DATE: August 28, 2001

MEMORANDUM

SUBJECT: ***Inorganic Chromium*** - Report of the Hazard Identification Assessment Review Committee.

FROM: Jonathan Chen, Ph.D.
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THROUGH: Jess Rowland, Co-Chair
and
Elizabeth Doyle, Co-Chair
Hazard Identification Assessment Review Committee
Health Effects Division (7509C)

TO: Norm Cook, Chief
Risk Assessment and Science Support Branch
Antimicrobial Division (7510C)

PC Code: 021101, 068302, 068304

On August 28, 2001, the Health Effects Division's Hazard Identification Assessment Review Committee (HIARC) evaluated the toxicology data base of **hexavalent Inorganic Chromium [Cr(VI)],** established the toxicological endpoints for incidental residential oral exposure as well as occupational exposure risk assessments. The Committee's conclusions are presented in this report.

Committee Members in Attendance

Members present were: W. Burnam, E. Doyle, P. Hurley, D. Nixon, A. Assaad, J. Liccione, J. Rowland, B. Tarplee, J. Chen and P. Deschamp.

Also in attendance were: Doreen Aviado of the Antimicrobial Division.

Data evaluation prepared by: Steve Malish of the Antimicrobial Division.

Data Evaluation / Report Presentation :

Jonathan Chen	And	Tim Mcmahon
Toxicologist		Senior Scientist

1 INTRODUCTION

In order to support a Reregistration Eligibility Decision (RED) for the non-food use of chromium (VI) as contained in the wood preservative Chromated Copper Arsenate (CCA) , on August 28, 2001, the Health Effects Division's Hazard Identification Assessment Review Committee (HIARC) evaluated the toxicology data base of **hexavalent Inorganic Chromium [Cr(VI)],** and established toxicology endpoints for assessment of incidental oral , dermal, and inhalation exposure in the occupational and residential settings.

In this report, the NOAEL/LOAEL values are denoted as the weight of the Cr(VI) compound actually used in the study in mg/kg/day. The molar equivalents of Cr(VI) in mg/kg/day is also included and this value is denoted in brackets "[ ]".

2 HAZARD IDENTIFICATION

2.1 Acute Reference Dose (RfD)

Cr (VI), as contained CCA, is not listed for food use. Therefore, an acute RfD is not required.

2.2 Chronic Reference Dose (RfD)

Cr (VI), as contained CCA, is not listed for food use. Therefore, a chronic RfD is not required.

2.3 Occupational/Residential Exposure

Although CCA is not listed for food use, under certain situations (for example, the hand-to-mouth activity for children playing around playground equipment), human may be exposed to the chemical of concern through the oral route. The committee thus selected short- and intermediate-term incidental oral exposure endpoints based on potential oral exposures in the occupational and residential settings.

2.3.1 Short-Term Incidental Oral (1-30 days) Exposure

Study Selected: Developmental/Rabbit [Tyl, 1991] § 870.3700

MRID No.: 421712-01

Executive Summary:
The developmental and maternal effects of daily administration of chromic acid (55.0% a.i.) at dosages of 0, 0.1, 0.5, 2.0 or 5.0 mg/kg/day by gavage were studied in rabbits.

Clinical signs of toxicity , including diarrhea, and slow, audible or labored breathing were observed predominately in the 2.0 and 5.0 mg/kg/day groups.

These signs were observed in slightly higher incidence at the 2.0 mg/kg/day dose level than at the 5.0 mg/kg/day dose level. However, the incidence of mortality (at 2.0 mg/kg/day, one doe died on gestation day (GD) 28; at 5.0 mg/kg/day, 5 does died (one each on GD 10, 14, two on GD 15, and one was sacrificed on GD 24) and the magnitude of decreased body weight gain during the dosing period (average weight loss of 48 grams at 2.0 mg/kg/day and average weight loss of 140 grams at 5.0 mg/kg/day during gestation days 7-19) were observed to occur in a dose-related fashion at 2.0 and 5.0 mg/kg/day. Food efficiency was also observed to be significantly lower during the dosing period in the 5.0 mg/kg/day dose group. Cesarean section observations were unremarkable in this study at any dose level tested. No treatment related effects on either fetal malformations or variations were observed.

The Maternal NOAEL = 0.5 [0.12] mg/kg/day and LOAEL = 2.0 [0.48] mg/kg/day (based on the increased incidence of maternal mortality and decreased body weight gain). The Developmental NOAEL = 2.0 [0.48] mg/kg/day and LOAEL > 2.0 [>0.48] mg/kg/day based on the lack of developmental effects at any dose level tested.

Dose and Endpoint for Risk Assessment: The **maternal NOAEL = 0.5 [0.12]** based on **increased mortality and decreased body weight gain at 2.0 [0.48] mg/kg/day.**

Comments about Study/Endpoint:
The one doe died at 2.0 mg/kg/day on gestation day (GD) 28; whereas death of the four rabbits died at the 5.0 mg/kg/day dose level occurred on GDs 10-15 (one rabbit was sacrificed on day 24). Although only one animal died at the 2.0 mg/kg/day dose, there was commonality of symptoms prior to death at both the 2.0 and 5.0 mg/kg/day doses. All animals displayed weight loss and few feces prior to death. In addition, there was a temporal relationship of mortality with increasing doses. Thus, the committee included mortality as part of the selection of the LOAEL for this study.

2.3.2 Intermediate-Term Oral (1- 6 months) Exposure

Study Selected: Developmental/Rabbit [Tyl, 1991] § 870.3700

MRID No.: 421712-01

Executive Summary:
See Short-Term Incidental Oral (1-30 days) Exposure above.

Dose and Endpoint for Risk Assessment:
The **maternal NOAEL = 0.5 [0.12]** based on **increased mortality and decreased body weight gain at 2.0 [0.48] mg/kg/day.**

Comments about Study/Endpoint:
Same as Short-term Incidental Oral Exposure.

Two other studies were also considered in the meeting for selection of the intermediate-term incidental oral endpoint:

(1). Mackenzie. R.D., Byerrum, R.U. Decker, C.F. et al. 1958. Chronic toxicity studies. II Hexavalent and trivalent chromium administered in drinking water to rats. AMA. Arch Industrial Health 18: 232-234., and

(2). Zhang, J; and Li, S. 1987. Chromium pollution of soil and water in Jinxhou. J. Chin. Prevent Med. 21:262-264.

and

Zhang, J; and Li, . 1997. Cancer motality in a Chinese Population Exposed to Hexavalent chromium in water. JOEM 39: 315-319.

These two studies are summarized below:

MacKenzie, et al. 1958
This is the principle study supporting the chronic RfD as published in the 1998 IRIS updated for Cr(VI). There are two experiments reported in the study. In the first study, groups of eight male and eight female Sprague-Dawley rats were supplied with drinking water containing 0.45-11.2 ppm (0, 0.45, 2.2, 4.5, 7.7, and 11.2 mg/L) hexavalent chromium (as K_2CrO_4) for 1 year. The control group received (10/sex) received distilled water. The second experiment involved 3 groups of 12 male and 9 female rats. One group was given 25 ppm (25 mg/L) chromium (VI) as K_2CrO_4, a second group received 25 ppm chromium in the form of chromium chloride (Cr III). And the controls again received distilled water.

No significant adverse effects were seen in appearance weight gain, or food consumption. There were no pathological changes in the blood or other tissues in any treatment group. The rats receiving 25 ppm of chromium (as K_2CrO_4) showed approximately a 20% reduction in water consumption. For rats treated with 0-11 ppm (in drinking water), blood was examined monthly, and tissues (livers, kidneys and femurs) were examined at 6 months and at 1 year. Spleens were also examined at 1 year. The 25 ppm groups (and the corresponding controls) were similarly examined, except that no animals were killed at 6 months. An abrupt rise in tissue chromium concentrations was noted in rats treated with more than 5 ppm. The authors stated “apparently tissues can accumulate considerable quantities of chromium before pathological changes result” in the 25 ppm treatment group.

Based on the body weight of the rat (0.35 Kg) and the average daily drinking water consumption for the rat (0.035 L/animal /day), this dose can be converted to mg/kg/day**. NOAEL:** 25 ppm = 2.5 [0.67] mg/kg/day; **LOAEL:** >25 ppm = >2.5

[>0.67] mg/kg/day (based on the 25 ppm HDT) dose level of potassium chromate.

Zhang and Li, 1987 and 1997

As summarized in in the 1998 IRIS updated for Cr(VI), in 1965, a study of 155 subjects exposed to drinking water at concentration of approximately 20 mg/L was conducted outside Jinzhou, China. Subjects were observed to have sores in the mouth, diarrhea, stomachache, indigestion, vomiting, elevated white blood cell counts with respect to the controls, and a higher per capita rates of cancers, including lung cancer and stomach cancer. Further statistical analysis revealed no clear association of cancer motality with exposure to Cr(VI) - contaminated groundwater. Precise exposure conditions, exposure durations, and confounding factors were not discussed, and this study does not provide a NOAEL for the observed effects. Based on the body weight of the man (70 Kg) and the average daily drinking water consumption for the rat (2 L/day). The estimated exposed would be around 6 mg/kg/day of Cr(VI).

By comparing the results of these studies to the results of the Tyl, 1991 study, the Committee concluded the end point selected based on the rabbit development study results would be appropriate for the Intermediate-Term Oral (1- 6 months) Exposure risk assessment. Reasons are:

(1). It is a well-designed multi-dose study;
(2). The study has better NOAEL/LOAEL than MacKenzie, et al. (1958) study, but does not conflict with the results of the study; and
(3). It is protective of effects seen in human study.

2.3.3 Dermal Absorption

Study Selected: Skin Permeation and Cutaneous Hypersensitivity as a Basis for Making Risk Assessments of Chromium as a Soil Contaminant [Bagdon, 1991]. .

Executive Summary: Sodium chromate (Cr VI) was applied to the skin of guinea pigs and the skin permeation was determined by assay of 51Cr content present in the excreta (1.11%) and organs (0.19%) after 24 hours. In this study in guinea pigs, skin penetration of chromium amounted to 1.30% of the applied dose after 24 hours (Bagdon, 1991)..

Using another in vivo method, a weighed amount of the agent was patched to the skin of guinea pigs and the concentration followed by determination of the remaining agent at the application site after different intervals. Skin penetration was concentration dependent. The range used was 0.0048 to 1.689 M. Dermal penetration for hexavalent chromium amounted to 2.6% of the applied dose of 0.0175 M/5 hours and 4.0% at 0.261 M/5 hours. At 0.261 M, the skin permeation rate was 700 mμM/cm2/hr. This procedure may overestimate skin penetration because chromium present in the skin depot would be calculated as part of the

residual test material at the skin's surface (Bagdon, 1991).

Dermal Absorption Factor: 1.3%

Comments about Study/Endpoint:
The dermal absorption factor of 1.3% is consistent with the results reported from other studies (ATSDR, 2000).

2.3.4 Dermal Exposure (All Durations)

Hexavalent chromium is a strong skin irritant. In addition, Cr (VI) is a strong skin allergen. The potent skin allergenicity of chromium has been well documented in the literature, and chromium compounds have been reported to be the most frequent sensitizing agent in man. Most of the occurrences of contact dermitis cited are the result of occupational exposures. For previously sensitized individuals, very low dosage of Cr(VI) can elicit allergic contact dermitis. In addition, a variety of animal models including guinea pigs and mice have conclusively demonstrated that hexavalent chromium is a potent skin sensitizer. Therefore, the Committee concluded that the skin irritation and the skin allergenicity effects are the primary concern for Cr(VI) through the dermal exposure route. No end point will be selected for risk assessment. The risk concern of the dermal contact of Cr(VI) should be addressed through warning language used on the labels.

2.3.5 Inhalation Exposure (All Durations)

Consistent with the Agency practice, the endpoint for inhalation exposure risk assessments is taken from the 1998 IRIS update for Cr(VI), and applies to all durations of inhalation exposure.

Study Selected: Linberg E and Hedenstierna, G. 1983. Chrom plating: Symptoms, finding in the upper airways, and effects on lung function.

Guideline #: NA

MRID No.: NA

Executive Summary:
Humans: Linberg, 1983 studied respiratory symptoms, lung function and changes in nasal septum in 104 workers (85 males, 19 females exposed in chrome plating plants. Workers were interviewed using a standard questionnaire for the assessment of nose, throat and chest symptoms. Nasal inspections and pulmonary function testing were performed as part of the study.

The median exposure time for the entire group of exposed subjects (104) in the study was 4.5 years (0.1-36 years). A total of 43 subjects exposed almost exclusively to chromic acid experienced a mean exposure of 2.5 years (0.2-23.6

years). The subjects exposed almost exclusively to chromic acid were divided into a low exposure group (8-hr TWA below 0.002 mg/m^3, N=19) and a high-exposure group (8-hr TWA above 0.002 mg/m^3, N=24). Exposure measurements using personal air samplers were performed for 84 subjects in the study on 13 different days. Exposure for the remaining workers 20 workers was assumed to be similar to that measured for workers in the same area. Nineteen office employees were used as controls for nose and throat symptoms. A group of 119 auto mechanics whose lung function had been evaluated by similar techniques was selected as controls for lung function measurements. Smoking habits of workers were evaluated as part of the study.

At mean exposures below 0.002 mg/m^3, 4/19 workers from the low-exposure group experienced subjective nasal symptoms. Atrophied nasal mucosa were reported in 4/19 subjects from this group and 11/19 had smeary and crusty and septal mucosa, which was statistically higher than the controls. No one exposed to levels below 0.001 mg/m^3 complained of subjective symptoms. At mean concentrations of 0.002 mg/m^3 or above, approximately 1/3 of the subjects had reddened, smeary or crusty nasal mucosa. Atrophy was seen in 8/24 workers, which was significantly different from controls. Eight subjects had ulcerations in the nasal mucosa and 5 had perforations of the nasal septum. Atrophied nasal mucosa was not observed in any of the 19 controls, but smeary and crusty septal mucosa occurred in 5/19 controls.

Short-term effects on pulmonary function were evaluated by comparing results of tests taken on Monday and Thursday among exposed groups and controls. No significant changes were seen in the low-exposure group or the control group. Non-smokers in the high-exposure group experienced significant differences in pulmonary function measurements from the controls, but the results were within normal limits.

The authors concluded that 8 hour exposure to chromic acid above 0.002 mg/m^3 may cause a transient decrease in lung function, and that short-term exposure to greater than 0.002 mg/m3 may cause ulceration and perforation. Based on the result of this study, a LOAEL of 0.002 mg/m^3 can be identified for incidence of nasal septum atrophy following exposure to chromic acid mists in chrome plating facilities. At TWA exposures greater than 0.002 mg/m^3, nasal septum ulcerations and perforations occurred in addition to the atrophy reported at lower concentrations. The LOAEL is based on an 8 hour TWA occupational exposure. The LOAEL is adjusted to account for continuous exposure according to the following equation.

LOAELc = 0.002 mg/m^3 x (MVo/MVh) x 5 days/7days, where: LOAELc is the LOAEL for continuous exposure.

MVho is the breathing volume for an 8 hour occupational exposure (10 m^3); MVh is the breathing volume for a 24 hour continuous exposure (20 m^3)

The LOAEL of 0.002 mg/m3 based on a TWA exposure to chromic acid was converted to a LOAEL for continuous exposure of 7.14 x 10-4 mg/m^3 based on ulcerations, perforations of the nasal septum and pulmonary function changes.

Dose and Endpoint for Risk Assessment: LOAEL for continuous exposure of 7.14 x 10-4 mg/m^3 based on ulcerations, perforations of the nasal septum and pulmonary function changes. NOAEL = 2.4 x 10-4 mg/m^3.

Comments about Study/Endpoint:
A MOE of 100 selected (10 x is applied to account for extrapolation from a LOAEL to a NOAEL and 10 x is applied to account for interhuman variation).

2.3.6 Margins of Exposure for Occupational/Residential Risk Assessments

A MOE of 100 is selected for short, and intermediate-term oral risk assessments. A MOE of 100 is selected for short, and intermediate, and long-term inhalation risk assessments.

3 CLASSIFICATION OF CARCINOGENIC POTENTIAL

The following information is taken from the IRIS summary of hexavalent chromium:

Under the current guidelines (EPA, 1986), Cr(VI) is classified in Group A - known human carcinogen by the inhalation route of exposure . The air unit risk was 1.2 x 10^{-2} per ($\mu g/m^3$). Carcinogenicity by the oral route of exposure cannot be determined and is classified in Group D.

4 FQPA CONSIDERATIONS

This is a non-food use chemical (inorganic chromium is a component of CCA-treated wood) and does not required any food tolerance. Consequently, it does not come under the Food Quality Protection Act of 1996.

5 HAZARD CHARACTERIZATION

Hexavalent chromium is characterized by significant lethality after acute exposures by the oral, dermal, and inhalation routes (LD50/LC50 values in the Toxicity Category I range). Hexavalent chromium also produces significant skin irritation and dermal sensitization. Dermal absorption of hexavalent chromium is low (absorption of 1.3% of an applied dose through the skin of guinea pigs). Relative bioavailability of hexavalent chromium through ingestion of soil and water is also low.

In a subchronic study in rats treated with potassium dichromate at up to [9.2] mg/kg/day (NTP, 1996), no treatment related findings were noted except for slight decreases in mean corpuscular volume and mean corpuscular hemoglobin, the NOAEL being [2.3] mg/kg/day. In a subchronic study in mice treated at up to [36.8] mg/kg/day with potassium dichromate (NTP, 1997a), hepatocytic cytoplasmic vacuolization was seen at [4.6] mg/kg/day, the NOAEL being [1.4] mg/kg/day.

In a developmental toxicity study in rabbits administered chromic acid (Tyl, 1991), maternal toxicity was observed at a (LOAEL) of [0.48] mg/kg. No developmental effects occurred at this dose. Mice administered chromic acid at doses up to 120 mg/kg/day showed maternal toxicity at the same doses at which developmental effects occurred. In a mouse reproductive study done by the "continuous breeding protocol" at up to 37 mg/kg /day potassium dichromate (NTP, 1997b), Cr (VI) was not considered a reproductive toxicant. Other studies on the developmental and reproductive toxicity of hexavalent chromium (ATSDR, 2000) have shown adverse effects including reduced number of corpora lutea and implantations, retarded fetal development, and embryo - fetotoxic effects, including reduced number of fetuses (live and dead) per dam and higherincidences of stillbirths and postimplantation loss in mice doses at 500 and 750 ppm without adverse effect in maternal animals. Additionally, in male rats administered 20 mg/kg/day chromium trioxide for 90 days by gavage, reduced testicular weight, decreased testicular testosterone, and reduced Leydig cell number have been observed (Chowdhury and Mitra, 1995).

In contrast to chromium VI, feeding of chromium oxide (III) to male and female rats at a dose of 1806 mg/kg/day in a developmental toxicity study (Ivankovic and Preussmann, 1975) had no effect on fertility, gestation length, or litter size.

In chronic toxicity studies, groups of eight male and eight female Sprague-Dawley rats [MacKenzie, 1958] were supplied with drinking water containing 0.45-11.2 ppm (0, 0.45, 2.2, 4.5, 7.7, and 11.2 mg/L) hexavalent chromium (as K_2CrO_4) for 1 year. The control group received (10/sex) received distilled water. No significant toxic effects were observed in this study despite the accumulation of chromium residues in tissues. The authors stated that “apparently tissues can accumulate considerable quantities of chromium before pathological changes result.” In a chronic toxicity study in dogs, dogs were orally exposed to potassium chromate in drinking water for 4 years at 0, 0.45, 2.25, 4.5, 6.75 and 11.2 ppm [Anwar, R.A. et al. (1961)]. No effects were observed with regard to gross and microscopic analysis of all major organs, urinanalysis and the weights of the spleen, liver and kidney.

In long-term inhalation studies, Glaser (1986, 1988) exposed groups of 20 male Wistar rats to aerosols of sodium dichromate ($Na_2Cr_2O_7$) at measured concentrations of 0.025, 0.05, and 0.1 mg Cr(VI)/m^3, 22 hr/day, 7 days/ week for 18 months in horizontal flow inhalation chambers. Three lung tumors, (one adenocarcinoma and two adenomas), were reported in the high-concentration group, although, it is not clear whether the adenocarcinoma and adenomas occurred in the same animal or in different animals (U.S. EPA 1998). A squamous cell carcinoma in the pharynx/larynx region was also observed in the high-concentration group. One primary lung adenoma was

observed in the chromium oxide (CrO_3) exposed group. No tumors were reported in the lungs or pharynx of control rats. All other tumors in other tissues were not considered to be related to treatment by the study authors.

The results of this study indicate that exposure to sodium dichromate or chromium oxide aerosols at levels of 100 μg Cr/m^3 result in a weak carcinogenic effect. However, the authors recommended further studies involving larger populations of animals and longer observation periods be conducted.

Hexavalent chromium (Cr VI) is known to be carcinogenic in humans by the inhalation route of exposure. Results of occupational epidemiologic studies of chromium-exposed workers are consistent across investigators and study populations. Dose-response relationships have been established for chromium exposure and lung cancer. Chromium-exposed workers are exposed to both Cr(III) and Cr(VI) compounds. Because only Cr(VI) has been found to be carcinogenic in animal studies, however, it was concluded that only Cr(VI) should be classified as a human carcinogen.

Under the current guidelines (EPA, 1986), Cr(VI) is classified as Group A - known human carcinogen by the inhalation route of exposure . The air unit risk was 1.2 x 10^{-2} per (g/m^3). Carcinogenicity by the oral route of exposure cannot be determined and is classified as Group D. Mutagenicity studies revealed that Cr(VI) is a potent mutagen in virtually all mutagenicity tests performed so far.

6 DATA GAPS

There is no data gap identified.

7 ACUTE TOXICITY

Acute Toxicity Summary of Cr(VI)

Guideline	Study Type [Substance]	MRID/Literature	Results	Toxicity Category
81-1 (OPPTS 870.1100)	Acute Oral/Rat [Chromic Acid, 100% a.i.]	434294-01	LD_{50} = ♂ 56 mg/kg = ♀ 48 mg/kg M+F = 52 mg/kg	I
81-2 (OPPTS 870.1200)	Acute Dermal/Rabbit [Chromic Acid, 100% a.i.]	434294-02	LD_{50} = ♂ >48 mg/kg = ♀ 48 mg/kg M+F = 57 mg/kg	I
81-3 (OPPTS 870.1300)	Acute Inhalation/Rat [Chromic Acid, 100% a.i.]	434294-03	LC_{50} = ♂ 0.263 mg/L = ♀ 0.167 mg/L M+F = 0.217 mg/L	I
81-4 (OPPTS 870.2400)	Primary Eye Irritation [Various Cr(VI) compounds]	Literature	Waiver Corrosive	I
81-5 (OPPTS 870.2500)	Primary Dermal Irritation [Various Cr(VI) compounds]	Literature	Waiver Corrosive	I
81-6 (OPPTS 870.2600)	Dermal Sensitization /Guinea Pig [Various Cr(VI) compounds]	Literature	Strong sensitizer	

8 SUMMARY OF TOXICOLOGY ENDPOINT SELECTION

The doses and toxicological endpoints selected for various exposure scenarios are summarized below.

EXPOSURE SCENARIO	DOSE (mg/kg/day)	ENDPOINT	STUDY
Acute Dietary	This risk assessment is not required.		
Chronic Dietary	This risk assessment is not required.		
Incidental Short- and Intermediate-Term Oral	NOAEL= 0.5of chromic acid [0.12 of Cr(VI)] MOE = 100	based on the increased incidence of maternal mortality and decreased body weight gain at LOAEL of 2.0 [0.48]	Developmental/Rabbit [Tyl, 1991]
Dermal Exposure[(b).] (All Duration)	Because the dermal irritation and dermal sensitization are the primary concern through dermal exposure route, no toxic end-point is selected. The risk concern should be address through labeling.		
Inhalation Exposure (All Duration)	LOAEL= 2.4 x 10^{-4} (mg/m^3) MOE = 100	nose and throat symptoms	Linberg E and Hedenstierna, G. 1983.

Note:

(a). MOE = Margin of Exposure; NOAEL = No observed adverse effect level; and LOAEL = Lowest observed adverse effect level.

(b). The dermal absorption factor = 1.3%.

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