MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

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INTEROFFICE COMMUNICATION

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November 5, 2015

To: File for Chromium (III) Oxide (CAS No. 1308-38-9)

From: Mike Depa, Toxics Unit, Air Quality Division

Subject: Initial Threshold Screening Level

Previously, the averaging time (AT) assigned to chromium (3) oxide was 24 hours, as per the default methodology (Rule 232(2)(b))(see attached memo from Marco Bianchi dated August 15, 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 (Ill) Oxide (CAS No. 1308-38-9)

From: Marco Blanchi, Toxics Unit, Air Quality Division

Subject: Initial Threshold Screening Level

The initial threshold screening level (ITSL) for chromium Ill oxide is 0.5 micrograms per cubic meter ($\mu g/m^3$) based on a 24-hour averaging time. It should be noted that there are other listings in the Registry of Toxic Effects of Chemical Substances (RTECS) for chromium oxide, but these listings distinguish the chemical name by valence designations and Chemical Abstract Service (CAS) numbers. This ITSL is specifically for chromium Ill oxide (CAS No. 1308-38-9), and should not automatically be used as a surrogate for other trivalent chromium or chromium oxide compounds without first conducting a toxicologic evaluation.

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, RTECS, Environmental Protection Bureau (EPB)-Chemical Criteria Database, EPB library, CAS-online, National Library of Medicine-online, International Agency for Research on Cancer (IARC)-on line, IARC monograph, National Institute for Occupational Safety and Health Pocket Guide, American Conference of Governmental Industrial Hygienists Guide, and the Agency for Toxic Substance and Disease Registry Toxicologic 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 the 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 the air by atmospheric fallout and precipitation.

Trivalent chromium compounds, such as chromium oxide, 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 µg/kilograms (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 milligram (mg)/kg/day for chromium III, 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. Until recently, trivalent chromium toxicity inhalation studies have been limited both in number and scope. But a recently published subchronic inhalation study (Derelanko, 1999) was found that described the toxic effects for the trivalent chromium compound, chromic oxide. In this study, chromic oxide was investigated in rats in a 13-week nose-only study that included a 13-week recovery period. Nose-only exposures to insoluble chromic oxide dust at 4.4, 15, or 44 mg/m^3 (trivalent chromium equivalent concentrations of 3, 10, and 30 mg/m^3) were carried out for six hours/day, five days/week. No compound-related mortality occurred. No apparent compound-related effects were noted for sperm motility or morphology for any concentration. The principal effect was primarily to the respiratory tract. Male and female body weights during exposures to chromic oxide were not statistically different from the control group's mean body weights in any week. Mean body weights of males exposed to the high concentration of chromic oxide were slightly lower than controls during the recover period, but weight gains for these animals were similar to controls. After 13-weeks of exposure, clinical pathology effects showed that none of the exposure groups for either sex exhibited a statistically significant difference from the control group for any hematological, serum biochemical, or urinalysis parameters.

None of the exposure groups demonstrated a statistically significant difference from the control group for any bronchoalveolar lavage evaluation. A yellow intracytoplasmic crystalline material was present with the mononuclear cells from all exposure groups. The relative amount of material and percentage of affected cells increased progressively with increasing exposure concentration. Small amounts of crystals were present in >90% of the cells observed from the low-exposure group animals and

moderate-to-large amounts of crystalline material were noted in >99% of the cells observed in all high-exposure group animals. The amount of crystals in the mid exposure group was intermediate to the other two groups.

Slight, yet statistically significant increases in mean absolute and relative lung/trachea weights occurred in the high-exposure group males. Lung weights were not affected in females. Other statistically significant increases were observed on the mean absolute and relative thyroid/parathyroid weight ratios in the high-exposure group females. These organ weight changes were very small and their biological importance could not be determined. At the recovery sacrifice, organ weights of all the exposure groups were comparable to the control group.

Exposure-related macroscopic findings at the terminal and recovery sacrifices were observed in the lungs and mediastinal lymph nodes of most animals in this study. Green lung discoloration was observed in animals exposed to chromic oxide at all exposure levels. The degree of discoloration increased with exposure level and was present both at the terminal and recovery sacrifices.

Exposure-related microscopic findings showed randomly distributed foci or aggregates of pigmented macrophages filled with dense black pigment. These macrophages were observed within alveolar spaces adjacent to the junctions of terminal bronchioles and alveolar ducts, and subjacent to the pleura in males and females from all chromic oxide treatment groups. Similar black pigment was also observed at the tracheal bifurcation in the peribronchial lymphoid tissue, and within the mediastinal lymph node. The presence of the pigment corresponded to the green discoloration seen macroscopically. Chronic interstitial inflammation was accompanied by septal cell hyperplasia (Type ll pneumocytes) in some mid- and high-exposure group males. The microscopic changes were generally associated with the pigment and corresponded to the increased lung weight observed for the males in the high-exposure group. Lymphoid hyperplasia of the node was also present in all exposure groups. No test article related lesions were seen in the nasal cavities of animals exposed to chromic oxide at any exposure level. When study animals were evaluated at recovery sacrifice (13-weeks post exposure), trace to mild macrophages were noticed in the lung, along with persistent black pigment in the peribronchial lymphoid tissue in all treatment groups for both sexes at approximately equal incidence and severity, as seen in the terminal sacrifice animals. Trace-to-mild septal cell hyperplasia and trace- to-mild chronic interstitial inflammation persisted in males of all treatment groups and females in the mid- and high-exposure groups. These lesions were the same or slightly increased in severity as compared to the terminal sacrificed groups. Trace-to-mild black pigment also persisted in mediastinal lymph nodes in all exposure groups with an apparent increase in incidence in some males in the two lowest exposure groups, compared to the terminal sacrifice group, suggesting pulmonary clearance via the lymphatic system. Most of the pathologic changes observed at the recovery sacrifice were of minimal severity. According to the study investigators, rats exposed to insoluble chromic oxide developed changes in the bronchial and mediastinal lymphatic tissue and lung. The changes appeared to be directly associated with the presence of pigment, observed both macroscopically and microscopically, in the affected tissues. They are believed to have

been a non-specific response to the physical presence of deposits of test material and not a direct toxic effect of the chromic oxide. 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 chromic oxide via the lymphatic system was occurring, although rather slowly. The slow clearance of chronic 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 on the respiratory tract, no evidence of systemic toxicity was observed from exposure to chromic oxide.

The study investigators concluded, that because of the microscopic effects observed in the respiratory tracts of some animals exposed to the lowest level of chromic oxide, a no-observed-adverse-effect level (NOAEL) was not established for this study. They further stated that, however, the low incidence and minimal severity of the pathological effects in the low-level animals suggests that 4.4 mg/m^3 is very near the NOAEL for subchronic exposure to chromic oxide.

After reviewing the Derelanko study, it was determined that 4.4 mg/m^3 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 chromic oxide justifies deriving an oral reference concentration (RfC) for this compound using the EPA's Method for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry guidance document (EPA/600/8-90/066F; 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 is 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 is required to determine how the dosimetric adjustment would apply to calculate an 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, which 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 chromic III 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 (g); the MMAD, 1.8 micrometers (µm); and geometric standard deviation, 1.93. The LOAEL was time adjusted as follows:

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

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

$$LOAEL_{HEC} = LOAEL_{adj} \times RDDR$$
$$LOAEL_{HEC} = 0.786\ mg/m^3 \times 0.577$$

$LOAEL_{HEC} = 0.454\ mg/m^3$

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:

$RfC = LOAEL_{HEC}/(UF1 \times UF2 \times UF3 \times UF4)$

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 $\mu g/m^3$: $0.0005\ mg/m^3 \times 1000\mu g/1mg = 0.5\ \mu g/m^3$

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

According to Rule 230(1)(a) the ITSL equals the RfC. The ITSL for chromium III oxide 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, chromic oxide, and basic chromium sulfate. Toxicological Sciences 52: 278-288.

2. U.S. Environmental Protection Agency. 1994. Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry Office of Research and Development, Washington D.C. EPA/600/8-90/066F.

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