MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

August 2, 1999

TO: File for Castor Oil (8001-79-4)

FROM: Dan O'Brien, Toxics Unit

SUBJECT: Initial Threshold Screening Level

The initial threshold screening level for castor oil is 50 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; EPA's Integrated Risk Information System (IRIS) and Health Effects Assessment Summary Tables (HEAST); American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Value (TLV) Booklet; National Institute for Occupational Safety and Health (NIOSH) Pocket Guide to Chemical Hazards and Registry of Toxic Effects of Chemical Substances (RTECS); National Toxicology Program (NTP) World Wide Website (WWW), MDEQ Library; International Agency for Research on Cancer (IARC) WWW; Chemical Abstract Service (CAS) On-line and National Library of Medicine (NLM) Toxline (1967–April 19, 1999), Chemical Evaluation Search And Retrieval System (CESARS), Handbook of Environmental Data on Organic Chemicals, Patty's Industrial Hygiene and Toxicology, Merck Index and the Condensed Chemical Dictionary.

Castor oil is a pale yellow viscous oil derived from the seeds of *Ricinus communis*, the castor bean (Hawley, 1981). It has been described as tasting "slightly acrid, with a decidedly nauseating aftertaste" (Merck, 1983). Its principal therapeutic use in medical applications is as a cathartic, but it has numerous commercial uses, including as a plasticizer in lacquers and nitrocellulose; in polyurethane coatings, elastomers and adhesives; in fatty acids, surface-active agents, hydraulic fluids, pharmaceuticals, electrical insulating compounds and industrial lubricants. It is also used as a rubber preservative and mold lubricant, as a constituent of embalming fluids, in soap manufacture, as an emollient in cosmetics, in dyeing, in duplicating and stencil inks, and as a release and anti-sticking agent in hard candy manufacture (Merck, 1983; Hawley, 1981).

Toxicological data for castor oil are sparse. Although no specific acute toxicity studies for castor oil were located in the course of our searches, an abstract

located *via* NLM Toxline search notes that its acute oral toxicity was low (BIBRA working group, 1990). The same abstract also notes that ingestion of high doses of castor oil in humans "has resulted in vomiting, nausea, colic and, in one individual, coma." With respect to systemic toxicity in humans, Steingrub and colleagues (1988) have reported a case of amniotic fluid embolism causing a cardiorespiratory arrest associated temporally with ingestion of castor oil. Castor oil is considered minimally toxic when administered orally to humans; the estimated lethal oral dose is 1-2 pints (473-946 ml) of undiluted oil (Gosselin *et al.*, 1976). Systemic hypersensitivity reactions such as angioedema, rhinitis and asthma have been reported in factory workers involved in the extraction of castor oil or its ingestion (Irwin, 1992).

The only major laboratory animal toxicological study found was a thirteen-week feed study conducted by NTP (Irwin, 1992). In that study, groups of 10 rats and 10 mice per sex were randomized by weight into dose groups where they received castor oil at rates of 0, 0.62%, 1.25%, 2.5%, 5% or 10% incorporated into their feed. These diets, as well as water, were available *ad libitum.* Ten additional rats/sex were included at each dose level for evaluation of non-fasting hematology[1] and serology[2]. Blood was collected from these animals on days 5 and 21. Blood samples for hematology and serology were also collected from core-study rats at termination of the study; blood analyses were not performed on the mice. At termination of the study, all animals were euthanized with CO_2 and subjected to gross necropsy. Complete histopathological exams on a battery of 44 separate tissues were performed on rats and mice from the control and high dose groups; livers in male rats were examined in all other dose groups. All gross lesions from all animals regardless species, sex or dose were examined histologically. Body and organ weights[3] were also determined. To screen for potential reproductive toxicity, sperm motility and morphology were evaluated at necropsy, and vaginal cytology was evaluated on core study animals during the week just preceding necropsy, following collection by daily saline vaginal lavage for the twelve days prior to sacrifice. The statistical significance of differences among groups within sex were made by one-way analysis of variance (ANOVA), followed by Dunnett's test (where pairwise tests were indicated); a $p<0.05$ was considered significant.

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[1]Red blood cell counts and morphology, hematocrit, hemoglobin concentration, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, absolute and differential white blood cell counts, reticulocyte and platelet counts.
[2]Alkaline phosphatase, albumin, blood urea nitrogen, creatinine, alanine aminotransferase, total bile acids, sorbitol dehydrogenase, total protein and creatine kinase.
[3]Liver, right kidney, right testes, heart, thymus, and lung.

There was no significant adverse effect of castor oil ingestion on survival rates or body weights at any of the doses tested in either sex of either species. The only statistically significant changes in hematological parameters in the rats were decreased mean corpuscular volume in the high dose males and decreased reticulocytes in the 0.62% and 10% females. Neither of these was thought to be biologically significant. A dose-related increase in serum alkaline phosphatase was noted in rats of both sexes at all three sampling dates (Days 5, 21 and at termination). Total bile acids in males were elevated at the first two sampling dates in the 5% and 10% dose levels, but not at termination. Other serological changes were judged to be minor and appeared unrelated to castor oil exposure. Absolute liver weights were significantly increased in male rats receiving the 10% dose, and in male and female mice receiving the 5% and 10% doses; absolute kidney weights were significantly increased in female mice at the two highest dose groups as well. However, no associated morphological lesions were found, nor were there any exposure-related morphological changes in any organ examined in either sex of either species. A slight (7%) decrease in epididymal weights in rats was reported in the middle and high dose groups, but the decrease was not dose related. There were no other exposure-related reproductive effects in either sex of either species at any of the tested dose levels.

In the discussion and conclusions of the study, it was noted that the increased liver weights observed were not unexpected, and would be consistent with the elevated metabolic activity associated with increased lipid absorption (castor oil is composed of triacylglycerols), rather than a toxic response. This explanation is also consistent with the serological findings of increased alkaline phosphatase and bile acids, since these enzymes are both involved in absorption and metabolism of lipids from the gut, and serum concentrations are normally increased in association with ingestion of a lipid-rich diet. In summary, it was concluded that under conditions of the study, administration of castor oil in the diet of rats and mice for thirteen weeks at doses as high as 5835 mg/kg-day (rats) or 16,786 mg/kg-day (mice) was not associated with toxicity to any specific organ, organ system, or tissue. These doses can be considered No Observed Adverse Effect Levels (NOAELs) in each species; no threshold for toxicity was found by this study. The NTP Peer Review Panel accepted the study report as written with no comments other than those concerning editorial matters.

Other toxicity data suggest that castor oil has little potential for mutagenicity, having been found negative for mutation induction in *Salmonella typhimurium*, negative for induction of micronuclei in the peripheral blood erythrocytes of mice, and negative for induction of sister chromatid exchanges or chromosomal aberrations in Chinese hamster ovary cells (NTP, 1999; Zeiger *et al.*, 1988;

BIBRA working group, 1990). With respect to eye and skin irritation, RTECS (1999) cites results of standard Draize assays showing only mild irritation to the skin of humans, rats, rabbits and guinea pigs, and to the eyes of rabbits. However, other data suggest that contact dermatitis and skin hypersensitivity reactions have occurred with exposures to products containing castor oil, or in association with its ingestion (Irwin, 1992).

ACGIH has established a TLV of 10 mg/m^3 for the parent chemical family of castor oil, vegetable oil mists (ACGIH, 1992*b*), but notes that the TLV for the group does not apply to "castor, cashew nut, and similar irritant oils," because of the propensity of those oils to cause "occupational dermatitis and/or respiratory irritation." ACGIH considers non-irritant vegetable oils to be "nuisance" particulates "which seem to have little adverse effect on the lung and do not produce significant organic disease or toxic effects when exposures are kept under reasonable control." NIOSH has derived a Recommended Exposure Level (REL) for vegetable oil mists as well, 10 mg/m^3 (total) and 5 mg/m^3 (respirable particulate). While the background documentation for the vegetable oil mist REL was not available for our review, the published REL does not appear to carry with it a specific exclusion of castor oil based on irritancy similar to that accompanying the vegetable oil mist TLV. ACGIH (1992*a*) has also published a TLV of 5 mg/m^3 for mineral oil mists, in which they note that a series of site investigations made by NIOSH (1978, 1979*a*,*b*) in industrial plants where oil mist was known to occur identified no "evidence of skin or respiratory tract irritation from exposures to oil mist that were at levels below the 5 mg/m^3 TLV." ACGIH is careful to point out that this TLV applies to "oil mist alone" and "it is not possible to conclude from these limited human studies that 5 mg/m^3 is an acceptable exposure limit for all types of oils. Thus, it is not advisable to apply the 5 mg/m^3 oil mist TLV to oils containing unknown concentrations and types of additives."

In summary, these documents suggest, based on those human occupational data that currently exist, that: 1) human exposures to pure oil mists that do not exceed 5 mg/m^3 are generally free from irritative effects; and 2) that the vegetable oil mist TLV of 10 mg/m^3 for a time weighted average (TWA) workday may not be protective against the irritative effects of exposures to "irritant" vegetable oil mists (such as castor oil). Taking these data together, it seems reasonable to conclude that a concentration of 5 mg/m^3 would likely provide a reasonable OEL for castor oil and other "irritant" vegetable oils. Notably, this concentration is identical to the NIOSH REL for the respirable fraction of vegetable oil mist. It should also be mentioned here that while "vegetable oil mist" is specifically exempted from definition as a Toxic Air Contaminant (TAC) by R120(f)(xxxviii), castor oil mist is not. The aforementioned irritative qualities of castor oil mist sufficiently distinguish it from other vegetable oil mists to the

extent that the exemption for vegetable oil mist should not and will not be applied to castor oil. It will be considered a TAC, and thus derivation of a screening level is called for.

ITSL Derivation: In choosing data for screening level development, preference is generally given to human epidemiologic data or chronic laboratory animal inhalation 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. With respect to castor oil, no RfD is available. Evidence exists (ACGIH, 1992*b*; Cooper, 1989) to suggest that portal of entry effects may make an oral to inhalation extrapolation unwise (*viz.*, ACGIH's note that castor oil and similar irritant oils "have caused occupational dermatitis and/or respiratory irritation"). This argument is strengthened by the finding of NOAELs in the NTP study that were orders of magnitude higher than the OELs for vegetable oil mists. Thus, the available literature suggests that the threshold for systemic toxicity of castor oil lies considerably above that for respiratory irritation, and setting a health-based screening level based on protection from respiratory irritation is likely to protect against other toxic effects as well. Consequently, it is considered appropriate here to use the NIOSH REL for vegetable oil mists (5 mg/m^3 respirable particulate) as the basis for the ITSL for castor oil. Consistent with R 232(1)(c), the REL is used in preference to the ACGIH TLV, since it is the lower of the two values, and because of ACGIH's suggestion that its TLV for vegetable oil mists may not protect against skin and respiratory irritation caused by exposure to castor oil and similar "irritant" oils.

Per Rule 232(1)(c), of Act 451, as amended:

$$\textbf{ITSL} = \text{OEL} \times \frac{1}{100} = 5\ \text{mg/m}^3 \times \frac{1}{100}$$

$$= 0.05\ \text{mg/m}^3 \times \frac{1000\ \mu\text{g}}{1\ \text{mg}}$$

$$= \mathbf{50\ \mu g/m^3}$$

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 to the effects of exposure to castor oil 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.

Per R 232(2)(a), since the screening level is based on an OEL with a time-weighted average (TWA) exposure, an **8-hour averaging** time applies to this ITSL.

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