MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

TO: File for Phthalic anhydride (CAS # 85-44-9)

FROM: Doreen Lehner, Toxics Unit, Air Quality Division

DATE: January 28, 2015

SUBJECT: Screening Level for Phthalic anhydride (CAS # 85-44-9)

The initial threshold screening level (ITSL) for phthalic anhydride (CAS # 85-44-9) is 20 µg/m^3 with an annual averaging time.

Phthalic anhydride (CAS # 85-44-9) also known as 1,3-isobenzofuradione is a colorless crystalline powder with a characteristic acrid, choking odor. It has a molecular weight of 148.1 g/mol and a melting point of 131.6°C and can sublime when heated to 295°C. Phthalic anhydride is used: as a monomer for polyester resins and alkyd resins used in paints and lacquers; chemical intermediate in production of phthalate esters, and dyes (anthraquinone, phthalein, rodamine, phthalocyanine, fluorescin, and xanthene dyes); insect repellants; polyester polyols for polyurethanes; rubber scorch inhibitor and retarder; organic synthesis; as a chemical intermediate in the production of plastics from vinyl chloride; in the production of PVC products such as cables, pipes and hoses, leather cloth, shoes, film for packaging; and in medicine (enteric coatings). (Wikipedia, 2014; OEHHA, 2000).

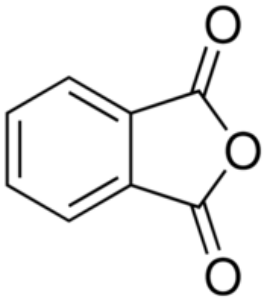

Figure 1. Structure of phthalic anhydride.

A literature review was conducted to determine an initial threshold screening level (ITSL) for phthalic anhydride. The following references and databases were searched to derive the above screening level: United States Environmental Protection Agency (US EPA) Integrated Risk Information System (IRIS), National Institute for Occupational Safety and Health (NIOSH), American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Values and Biological Exposure Indices (TLV/BEI) 2014 guide, National Toxicology Program (NTP) Study Database, International Agency for Research on Cancer (IARC), Acute Database, Chemical Abstract Service (CAS) Online (searched 11/6/14), National Library of Medicine (NLM)-online, EPA Aggregated Computational Toxicology Resource (ACToR) Database, US EPA TSCATS database, and Hazardous Substances Data Bank (HSDB).

OEHHA (2000) has determined a noncancer chronic inhalation Reference Exposure Level (REL) of 20 µg/m^3 based on increased incidence of conjunctivitis, rhinitis, asthma, and chronic bronchitis in occupationally exposed workers based on the studies by Neilsen et al. (1988; 1991).

In the Neilson et al. (1988) study, two plants producing alkyde and unsaturated polyester resins had a time-weighted average air level of phthalic anhydride (PA) at 6.5 (1.5 to 17.4) mg/m^3, during loading activities. In a full workday, the level of phthalic anhydride was 0.4 mg/m^3. "In 60 workers, symptoms of rhinitis and/or conjunctivitis were frequently reported, mostly by heavily exposed workers (69%). Five workers (14%) with PA-associated asthma were found. All were heavily exposed during some period. There was no difference between the exposure groups with regard to total serum level of IgE, IgG, and IgM, nor specific IgE and IgM against PA. There was a significant difference of specific IgG against PA between heavy and low exposure groups (p=0.01). One worker with asthma had an increased specific IgE level. Subjects with symptoms did not differ from subjects without symptoms in total serum IgE, IgM, IgA, or specific IgE and IgM. However, subjects with rhinoconjunctivitis had *lower* total IgG than the other workers (p=0.01). The subjects with asthma had significantly higher values for specific IgG than the asymptomatic subjects (p=0.005). Four subjects had specific IgG antibodies of subclass 4 (IgG_4). Three of these four subjects had asthma, and one had rhinitis. These findings demonstrate that specific IgG is an index of PA exposure and support the hypothesis that specific IgG_4 under some circumstances, may be a pathogenetic factor in asthma" (Nielsen et al., 1988).

In the Neilson et al. (1991) study, "a total of 23 phthalic anhydride (PA)- exposed workers (air levels up to 17 mg/m^3) showed significantly (P less than 0.01) more work related symptoms in their eyes (48% vs 6%) and nose (39% vs 0) than did 18 unexposed control subjects. Two of the exposed workers had PA- associated asthma. Surprisingly, the control group exhibited significantly (P less than 0.05) more symptoms of nonspecific bronchial hyperreactivity (44% vs 13%). The exposed workers showed significantly higher levels of total serum IgE (medians, 32 vs 15 kIU/l, P less than 0.05), although values for specific IgE against PA did not differ. This may indicate that such exposure can facilitate the entry of common allergens. There was a significant difference in PA-specific IgG [enzyme-linked immunosorbent assay (ELISA) ratios 0.21 vs 0.12; P less than 0.01]. There were no differences in lung function with regard to vital capacity (VC) and forced expiratory volume (FEV1), closing volume expressed as a percentage of VC (CV%), volume of trapped gas (VTG) before and after inhalation of metacholine, or carbon monoxide transfer factor (TLCO), whereas exposed workers displayed significantly higher late expiratory flow rates (MEF50 and MEF25). In a [99mTc]-diethylenetriamine penta-acetate (DTPA) clearance test, there was no difference between exposed subjects and controls. In summary, exposure to PA did not cause subclinical effects of the lungs. Subjects with lower-airway symptoms showed lower FEV1, MEF50, and MEF25 values and higher VTG (after metacholine) than did those without symptoms" (Neilson et al., 1991).

A study by Sarlo et al., (1994), exposed guinea pigs via inhalation to phthalic anhydride dust at 0.5, 1.0, and 5.0 mg/m^3, 3 hours/day for 5 consecutive days. Inhalation challenge with aerosolized phthalic anhydride-guinea pig serum albumin (PA-GPSA) conjugate showed immediate-onset respiratory reaction in animals exposed to all three levels of dust. An inhalation challenge of a subgroup of animals with phthalic anhydride dust did not elicit an immediate response, as measured by changes in respiratory frequency and plethysmograph pressure. Serologic studies showed that these animals had allergic IgG1a antibody to PA-GPSA. There was a dose-dependent increase in specific IgG antibody activity, as measured by ELISA. Animals exposed to and challenged with 5.0 mg/m^3 phthalic anhydride dust had significant

numbers of hemorrhagic lung foci. Those animals with the greatest number of foci had high IgG antibody activity to phthalic anhydride, as measured by ELISA. This study showed that exposure to levels of phthalic anhydride dust as low as 0.5 mg/m^3 can sensitize animals to produce an allergic reaction and may cause hypersensitivity after initial exposure.

OEHHA (2000) determined the LOAEL at 6.5 mg/m^3 (which is the mean of 6.1 and 6.8 taken from the Neilsen et al. (1988) study. There was not reported NOAEL. The worker exposure averaged 8 hours a day, 5 days a week with a reported mean of 13.3 years. OEHHA (2000) calculated the average experimental exposure at 2.3 mg/m^3 (6.5 mg/m^3 x 10/20 x 5/7) which adjusted from an 8 hour workday (which assumes a worker breathes in 10m^3 while at work and is expected to breath in 20m^3 air a day) and an exposure of 5 days a week to extrapolate to a 24-hour a day lifetime exposure. OEHHA used an uncertainty factor of 100 (10 for LOAEL to NOAEL and 10 for intraspecies uncertainty factor to account for susceptible individuals) resulting in an inhalation reference exposure level of 0.02 mg/m^3. OEHHA chronic reference exposure levels are based on a lifetime exposure.

According to Rule 232(1)(a), if an inhalation reference concentration (RfC) is available, then the ITSL equals the RfC. Since OEHHA (2000) has determined a chronic REL of 20 µg/m^3, then the ITSL for phthalic anhydride (CAS # 85-44-9) is 20 µg/m^3 based on an annual averaging time.

References:

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