Michigan Department of Environmental Quality

Interoffice Communication

TO: File for Maleic acid (CAS# 110-16-7)

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SUBJECT: Screening Level for Maleic acid (CAS# 110-16-7)

DATE: December 20, 2012

After a review of all the available data, maleic acid (CAS# 110-16-7) is assigned the default ITSL due to the absence of adequate toxicity data. Therefore, the ITSL for maleic acid (CAS# 110-16-7) is 0.1 µg/m^3 (annual averaging time).

Maleic acid (also known as [Z]-2-butenedioic acid and toxilic acid) has a molecular weight of 116.07. It is a white crystal with a faint acid odor and is a skin and eye irritant. Maleic acid is used: in the production of phthalic-type alkyd and polyester resins, surface coatings, copolymers, lubricant additives, and agricultural chemicals; in adhesives and sealants; as an ingredient in maleate salts of antihistamines and similar drugs; to prevent rancidity in oils and fats; in dyeing and finishing wool, cotton, and silk; and as an intermediate in the production of maleic anhydride, tetrahydrofuran, and fumaric acid (OECD, 2004).

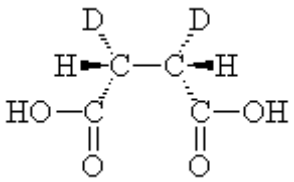

Figure 1. Structure of Maleic acid

A literature review was conducted to determine an initial threshold screening level (ITSL) for maleic acid. The following references and databases were searched for information relevant to the derivation of a screening level: the DEQ's Chemical Criteria Database (CCD), 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) 2012 guide, National Toxicology Program (NTP) Study Database, International Agency for Research on Cancer (IARC), the AQD's Acute Toxicity Database, Chemical Abstract Service (CAS) Online (searched 12/11/12), National Library of Medicine (NLM)-online, EPA Aggregated

Computational Toxicology Resource (ACToR) Database, US EPA TSCATS database, and Hazardous Substances Data Bank (HSDB).

Animal Studies

EPA RfC or RfD values are unavailable. There is no NIOSH recommended exposure limit available for this compound or a threshold limit value from ACGIH. Fitzhugh and Nelson (1947) studied maleic acid in male and female Osborne Mendel rats which were fed 0, 0.5, 1.0, or 1.5% (0, 5000, 10000, and 15000 ppm) in feed for 2 years. "These concentrations can be approximated to correspond with doses of (0, 250, 500, and 750 mg/kg/day) assuming a 0.4 kg rat eats 20 g food/day. Concentrations of 1.0 and 1.5% maleic acid retarded the growth rate and all concentrations of maleic acid increased mortality rates. The authors reported no major visceral damage, although rats fed 1.5% maleic acid showed more atrophy of the liver than controls" (OECD, 2004). Since all levels of maleic acid caused an increase in mortality – mortality being a significant frank effect, no NOAEL or LOAEL can be determined from this data. Also, there would be a concern for the use of a feeding study for inhalation risk assessment, because route-to-route extrapolation would not account for the potential portal-of-entry irritancy with inhalation exposure. There were no 7-day inhalation studies which would yield a LOAEL or NOAEL and no acute inhalation data where an LC_{50} can be derived. There was a rat oral LD_{50} of 708 mg/kg for maleic acid, but the data "are from a secondary source, which references values from unpublished reports" (OECD, 2004). Use of the algorithm for ITSL derivation based on an LD50 would result in a potential ITSL of 2 ug/m3. However, the source of this information is not available and cannot be verified, therefore it is not useful for derivation of an ITSL for maleic acid. The CAS Online search provided a study citation (Worthen, 1963) for a paper that was not obtainable; the title suggests that renal toxicity was investigated, but the route of administration may have been non-inhalation and therefore not capable of informing the portal-of-entry effect concern. This paper was not cited or described in the literature review by OECD (2004).

Although studies link maleic anhydride to sensitization in workers, no sensitization data exist for maleic acid and it is not predicted to be either a skin or respiratory sensitizer (OECD, 2004).

OECD (2004) reports that maleic anhydride rapidly hydrolyzes to maleic acid: "the half-life of the hydrolysis of maleic anhydride to maleic acid in water at 25°C has been determined to be approximately 22 seconds." Maleic anhydride forms a hydroxyl radical in air, with a half-life in air estimated to 4.2 to 18.6 hours. For maleic acid, the half-life in air is estimated to be 1.3 days (OECD, 2004). They state that renal toxicity that was reported for maleic anhydride at ≥ 100 mg/kg-d via feed is likely due to maleic acid. However, they also note that renal toxicity did not occur in rats at 32 or 100 mg/kg-d maleic anhydride for 2 years via diet, and no adverse effects were seen in dogs dosed at 20, 40, or 60 mg/kg maleic

anhydride 7 days/week for 90 days via feed. OECD (2004) also cites reproductive and developmental studies of maleic anhydride dietary exposure in animals, which found a LOAEL for parental effects (in the kidney and bladder) at 20 mg/kg-d, a NOAEL for reproductive effects at 55 mg/kg-d, and a NOAEL for developmental effects at 140 mg/kg-d. The OECD (2004) stated that, "Negative results for reproductive and developmental toxicity of maleic acid are inferred from the rapid hydrolysis of maleic anhydride to maleic acid". Further, they noted that key differences between maleic anhydride and maleic acid are: maleic anhydride has the potential to form haptens by acylating with amino acids, resulting in an immunological response (dermal and respiratory sensitization), and; maleic anhydride would have immediate irritant effects at the site of contact largely due to the exothermic reaction from the hydrolysis of maleic anhydride to maleic acid.

EPA (2006) determined that there was sufficient toxicity data and information available to qualitiatively assess the health hazards of maleic anhydride and maleic acid associated with the low levels of exposure expected from the use of these compounds as inert ingredients in pesticide formulations. Their hazard assessment was developed from the OECD (2004) SIDS report, which they state was prepared by EPA and submitted to OECD under the SIDS High Production Volume Chemicals Program. Maleic anhydride was noted to have an odor of "irritating, choking", while maleic acid had an odor of "faint acidulous". They concluded that respiratory tract and eye irritation are likely following repeated inhalation exposure to maleic anhydride and maleic acid, but dose/response data were not given. They report that a 1-hour inhalation exposure of rats to 0.72 mg/l of maleic acid produced generalized inactivity, hyperpnea and sedation within 15 minutes of exposure; gross necropsy revealed no significant findings; no neurotoxic effects have been reported in the available studies (EPA, 2006). They noted limited information available to assess metabolism and pharmacokinetics of maleic anhydride and maleic acid; maleic anhydride is rapidly metabolized to maleic acid under aqueous conditions. "Unlike maleic acid, maleic anhydride has the potential to form haptens by acrylating with amino acids, resulting in an immunological response (dermal and respiratory sensitization)" (EPA, 2006).

In conclusion, there is a lack of sufficient toxicity data on maleic acid for ITSL derivation. Maleic acid in the ambient air may be reasonably anticipated to be an irritiant to mucous membranes of the eyes, nose and throat, however, there is a lack of data to characterize the dose-response or to derive an ITSL based on this specific effect. Although maleic anhydride has a relatively low ITSL of 0.1 ug/m3 (8 hr AT) based on an OEL and sensitization in workers, the OECD (2004) and EPA (2006) cite a lack of information to associate that hazard with maleic acid, a hydrolysis product of maleic anhydride.

References

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