MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

_____

INTEROFFICE COMMUNICATION

_____

November 5, 2015

To: File for Chromium (III) Hydroxide (CAS #1308-14-1)

From: Mike Depa, Toxics Unit, Air Quality Division

Subject: Initial Threshold Screening Level

Previously, the averaging time (AT) assigned to chromium (3) hydroxide was 24 hours, as per the default methodology (Rule 232(2)(b))(see attached memo from Marco Bianchi dated September 13, 2000). The current file review concludes that the AT may appropriately be set at annual, based on the nature and duration of the key study and the ITSL value derivation, as allowed under Rule 229(2)(b). Therefore, the AT is set to annual.

MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

September 13, 2000

To: File for Chromium (III) Hydroxide (CAS #1308-14-1)

From: Marco Blanchi, Toxics Unit, Air Quality Division

Subject: Initial Threshold Screening Level

The initial threshold screening level (ITSL) for chromium III hydroxide is 0.5 micrograms per cubic meter (µg/m^3) based on a 24-hour averaging time.

The following references or databases were searched to identify data to determine the ITSL: Integrated Risk Information System-online, Health Effects Assessment Summary Table, National Toxicology Program Management Status Report-online, Registry of Toxic Effects of Chemical Substances, Environmental Protection Bureau (EPB) Chemical Criteria Database, EPB library, Chemical Abstract Service (CAS)-online, National Library of Medicine-online, International Agency for Research on Cancer (IARC)-online, IARC monograph, National Institute for Occupational Safety and Health Pocket Guide, American Conference of Governmental Industrial Hygienists (ACGIH) Guide, and the Agency for Toxic Substance and Disease Registry Toxicological Profile for chromium.

Chromium occurs with oxidation states from -2 to +6; however, only the free metal state (valence = 0), chromic salts (+3), and chromate salts (+6), are in common use. Chromium in the ambient air occurs from natural sources, industrial and product uses, and burning of fossil fuels and wood. The most important industrial source of chromium in the atmosphere originates from ferrochrome production. Under normal conditions, Cr(+3) and Cr(0) in the air generally do not undergo any reaction. Cr(+6) in air may react with dust particles or other pollutants to form Cr(+3); however, the exact nature of such atmospheric reactions has not been studied extensively. Chromium is removed from air by atmospheric fallout and precipitation.

Trivalent chromium compounds such as chromium hydroxide are usually considered insoluble, but can have differing insolubilities within this classification. Trivalent chromium is also an essential dietary nutrient with a recommended daily intake for adults of 50-200 micrograms per kilograms per day (µg/kg/day). It plays an essential role in the metabolism of glucose, fat, and protein by potentiating the action of insulin. Additionally, trivalent chromium is the more stable oxidation state and under physiological conditions may form complexes with ligands such as nucleic acids, proteins, and organic acids. Biological membranes are thought to be impermeable to trivalent chromium, although phagocytosis of particulate trivalent chromium can occur. Hexavalent chromium usually forms strongly oxidizing chromate and dichromate ions,

which readily cross biological membranes and are easily reduced under physiological conditions to trivalent chromium. Data available on the toxicity of trivalent chromium compounds via the oral route suggest that these materials are much less toxic than are the hexavalent compounds and that the toxicity varies with water solubility. This implies that insoluble chromium compounds are not absorbed systemically to any significant degree as compared to soluble chromium compounds.

There have been many oral toxicity studies of trivalent chromium compounds due to its use as a food additive. These studies have provided enough information for the U.S. Environmental Protection Agency (EPA) to establish an oral reference dose (RfD) (risk reference concentration) of 1 mg/kg/day for chromium Ill, insoluble salts. While this value may adequately address the associated risks from oral exposures, it doesn't address the inhalation toxicity of these compounds. Adverse effects from oral dose studies show changes in spleen and liver weights, while adverse effects from inhalation studies show biochemical and functional changes of the lung.

A detailed chemical evaluation of chromium hydroxide revealed no specific toxicological study that would lend itself to deriving an ITSL for this compound. However, the Air Quality Division (AQD) previously conducted chemical evaluations on two similar compounds that could possibly be used to establish a screening level for chromium hydroxide. These chemicals are chromium Ill compounds and chromium Ill oxide. The ITSL for chromium Ill compounds is 5 $\mu g/m^3$ (8-hour averaging) based on an ACGIH threshold limit value of 0.5 mg/m^3 for non-specific trivalent chromium compounds. The ACGIH recommendation was not based on a specific trivalent chromium study, but from historical data showing that the effects of soluble Cr(+3) salts have not caused changes of pathophysiological significance at exposures below 0.5 mg/m^3. In contrast, a recently published subchronic inhalation study (Derelanko, 1999) was found that described toxic effects due specifically to chromium oxide exposure. The Derelanko study showed that rats exposed to chromium oxide dust developed changes in the bronchial and mediastinal lymphatic tissue and lung. These changes appeared to be directly associated with the presence of black pigment, observed both macroscopically and microscopically. They were believed to have been a non-specific response to the physical presence of chromium oxide and not a direct toxic effect from it. A significant amount of pigment was still present in the respiratory tract of exposed animals after the 13-week recovery period along with the earlier observed pathological effects. Increased pigment in the lymphatic tissue suggests pulmonary clearance of the chromium oxide via the lymphatic system was occurring, although rather slowly. The slow clearance of chromium oxide from the lungs may have been due to its insolubility resulting in decreased systemic absorption and/or reduced clearance from the lung by normal clearance mechanisms. Other than the localized effects in the respiratory tract, no evidence of systemic toxicity was observed from exposure to chromium oxide. This study was used to establish an AQD derived inhalation reference concentration (RfC) which resulted in an ITSL for chromium oxide of 0.5 $\mu g/m^3$ with a 24-hour averaging time.

Although either of the above chemical evaluations could be used as a surrogate study for chromium hydroxide, a determination will be made to see if one is more appropriate

to use than the other. If the chemical or physical properties are similar between chromium hydroxide and chromium oxide, then the Derelanko study will be used to set an ITSL. If this similarity cannot be made between the two compounds, then the decision will default to the ACGIH derived value for non-specific trivalent chromium compounds.

It was found that chromium hydroxide and chromium oxide differ slightly in their chemical and physical states. Chromium hydroxide is a green gelatinous precipitate that is insoluble in water, but soluble in acids and strong bases; the oxide is comprised of hard green crystals and is insoluble in water. Chromium hydroxide is also known to decompose to chromium oxide upon heating. Although there are slight differences ¡n physical and chemical properties between chromium oxide and chromium hydroxide, ¡t seems reasonable to conclude that the hydroxide would be distributed in the respiratory system and metabolized in the same manner as the oxide. Exposure to the hydroxide would probably result in accumulation ¡n the lung tissue since this compound precipitates in neutral solutions. This compound is only soluble in acids and strong bases, and would therefore remain inert at physiologic pH (7.2-7.4). If any decomposition of the hydroxide did occur, it would probably result in the oxide. In conclusion, chromium oxide and chromium hydroxide seem similar enough in their chemical and physical properties to justify using the oxides ITSL of 0.5 µg/m³ (24-hour averaging) as a surrogate value for the hydroxide. This value is more conservative than the ITSL for chromium III compounds, but seems more appropriate since the actual metabolism for chromium hydroxide is uncertain. The ITSL for chromium hydroxide will be 0.5 µg/m³ (24-hour averaging).

The remaining portion of this evaluation describes the methodology used to derive the ITSL for the surrogate compound, chromium oxide. It is provided here to facilitate this review. If the full chemical evaluation is needed, please refer to chromium III oxide (CAS #1308-38-9) August 2, 2000.

Chromium Oxide Methodology

The study investigators concluded that because of the microscopic effects observed in the respiratory tracts of some animals exposed to the lowest level of chromium oxide, a no-observed-adverse-effect level (NOAEL) was not established for this study. They further stated, however, the low incidence and minimal severity of the pathological effects in the low-level animals suggests that 4.4 mg/m³ is very near the NOAEL for subchronic exposure to chromium oxide.

After reviewing the Derelanko study, it was determined that 4.4 mg/m³ will be used as a lowest-observed-adverse-effect level (LOAEL) to calculate the ITSL. An uncertainty factor (UF) of 10 will be used to account for human sensitivities; UF3 for interspecies variability using the Regional Deposited Dose Ratio (RDDR) model (as explained below); UF10 for subchronic to chronic extrapolation; and an UF3 for LOAEL to NOAEL extrapolation due to no increase in target organ weight, but trace-to-mild septal cell hyperplasia and trace-to-mild chronic interstitial inflammation in males in the lowest treatment group.

The Derelanko study used to evaluate chromium oxide justifies deriving an RfC for this compound using the EPA's Method for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry guidance document (EPAI600/8-90/066F; October 1994). According to this guidance document, a key element in extrapolating laboratory animal inhalation data to humans is estimating the human equivalent concentration (HEC) or "dose" (i.e., agent mass deposited per unit surface area or tissue volume) delivered to specific target sites in the respiratory tract or made available to uptake and metabolic processes for systemic distribution. This ¡s considered with mechanistic determinants of toxicant-target interactions and tissue responses. The HEC is the basis for comparison and choice of the critical effect and study. Calculating a HEC is a stepwise procedure. First, adjustment factors are used to determine the observed exposure effect levels in laboratory animals to estimate a concentration that would be an equivalent exposure to humans. The next step is converting the exposure regimen of the experiment to that of the human exposure scenario; that is, a continuous (24-hour/day) lifetime (70-year) exposure. Then, dosimetric adjustments are appropriately applied for the type of toxicant being assessed (particle or gas) and the effect to be assessed (respiratory tract or extra-respiratory toxicity) resulting from an inhalation exposure.

Deposition data are usually reported as the deposition fraction for each respiratory tract region of the species of interest. Deposition fraction is the ratio of the number or mass of particles deposited in the respiratory tract to the number or mass of particles inhaled. Deposition data also may be expressed as efficiencies, that is the amount deposited in a particular region normalized for the amount entering that region, Particulate exposure is characterized by particle diameter (e.g., aerodynamic equivalent diameter [d_{ae}], aerodynamic resistance diameter [d_{ar}], mass median aerodynamic diameter [MMAD]), and the geometric standard deviation (sigma g).

For particles, the determination of the RDDR (regional deposited dose ratio) is required to determine how the dosimetric adjustment would apply to calculate a HEC. The RDDR is a multiplicative factor used to adjust an observed inhalation particulate exposure concentration of an animal (A) to the predicted inhalation particulate exposure concentration for a human (H) that would be associated with the same dose delivered to the r^{th} region or target tissue. The r^{th} region refers to the three respiratory tract regions; extrathoracic, tracheobronchial, or pulmonary that are described in the table below.

Table 1. Respiratory Tract Regions

Extrathoracic	Nose, mouth, nasopharynx, oropharynx, laryngopharynx, larynx
Tracheobronchial	Trachea, bronchi, bronchioles (to terminal bronchioles
Pulmonary	Respiratory bronchioles, alveolar ducts, alveolar sacs, alveoli

(Method for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry; EPA /600/8-901066F; October 1994)

The pulmonary region of the respiratory tract was used for the dosimetric adjustment in this evaluation because the pathology from chromium Ill oxide exposure showed randomly distributed foci or aggregates of pigmented macrophages filled with dense black pigment within alveolar spaces adjacent to the junctions of terminal bronchioles alveolar ducts in test animals. A RDDR of 0.577 for pulmonary effects was calculated from the EPA (1994) RDDR computer program. The study specific data required for this program included: weight of test animal (rat) 152 grams; the MMAD, 1.8 µm; and geometric standard deviation, 1.93. The LOAEL was time adjusted as follows:

$LOAEL_{adj}$ = LOAEL x hours/day x days/week
$LOAEL_{adj}$ =4.4 mg/m^3 x 6/24 x 5/7
$LOAEL_{adj}$ = 0.786 mg/m^3

The $LOAEL_{adj}$ was then converted to the HEC by multiplying the $LOAEL_{adj}$ by the RDDR of 0.577 as follows:

$LOAEL_{HEC}$ = $LOAEL_{adj}$ x RDDR
$LOAEL_{HEC}$ = 0.786 mg/m^3 x 0.577
$LOAEL_{HEC}$ = 0.454 mg/m^3

The UFs were then applied to account for recognized uncertainties in the extrapolation from the experimental data conditions to an estimate appropriate to the assumed human scenario. The RfC was calculated as follows:

RfC = $LOAEL_{HEC}$/(UF1 x UF2 x UF3 X UF4)

Where,
UF1 = 10; to account for the uncertainty of sensitive individual,
UF2 = 10; to account for the uncertainty of subchronic to chronic extrapolation,
UF3 = 3; to account for interspecies variability using the RDDR model,
UF4 = 3; to account for a LOAEL (with trace-to-mild effects) to a NQAEL

RfC = 0.454 mg/m^3/10x10x3x3
RfC = 0.0005 mg/m^3

Conversion of mg/m^3 to $\mu g/m^3$: 0.0005 mg/m^3 x 1000µg/1mg = 0.5 $\mu g/m^3$

RfC = 0.5 $\mu g/m^3$

According to Rule 230(1)(a) the ITSL equals the RfC. The ITSL for chromium III hydroxide is 0.5 $\mu g/m^3$ based on a 24-hour averaging.

References:

1. Derelanko, MJ et al. 1999. Thirteen-week subchronic rat inhalation toxicity study with a recovery phase of trivalent chromium compounds, chromium oxide, and basic chromium sulfate. Toxicological Sciences 52: 278-288.

2. Documentation of Threshold Limit Values and Biological Exposure Indices. 1996. Supplement. Chromium. ACGIH, 6th Edition.

3. EPA. 1994. Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry. Office of Research and Development, Washington D.C. EPA/60018-901066F.

MB:SLB
cc: Cathy Simon, AQD
Mary Lee Hultin, AQD