MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

December 27, 1995

TO: File for Chromium III (CAS# 16065-83-1)

FROM: Michael Depa, Toxics Unit

SUBJECT: Screening Level Determination

The initial threshold screening level (ITSL) for chromium III is 5 $\mu g/m^3$ based on an 8 hour averaging time.

The following references or databases were searched to identify data to determine the IRSL: IRIS, RTECS, ACGIH Threshold Limit Values, NIOSH Pocket Guide to Hazardous Chemicals, Environmental Protection Bureau Library, IARC Monographs, CAS Online (1967 - June 15, 1995), National Library of Medicine, Health Effects Assessment Summary Tables, and NTP Status Report. Review of these sources found that EPA has not established an RfC for chromium III. An RfD has been established at 1 mg/kg/day. The ACGIH and NIOSH established occupational exposure limits (OELs) for chromium III at 0.5 mg/m^3.

In one subchronic and two subacute inhalation studies it was shown that chromium III affects alveolar macrophages in the rabbit lung (Johansson et al., 1986a, 1986b, 1987). Groups of 8 male rabbits (strain not specified) were exposed to 0 or 0.6 $\pm$0.4 mg/m^3 chromium III for 4-6 weeks, 5 days/week, for 6 hours/day (Johansson et al., 1986a). All rabbits had macroscopically normal lungs. The number of macrophages washed out from the chromium exposed lungs was not statistically different from control lungs. However, in the dose group, the number of laminated inclusions per macrophage and the percentage of cells containing inclusions were significantly increased over controls ($p<0.01$). Also, a significant increase was found in the percentage of cells with a smooth cell surface and of cells with enlarged golgi apparatus with dilated cisternae ($p<0.02$). Chromium III produced functional differences in macrophages. The oxidative metabolic activity of the macrophages was measured by their ability of reduce nitroblue tetraolium (NBT) to formazan at rest and in the presence of Escherichia coli bacteria. The macrophage NBT reductions at rest and after stimulation with E. coli bacteria were higher than control ($p<0.001$ and $p<0.05$, respectively). The phagocytic activity of the macrophages was also tested. A significantly lower number of intracellular particles were found in the macrophages from rabbits exposed to Chromium III ($p<0.05$). No other tests were performed on the rabbits to determine the toxicity of chromium III exposure. The authors mentioned that the chromium III solution used for generation of the aerosol had a pH of 3 and that this low pH might explain the results. The authors said that this, "does not seem probable because some neutralization by ammonia

should occur in the cages and in the airways of the rabbits." The same $Cr(NO_3)_3 \times 9H_2O$ chromium solution was used in the following two inhalation studies by Johansson et al.

In a similar study, Johansson et al. (1986b) exposed groups of 8 male rabbits (strain not specified) to 0.6 mg/m³ for one month (5 days/week, 6 hours/day). The authors did not mention any statistically significant differences between controls and exposed rabbits. Five out of eight exposed rats had an abnormal macrophage reaction revealed by increased intraalveolar or intrabronchiolar accumulation of macrophages, some of which were enlarged, multinucleated, or strikingly vacuolated. In none of the chromium exposed animals was there evidence of epithelial destruction or abnormal proliferation of epithelial cells. One animal exposed to chromium III had two minor fibrotic nodules. The macrophages of the exposed rabbits had numerous intracellular laminated inclusions, large lysosomes containing membrane figures and distinct black inclusions. There was no difference in the total or relative amount of phospholipids between dosed and exposed rabbits. No other biological tests were performed on the rabbits.

In another study by Johansson et al. (1987) groups of 8 male rabbits (strain not specified) were exposed to 0, 0.6 ± 0.4 or 2.3 ± 1.1 mg/m³ chromium III for about 4 months (range 17-21 weeks), for 5 days/week, 6 hours/day. The pleural surface of the lungs from the high dose exposed rabbits had a grayish color, but otherwise the lungs from all three groups appeared normal. Lung weights were normal. The number of cells washed out of the high dose group was significantly higher ($p<0.001$) than the number washed out from the control group. All animals in the high dose group showed a prominent nodular accumulation of macrophages in terminal airspaces. Two animals in the low dose group showed the same reaction. Five more animals in the low dose group showed a similar reaction but to a lesser extent. The number of laminated inclusions per cell was significantly increased in both exposed groups ($p<0.001$). Macrophages with a smooth surface were significantly more numerous in both exposed groups than in the control group ($p<0.01$). In the high dose group, but not the low dose group, the number of macrophages with elongated shape was significantly increased ($p<0.01$). The amount of total phospholipids in the low dose, but not the high dose, was significantly higher than that in controls ($p<0.05$). No other results were presented.

Table 1. Summary of Johansson et al. Chromium III Inhalation Studies of Rabbit Lungs and Alveolar Macrophages

Study	Dose Level*; Duration	Effects
Johansson et al., 1986a	0.6 mg/m³; 1 month	1. increased laminated inclusions per macrophage 2. increased percentage of macrophages with smooth cell surface and enlarged golgi apparatus with dilated cisternae 3. increased oxidative metabolic activity 4. decreased phagocytic activity
Johansson et al., 1986b	0.6 mg/m³; 1 month	increased intraalveolar and intrabronchiolar accumulation of macrophages
Johansson et al., 1987	0.6 mg/m³; 4 months	1. seven out of eight rabbits had increases in nodular accumulation of macrophages in terminal airspaces 2. increased number of laminated inclusions in macrophages and macrophages with smooth surface 3. increased amount of total phospholipids
	2.3 mg/m³	4. increased number of cells washed out 5. prominent nodular accumulation of macrophages in terminal airspaces in all rabbits 6. increased laminated inclusions in macrophages 7. increased number of elongated macrophages 8. increased number of macrophages with smooth surface

* Chromium III aerosols ($Cr(NO_3)_3 \times 9H_2O$) had pH of 3.

The Johansson et al. inhalation studies were found to be limited in their investigation because only alveolar macrophage structure and function were analyzed along with lung histopathology. Still, useful information was obtained from these studies. During the evaluation of these studies special attention was placed on the identification of adverse[1] effects. Macrophages have the ability to be "activated", a process that results in an increase in cell size, increased levels of lysosomal enzymes, more active metabolism and a greater ability to phagocytize (Robbins and Kumar, 1987). The chromium III exposed macrophages described in these studies appear to be activated, explaining the increased oxidative metabolism (Johansson et al., 1986a). However, the decreased phagocytic activity observed in the 1 month, 0.6 mg/m³ exposure scenario should be designated a functional deficit but

[1] The EPA (1994) describes a lowest observed adverse effect level (LOAEL) as, "Reversible cellular changes including cloudy swelling, hydropic change, or fatty changes." Effects also considered LOAELs are, "Degenerative or necrotic tissue changes with no apparent decrement in organ function."

should not be considered a degenerative tissue effect. In the 4 month study (Johansson et al., 1987) the low dose (0.6 mg/m³) had an increased amount of total phospholipid which was not seen at the high dose (2.3 mg/m³). It is unclear if this is an "adverse" effect. Likewise, the prominent nodular accumulation of macrophages in the terminal airspaces is probably a reversible cellular phenomenon related to the chromium III exposure and, therefore, should not be considered an adverse effect. Unfortunately, in the 4 month study the authors did not analyze for either macrophage or lung function. Without substantiated organ function changes one should not conclude that the 0.6 and 2.3 mg/m³ dose levels produced adverse effects. In addition, a viable but untested hypothesis is that the acid nature of the $Cr(NO_3)_3 \times 9H_2O$ aerosol (pH 3) may have contributed to the morphological and functional changes seen in the rabbits. Given the limited nature of the toxicological investigation a LOAEL was not identified from these studies.

As noted above, the RfD for chromium III is 1 mg/kg/day. A surrogate ITSL based on the RfD was calculated using Rule 232(1)(b) and determined to be 3500 µg/m³. Chromium III is a particulate at standard temperature and pressure. Considering that the NAAQS for particulates is 50 µg/m³ (annual averaging time) and 150 µg/m³ (24 hour averaging time) it was deemed that an RfD derived ITSL would be inadequate to protect against particulate induced health effects. Also, the effects seen in the oral studies used to derive the RfD were different from those seen in the Johansson et al. studies. These differences indicate that the oral to inhalation route extrapolation is not appropriate.

During the literature search a source was found that mentions a "reference air concentration" or RAC of 1000 µg/m³ for chromium III. This RAC was developed to limit the emissions of boilers and industrial furnaces. It was found that it was based on the RfD and determined to be inadequate to protect public health based on the expected particulate effects as mentioned above.

In the ACGIH Documentation of Threshold Limit Values (TLVs), the ACGIH does not provide much toxicological rationale for the chromium III standard. Still, the ACGIH stated, "Early studies indicated that trivalent chromium and divalent chromium compounds have a low order of toxicity" (ACGIH, 1993). After a literature search, it became evident that there is little inhalation toxicity information on chromium III. The inhalation data available was insufficient to derive a reference concentration for chromium III. The occupational exposure limit has been in existence for chromium III since 1946, and reports of chromium III health effects above the OEL are not noted in the literature. This provides some support for using the OEL for the derivation of the ITSL. Further support comes from the Johansson et al. studies mentioned above. An adverse effect level was not identified at the low dose of 0.6 mg/m³, which can be related to the OEL of 0.5 mg/m³.

Rule 232 hierarchy describes that the ITSL is to be based on an RfC when available (Rule 232(1)(a)). There was no RfC available for chromium III. The RfD, next in line for the derivation of the ITSL, was determined to be inadequate to protect public health based on particulate effects and the oral to inhalation route extrapolation differences mentioned above. There was no information indicating that

an OEL derived ITSL would be inappropriate. Therefore, the ITSL is based on the TLV; its derivation is described below according to Rule 232(1)(c).

ITSL = OEL divided by 100

Where OEL is the TLV, or REL.

ITSL = 0.5 mg/m^3 ÷ 100 = 0.005 mg/m^3

0.005 mg/m^3 x (1000 μg)/(1 mg) = 5 $\mu g/m^3$

The ITSL for chromium III is 5 $\mu g/m^3$ based on an 8 hour averaging time.

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