc. for the Exxon Corporation. Additionally, two subchronic rat inhalation studies from the Petroleum Product Stewardship Council (PPSC) were found that also provided supporting toxicity data on LAN-distillates; referred to as LAND and LAND-2. (LAN is

predominately made up of C_7-C_{10} carbon units, while LAND-2 and LAND are comprised predominately of C_4-C_{10} and C_4-C_6 carbon units, respectively.) These PPSC studies investigated neurotoxicity and reproductive/developmental effects on Sprague-Dawley rats. In the neurotoxicity study, exposure to LAND-2 did not produce neurotoxicity as measured by motor activity, functional operational battery, or neuropathology assessments. The no-observed-effect-level for LAND-2 was the highest dose of 2220 parts per million (ppm) (8.1 grams per cubic meter [g/m^3]). Likewise, in the reproductive/developmental investigation LAND produced no clinical or histopathological changes to the F_0 and F_1 generation. Parental food consumption, body weights, absolute and relative organ weights, and reproductive indices were also not affected by the test compound. The no-observed-adverse-effect-level (NOAEL) for this compound was greater than 24.7 g/m^3 (analytical concentration).

In the TSCA 8(e) inhalation study by Exxon Corp., two groups of 35 male and 35 female Sprague-Dawley rats were exposed to a mean concentration of 0, 385, and 1180 ppm LAN; six hr/day, five days/wk for 12 weeks. Prior to testing, ten animals/sex were sacrificed to obtain baseline information on clinical chemistry, hematology, and lung, adrenal, liver, kidney tissue. Ten animals/sex/group were sacrificed after four and eight weeks of exposure and all remaining animals were sacrificed after 12 weeks of exposure. According to the investigators, several animals in all groups exhibited dry rales, and red and mucoid nasal discharge. The pathologist's evaluation revealed a moderate incidence of lung discoloration and randomly occurring chronic pneumonia for all groups. No treatment related mortality occurred during the study. The only in-life observation that occurred in a dose response pattern was yellow staining of the ano-genital fur, observed predominately in the high dose group. Although some hematocrit, hemaglobin and red cell values were significantly decreased, the investigators found that all values were within normal biological limits and thus could be the result of normal biological variability. All other hematology findings were unremarkable. Some clinical chemistry parameters were also significantly different in high dose animals, but these values were transient in nature, occurring at the four and eight-week sacrifices, but not the 12-week sacrifice. There was a significant decrease in mean serum glutamic pyruvate transaminase in high dose females, as well as a significant decrease in mean glucose levels in high dose males and females. The pathologist's report made no mention of adverse liver histology due to LAN exposure. The remaining clinical chemistry parameter that was elevated was mean blood urea nitrogen level. For this parameter, there was a statistical increase in low and high dose males and in low dose females, but again these effects were transient throughout the study. Analysis of absolute and relative organ/body weight ratios only showed an increase in both absolute and relative mean kidney weights in the low and high dose males at week 12 when compared to control values. Correlating this increase in male kidney weights was the pathologist's report stating that exposure to LAN revealed a moderate incidence of mild to moderate individual tubular injury in low and high dose males. This chronic inflammation appears to be related to the α2u-globulin-associated nephropathy, a condition occurring only in certain strains of male rats, whereby, hyaline droplets found in the kidney containing α2u-globulin leads to the production of renal necrosis and tumors. It is not considered an adverse effect from chemical exposure to LAN, because

this condition occurs only in certain strains of male rats and has no relevance to humans.

From the TSCA 8(e) investigation presented above, it appeared this 90-day study had the necessary data requirements to derive an Inhalation Reference Concentration. But there were data gaps that raised uncertainties. The study is of sufficient duration, examined a number of physical, histological and pathological parameters. But there were only two dose groups, and over half of the test animals were sacrificed at just over the halfway point of the 90-day study. Additionally, there is uncertainty regarding a NOAEL, since none was established for this study. Except for the α2u-globulin effect, a number of clinical and blood chemistry observations were subject to interpretation as to whether they were truly dose-related effects. Certain hematological values were statistically different from controls, as were certain blood chemistry values. The study investigators dismissed these effects as a result of normal biological variability because they occurred sporadically and transiently, and didn't follow a dose-response relationship. Some of these effects occurred after 12-weeks, but only in the low dose group. Other effects occurred at the four or eight-week sacrifice only. The greatest uncertainty was the possibility of animals being selected out of the study during the four and eight-week sacrifices that exhibited blood chemistry and hematological effects. How were these animals selected for mid-term sacrifice? Is this why no effects were seen in some of the animals at terminal sacrifice? In order to determine if this was the case, Exxon Corporation was contacted to provide the raw data for the study. However, due to confidentiality reasons, Exxon expressed regrets they could not provide the necessary information to resolve this problem. Therefore, it seems appropriate to establish a lowest-observed-adverse-effect-level (LOAEL) instead of a NOAEL for this compound due to uncertainty from blood chemistry and hematology parameters observed in the test animals. Since the blood chemistry and hematological effects didn't bring about major clinical or pathologic changes to the test animals, the high dose group of 1180 ppm (5502 milligrams per cubic meter [mg/m^3]) will be considered a LOAEL for deriving a screening level as per Rule 232(1)(d)*. This should provide a derived ITSL concentration that is protective of human health from acute and chronic exposures to LAN.

The ITSL was derived as follows:

LOAEL = 1180 ppm
Molecular Weight = 114 (as provided by Pharmacia Upjohn, Inc.)

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*If an initial threshold screening level cannot be determined under the provisions of subdivision (a), (b), or (c) of this subrule, then the initial threshold screening level may be determined from a seven-day, inhalation, NOAEL or LOAEL; where, an uncertainty factor with a value of one to ten will be used and determined on a case-by-case basis, considering type and severity of effect. Additionally, the ITSL may be determined on a case-by-case basis using NOAELs or LOAELs from repeated dose studies other than seven-day studies.

Conversion of ppm to mg/m^3

$$mg/m^3 = \frac{ppm \times Molecular\ Weight}{24.45}$$

$$mg/m^3 = \frac{1180\ ppm \times 114}{24.45} = 5502\ mg/m^3$$

LOAEL = 5502 mg/m^3
NOAEL to LOAEL uncertainty factor of 10
Uncertainty factor of 35 reduced to 10 because of 13 week (90 day) study

$$ITSL = \frac{LOAEL}{10 \times 10 \times 100} \times \frac{6}{24}$$

$$ITSL = \frac{5502\ mg/m^3}{10 \times 10 \times 100} \times \frac{6}{24} = 0.138\ mg/m^3$$

Conversion of mg/m^3 to ug/m^3

$$0.138\ mg/m^3 \times 1000 = 138\ ug/m^3$$

The ITSL for light alkylate naphtha = 138 μg/m^3 based on an annual averaging.

References:

1. Schreiner, E. et al. 1998. Toxicity Evaluation of petroleum blending streams: inhalation subchronic toxicity/neurotoxicity study of a light alkylate naphtha distillate in rats. Petroleum Products Stewardship Council, Washington DC. Journal of Toxicology and Environmental Health, Part A. 55:277-296.

2. Bui, Q. et al. 1998. Toxicity evaluation of petroleum blending streams: reproductive and developmental effects of a distillate from light alkylate naphtha. Petroleum Products Stewardship Council, Washington DC. Journal of Toxicology and Environmental Health, Part A. 53:121-133.

3. TSCA 8(e) Submittal. 1979. A 12-week inhalation toxicity study of MRD-78-26 in the rat. Project No. 78-7092B. Bio/dynamics. TSCA 8(e) new document I.D. 88-80000312 (old document I.D. 8EHQ-280-0312).

MB:SLB
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