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Attention: Section 8(e) Coordinator

Re: Notice of Substantial Risk under TSCA 8(e) for Chromium(III) Oxide
when Administered by Nose-only Inhalation to Rats for 90 Days
EPA Docket No. ---Unknown

Gentlemen:

This submission of information in accordance with the requirements of TSCA 8(e) is to supplement our letter of May 23, 1995 wherein preliminary results on basic chromium(III) sulfate were provided.

In addition to basic chrome(III) sulfate exposures described previously, animals were also exposed to chromium(III) oxide for 6 hours/day, 5 days/week for 13 weeks to concentrations of 0, 4.4, 15 and 44 mg/m³ of chromium(III) oxide which, again, corresponds to chromium(III) levels of 0, 3, 10 and 30 mg/m³, respectively.

The draft report for this series of exposures is now under review and it appears there were findings on chrome(III) oxide which were not appreciated until all data had been considered. Enclosed for your information is a copy of the summary for the draft report which includes results for both chromium compounds. The results on chromium(III) oxide appear to be typical of what might be expected from any inert particulate and does not really represent a "substantial risk" because of the high levels of exposure to rats which are not expected in an industrial setting.

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It is expected that the final audited report will be available within the next several months and a copy will be submitted to your office when available.

The IHF acts as Agent for the Chromium Chemicals Health and Environmental Committee, the membership of which consists of Harcros Chemical Group (American Chrome and Chemicals, British Chrome and Chemicals and Wayne Chemical Corporation), AlliedSignal, Inc., Bayer AG, and Occidental Chemical Corporation.

Should you have any questions, you may contact me at 412/363-6600.

Sincerely,

William E. Rinehart
William E. Rinehart, Sc.D.
Consultant in Toxicology

WER:la

Enclosure



1. SUMMARY: Thirteen Week Subchronic Inhalation Toxicity (with Recovery) Study on Chromic Oxide and Basic Chrome Sulfate in Rats

The objective of this study was to evaluate the subchronic toxicity of chromic oxide and basic chrome sulfate when administered to rats via nose-only inhalation exposure for thirteen (13) consecutive weeks. These test articles were selected as representative of various families of chromium compounds. The desired exposure levels were selected by the Sponsor to be multiples of the threshold limit value (TLV) for trivalent chrome and set at chrome equivalents of 3, 10 and 30 mg/m³ for each test article. This study consisted of seven (7) groups of fifteen (15) male and fifteen (15) female Fischer rats. One group (Group 1) served as the negative control (0 mg/m³), three (3) treatment groups (Groups 2, 3 and 4) were exposed to chromic oxide (Cr₂O₃) and the three (3) other groups (Groups 5, 6 and 7) were exposed to basic chrome sulfate (Cr₂(OH)_x(SO₄)_y · nH₂O · zH₂O).

The desired exposure levels were 4.4, 15 and 44 mg/m³ for chromic oxide and 17, 58 and 175 for basic chrome sulfate. The exposures were conducted in 75 and 73-liter nose-only exposure chambers, for six (6) hours daily for thirteen (13) weeks (excluding weekends and holidays). Each animal was observed immediately prior to and following each exposure for overt toxicity and mortality. Body weights and clinical signs were recorded weekly for each rat. After 13 weeks of exposure, ten (10) males and ten (10) females from each group underwent hematologic, serum biochemical, urological, ophthalmologic and sperm characteristic (males only) evaluations, as well as a complete necropsy examination and histopathologic evaluations. After a thirteen (13) week post-exposure recovery period, the remaining animals also underwent a complete necropsy examination and limited histopathologic examinations.

During study weeks seven (7) and eight (8), an additional five (5) male and five (5) female Fischer rats were exposed for five (5) consecutive days at each exposure level. On the day following exposure, each rat was evaluated for various bronchoalveolar lavage fluid (BALF) parameters.

Six animals died on exposure day 1 as a direct result of the restraint tubes. These animals were replaced with animals of similar weight from the same purchase order shipment. One animal mortality (Group 7, male) occurred on exposure day 4 of this study. The cause of death for this animal is not completely clear. The death may be related to the six animals found dead on exposure day 1. However, macroscopic examination at necropsy did not reveal any evidence of trauma. Assigning this death as an exposure-related mortality does not seem appropriate because no other exposure-related mortalities occurred during the conduct of this study. No exposure-related effects were noted in the clinical signs or the ophthalmologic evaluations.

Exposure-related reduced body weight gains, some statistically significant at the p < 0.1 level, were observed in the mid and high exposure levels for basic chrome sulfate. At the terminal sacrifice, the control group males had gained approximately 51% in mean body weight, while the Group 5, 6, and 7 males gained approximately 50%, 46% and 39%, respectively. The Group 7 females gained 33% compared to a 38% weight gain in the control group females.

At the recovery sacrifice, the Group 6 and 7 males continued to exhibit a mean body weight that was significantly lower than the control group, but the approximate weight gains for the recovery period were slightly greater than the control group males (26% for control group, 29 - 32% for Groups 5, 6 and 7). The female mean body weights and body weight gains in Groups 5, 6 and 7 were comparable to the control group at the recovery sacrifice. After 13 weeks of exposure, the mean body weights of animals exposed to chromic oxide were comparable to the control group with the males gaining 50% in each group and the females gaining 35 - 38%. During the recovery period, the body weight gains continued to be similar to the control group. Group 2, 3, and 4 males gained 27 - 29% compared to 26% for the control group males, and the females gained 20 - 21% compared to 20% for the control group females.

No apparent exposure related effects were noted for sperm motility, sperm morphology and concentration for either test material.

Most hematology, serum biochemistry, and urinalysis values from all treatment groups were similar to the control group. Increased leukocytes and segmented neutrophils, some statistically significant, were noted in Groups 6 and 7 males and females. Other findings noted were considered incidental.

No exposure related changes in BALF parameters were observed for animals exposed to chromic oxide, however a yellow crystalline material was present within the mononuclear cells from Groups 2, 3 and 4. The BALF values from animals exposed to basic chrome sulfate showed several treatment related effects, including decreased total nucleated cell counts, increased protein and lactate dehydrogenase activity, increased cell debris and lysed cells.

Macroscopic examination at the terminal sacrifice showed green discoloration in the lungs and lymph nodes of animals exposed to chromic oxide and a corresponding gray discoloration in the animals exposed to basic chrome sulfate. Some of the discoloration was resolved by the recovery sacrifice.

Statistically significant increases ($p < 0.01$) in the mean lung/trachea organ weights, lung/trachea to body weight ratios and lung/trachea to brain weight ratios were noted for the chromic oxide, Group 4 males and the basic chrome sulfate, Group 5, 6 and 7 males and females at the terminal sacrifice. These organ weight changes correspond to changes observed microscopically. At the recovery sacrifice, the basic chrome sulfate, Group 6 and 7, males and females continued to exhibit statistically significant increases ($p < 0.01$) in the lung/trachea organ weights and associated ratios. Other organ weight and organ weight-ratio changes were observed in the liver, kidney, spleen and thyroid/parathyroid, some statistically significant at the $p < 0.05$ or $p < 0.01$ levels, for the basic chrome sulfate Group 6 and 7 males and females at the terminal sacrifice. No corresponding changes were observed microscopically. The biological importance of these changes could not be determined from the data in this study. At the recovery sacrifice, with the exception of kidney weights in Groups 6 and 7, all other organ weights were comparable to the control values. Other findings noted were considered incidental. Values from the chromic oxide Groups 2 and 3 were comparable to the control values.

Exposure-related microscopic changes were observed in the lungs, lymphoid tissue and mediastinal lymph nodes at the terminal sacrifice for all groups males and females, exposed to chromic oxide. Exposure-related microscopic changes were observed in the lungs, larynx, mediastinal lymph node and nasal cavity at the terminal sacrifice of all groups, males and females, exposed to basic chrome sulfate. These changes varied from trace to severe and from focal to diffuse.

Animals exposed to chromic oxide developed lung changes with black pigment accumulated in macrophages and black pigment present in lymphoid tissue. The pigment observed stained black with hematoxylin and eosin stain and was presumed to represent the test article. The findings correspond to the green lung discoloration seen macroscopically and to the increased lung weight observed for the Group 4 males. The changes observed in the lungs, peribronchial lymphoid tissue and mediastinal lymph node are similar to those previously reported for other inhaled, insoluble, inert particles (Lee, et al., 1986; Muhle, et al., 1991).

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For animals exposed to basic chrome sulfate, pulmonary changes included chronic alveolar inflammation, chronic interstitial inflammation, granulomatous inflammation, septal cell hyperplasia, foreign material deposition and peribronchial histiocytosis. These changes correspond to the increased lung weights observed in all groups, males and females, exposed to basic chrome sulfate. The presence of numerous large foamy alveolar macrophages in the alveolar spaces correspond to the gray lung discoloration observed at necropsy. Foreign material and granulomatous inflammation was observed in the larynx. Nasal tissue changes consisted of acute inflammation and suppurative and mucoid exudate primarily in the highest dose groups, Groups 6 and 7.

At the recovery sacrifice, the microscopic changes observed at the terminal sacrifice in animals exposed to chromic oxide persisted with reduced severity and incidence. The pigmented macrophages and black pigment in the lymph tissue continued with approximately equal incidence and severity.

The basic chrome sulfate recovery group animals continued to exhibit most of the microscopic pulmonary changes observed at the terminal sacrifice with equal severity and incidence. The incidence and/or severity of foreign material and granulomatous inflammation decreased for all treated groups, males and females. Nasal cavity findings were not detected except for trace suppurative lesions in a few basic chrome sulfate treated animals.

The results of this study demonstrate that a no-observable-effect-level (NOEL) was not achieved for either test material. However, due to the low incidences and minimal severity of the pathologic changes for chromic oxide, the lowest dose level (4.4 mg/m³) was near the no-observable-adverse-effect level (NOAEL) for a 13 week subchronic exposure.

O.K.
NOEL AND COULD BE
CONSIDERED A NOAEL.

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