MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

July 28, 2015

To: File for Titanium Dioxide (CAS No. 13463-67-7)

From: Michael Depa, Air Quality Division, Toxics Unit

Subject: Screening Level Updates

The Initial Threshold Screening Level (ITSL) for titanium dioxide is 24 µg/m³ with an 8-hour averaging time.

The following information sources were searched in order to support the development of screening levels for titanium dioxide (TiO_2): United States Environmental Protection Agency's (EPA's) Integrated Risk Information System (IRIS), the Registry of Toxic Effects of Chemical Substances (RTECS, 2015), the American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Values (TLV), National Institute of Occupational Safety and Health (NIOSH) Pocket Guide to Hazardous Chemicals, Environmental Protection Bureau Library, International Agency for Research on Cancer Monographs, National Library of Medicine, Health Effects Assessment Summary Tables, and National Toxicology Program Status Report. The EPA has not established a reference concentration (RfC) for titanium dioxide. California Office of Environmental Health Hazard Assessment (Cal-OEHHA) has not established reference exposure levels for TiO_2. The U.S. Agency for Toxic Substances and Disease Registry (ATSDR) has not established a chronic minimal risk level for TiO_2. Provisional Peer Reviewed Toxicity Values (PPRTV) for TiO_2 are not available.

Occupational Exposure Limits

The ACGIH has established a Threshold Limit Value (TLV) for TiO_2 at 10 mg/m³. NIOSH developed 2 recommended exposure limits (RELs) for TiO_2, each based on a specific size fraction of particles. NIOSH recommends airborne exposure limits of 2.4 mg/m³ for fine (respirable) TiO_2 and 0.3 mg/m³ for ultrafine (<0.1 µm) TiO_2.

Evidence for Carcinogenicity

The International Agency for Research on Cancer (IARC, 2010) evaluated the available evidence that TiO_2 causes cancer and concluded that there is inadequate evidence in humans, but that there is sufficient evidence in experimental animals for the carcinogenicity of TiO_2. IARC designated TiO_2 as a group 2B carcinogen: "possibly carcinogenic to humans".

NIOSH also evaluated the relevance of the human and animal data available to determine the potential carcinogenicity of TiO_2. NIOSH concluded that the fine fraction of TiO_2 (respirable) is not carcinogenic to humans based on the animal studies. The only chronic

animal inhalation study (Lee et al. 1985), which demonstrated the development of lung tumors (bronchioalveolar adenomas) in response to inhalation exposure of rats to fine sized TiO_2 did so at a dose of 250 mg/m³ but not at 10 or 50 mg/m³. NIOSH states that:

> [E]xposure concentrations greater than 100 mg/m³ are generally not considered acceptable inhalation toxicology practice today. Consequently, in a weight-of-evidence analysis, NIOSH questions the relevance of the 250 mg/m³ dose for classifying exposure to TiO_2 as a carcinogenic hazard to workers and therefore, concludes that there are insufficient data at this time to classify fine TiO_2 as a potential occupational carcinogen.

Concerning the ultrafine fraction (<0.1 µm) of TiO_2, NIOSH states:

> [T]he responses observed in animal studies exposed to ultrafine and fine TiO_2 are consistent with a continuum of biological response to TiO_2 that is based on particle surface area. In other words, all the rat tumor response data on inhalation of TiO_2 (ultrafine and fine) fit on the same dose-response curve when dose is expressed as total particle surface area in the lungs.
>
> NIOSH has concluded that TiO_2 is not a direct-acting carcinogen, but acts through a secondary genotoxicity mechanism that is not specific to TiO_2 but primarily related to particle size and surface area.

Derivation of the ITSL

The RELs of 2.4 mg/m³ for fine (respirable) TiO_2 and 0.3 mg/m³ for ultrafine (<0.1 µm) TiO_2.are designed to prevent pulmonary inflammation, and thus prevent the development of secondary toxicity (including lung tumors). The RELs are preferred over the ACGIH TLV because they have been recently reviewed (NIOSH in 2010 vs ACGIH in 2001), and the derivation of which is more appropriate than the ACGIH TLV. The TLV was based on prevention of particle overload of the clearance mechanism in the lung, whereas the REL is based on the prevention of inflammation in the lung.

An ITSL based on the fine fraction will be established as follows:

ITSL = (OEL/100).

> Where the OEL is the occupational exposure limit, in this case the recommended exposure limit (REL) of 2.4 mg/m³.

ITSL = (2.4 mg/m³)/100 x (1000µg/mg)

ITSL = 24 ug/m³

An 8-hr averaging time was applied to the screening level pursuant to Rule 232(2)(a). The ITLS is to be applied to the respirable fraction of TiO_2 particles (i.e., PM10).

An ITSL for the ultrafine fraction will not be developed at this time because the ultrafine fraction is not likely to be an air contaminant from industrial processes. If it is found to be emitted and subject to the air permit process, an ITSL based on 1% of the REL for ultrafine fraction may be appropriate; i.e., 1% of 0.3 mg/m³ or 3 µg/m³, (8-hr averaging time).

References

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