MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

January 14, 1997

TO: File for 7-diethylamino-4-methyl coumarin [7D4MC] (CAS # 91-44-1)

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

SUBJECT: Initial Threshold Screening Level for 7D4MC

The initial threshold screening level (ITSL) for 7-diethylamino-4-methyl coumarin is 16 $\mu g/m^3$ based on an annual 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 -December 20, 1996), Handbook of Environmental Data on Organic Chemicals, Patty's Industrial Hygiene and Toxicology, Merck Index and the Condensed Chemical Dictionary.

Hawley (1981) lists the uses for 7D4MC as an optical bleach in the textile industry; in coatings for paper, labels, book covers, etc.; to lighten plastics, resins, varnishes and lacquers; and as an invisible marking agent. It is considered part of a group of chemicals known as Fluorescent Whitening Agents (FWAs) (Thomann and Krüger, 1975).

The toxicological data concerning 7D4MC are quite limited. Only a few references were located, and of these, only one (Thomann and Krüger, 1975) provided data potentially usable for the derivation of a screening level. In that report, the authors state that "standard procedures were used to determine acute oral toxicity. Young adult albino rats, albino mice, guinea pigs, rabbits, cats, and dogs were given a single dose, the maximum technically possible, and their reactions were recorded. Additional smaller doses were given as indicated and an LD_{50} was calculated wherever possible". Toxicity results are reported for multiple chemicals; in the case of 7D4MC, results indicate an LD_{50} of 5000 mg/kg in rats, apparently the only species tested. The authors do not identify the strain of rat tested. The compound was reported as "technically pure". No dermal or inhalation toxicity tests were performed for this chemical, but the primary skin irritation of 7D4MC was reported as "practically none" from tests in rabbits. The authors attribute the low order of acute systemic toxicity to the fact that "absorption of FWAs from the gastrointestinal tract is minimal".

Two citations of oral LD_{50}s without accompanying studies were also noted for this chemical, located *via* the RTECS database (RTECS, 1996). The first (MVCRB3, 1973) lists a oral LD_{50} of 5 g/kg in the rat, while

the second (SRTCAC, 1989) lists a mouse LD_{50} of 1780 mg/kg. Both citations were from foreign publications, neither of which was available for our review. However, it is notable that the LD_{50} reported by Thomann and Krüger (1975) is the same as that reported by the first RTECS citation (MVCRB3, 1973).

7D4MC was employed as a fluorescent tracer in a pair of studies designed to assess faceseal leak sites in half-mask respirators designed for occupational use (Oestenstadt *et al.*, 1990*a*,*b*). The chemical was dissolved in ethanol, aerosolized and blown into an exposure chamber covering the heads and shoulders of 73 human subjects wearing half-mask respirators. The subjects were about evenly split by gender, and five racial groups (Caucasians, African Americans, Asian Americans, Latinos and Asian Indians) were represented in the sample. By using specially configured photographic equipment, the authors were able to pinpoint the size and shapes of leaks in the respirator faceseals, since 7D4MC deposited on the skin fluoresces blue light when long wave ultraviolet light is incident upon it. One of the reasons that 7D4MC was chosen as the tracer for this study was that it was judged by the authors to be "essentially nontoxic" (Oestenstadt *et al.*, 1990*b*) In the exposure chamber, "concentrations were found to range from 18 to 50 mg/m^3 under various system operating conditions"; the average aerodynamic mass median diameter was 0.55 μ, with an average geometric standard deviation (σ_g) of 1.6. "Human tests were conducted for about 40 minutes at an average MDC [7D4MC] concentration of 38 mg/m^3". Exposures were ceased if leakage of the aerosol (as measured inside the respirator facepiece) were ≥ 10%. As this was an industrial hygiene study, rather than a toxicological one, no attention was directed toward measuring any toxicological endpoints. However, if one assumes a maximum inhalation exposure (*via* tolerated leakage) of 9.99% of the chamber concentration, and recognizing that the majority of the aerosol particles were small enough to penetrate to the alveolar level, a crude theoretical "maximum average" dose (range) for these subjects would have been ≤ 3,796 $\mu g/m^3$ (1,798-4,995 $\mu g/m^3$)[1] for a forty minute exposure. No overt adverse effects in any of the subjects were reported by the authors. So, while it is clear that these studies did not follow sufficient toxicological endpoints for a sufficient period of time to be useful in the quantitative derivation of a screening level, they nonetheless provide a degree of assurance that 7D4MC appears to have a low order of acute inhalation toxicity in humans.

No data concerning the carcinogenic or developmental effects of 7D4MC exposure were located in any of our searches. The mutagenicity of the compound was considered by Haworth *et al.* (1983). 7D4MC was found not to be mutagenic in four strains of *Salmonella* both with and without liver S-9 fractions.

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[1] Using the average chamber concentration of 7D4MC equal to 38 mg/m^3:

$$(38\ mg/m^3 \times 1000\ \mu g/1\ mg) \times 0.0999 = 3,796\ \mu g/m^3$$

The crude theoretical maximum dose range values were calculated similarly.

Derivation of the ITSL: The almost total lack of toxicity data is the overwhelming consideration in setting a screening level for 7D4MC. The acute oral toxicity report (Thomann and Krüger, 1975) provides a less than optimal level of detail with respect to the methodology employed. Ideally, such data as the number and sex of the rats at each dose level, observation period post-dosing, vehicle used (if any) and method of statistical analysis used to calculate the LD_{50} should be reported. However, this report is by far the best documented toxicological data for this chemical identified in our searches, and has presumably received some level of peer and/or editorial scrutiny prior to publication. Moreover, the low order of systemic toxicity indicated by the reported LD_{50} values suggests that setting the ITSL to trace (0.04 $\mu g/m^3$, annual averaging) per R232(1)(i) might result in an overly conservative screening level. In light of these observations, the Thomann and Krüger report is considered to provide an LD_{50} with a sufficient level of documentation for use in defining an ITSL. Consequently, the LD_{50} reported (5000 mg/kg) is used here to calculate the ITSL. Per R232(1)(h) of part 55, Act 451:

$$ITSL = \frac{1}{500} \times \frac{1}{40} \times \frac{1}{100} \times \frac{LD_{50}\ (mg/kg) \times W_A}{0.167 \times I_A}$$

where:

W_A = Body weight of a sex and strain unspecified rat (from MDEQ, 1996)

I_A = Daily inhalation rate of a sex and strain unspecified rat (from MDEQ, 1996)

So,

$$\textbf{ITSL} = (0.002) \times (0.025) \times (0.01) \times \frac{(5000\ mg/kg) \times (0.395\ kg)}{(0.167) \times (0.945\ m^3/kg) \times (0.395\ kg)}$$

$$= (0.0000005) \times \frac{5000\ mg/kg}{0.158\ m^3/kg}$$

$$= (0.0000005) \times (31{,}683\ mg/m^3)$$

$$= (0.0158\ mg/m^3) \times \frac{1000\ \mu g}{1\ mg}$$

$$= 15.8\ \mu g/m^3 \cong \mathbf{16\ \mu g/m^3}$$

Per 232(2)(c), an **annual averaging** time applies.

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DO:slb
cc: Asad Khan, Permits Section