CPMA
COLOR PIGMENTS
MANUFACTURERS
ASSOCIATION, INC.

DEC 1 2000

November 30, 2000

Dr. C. W. Jameson
National Toxicology Program
Report on Carcinogens
79 Alexander Drive, Bldg. 4401
Room 3127, MD EC-14
Research Triangle Park, NC 27709

Re: Comments of the Color Pigments Manufacturers Association, Inc. on the 10th Report on Carcinogens Concerning the Review of Nickel Compounds and Nickel Alloys and Nickel Containing Complex Inorganic Color Pigments

Dear Dr. Jameson:

I am writing on behalf of the Color Pigments Manufacturers Association, Inc. ("CPMA"), with respect to the National Toxicology Program ("NTP") call for public comments on its review of nickel, metal and compounds, for addition to the 10th edition of the "Report on Carcinogens". 65 Fed. Reg. 17889. This letter is provided to follow-up on our previous comments of June 2, 2000.

The CPMA is an industry trade association representing small, medium and large color pigment manufacturers throughout Canada, Mexico and the United States, accounting for approximately 95% of the production of color pigments in these countries.

Color pigments are widely used in product compositions of all kinds, including paints, inks, plastics, glass, synthetic fibers, ceramics, colored cement products, textiles, cosmetics, and artists' colors. Color pigment manufacturers located in other countries with sales in Canada, Mexico and the United States and suppliers of intermediates to the pigments industry are also members of the association.

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As discussed in our comments of June 2, 2000 to the NTP, complex inorganic color pigments containing nickel do not exhibit the toxicity characteristics of soluble or insoluble bioavailable nickel. (A complete copy of our earlier comments is attached.) All of the complex inorganic color pigments, including those which contain nickel, such as nickel antimony titanate, share stability characteristics. In these products nickel oxide is atomically dissolved into the crystalline lattice of another metal oxide, such as titanium dioxide. This intimate fusing of metal oxides takes place at extreme temperatures of approximately 2000 degrees Fahrenheit. The metal oxides fused into the host crystalline lattice completely lose their original chemical, physical and physiological properties, since they no longer exist as chemical individuals in the crystalline lattice. Again, it is important that the toxicological evaluation of these pigments be based on the extremely stable crystalline compound and not on the individual metal oxides used in the preparation of the pigment.

Complex inorganic color pigments containing nickel should not be elevated with all nickel compounds to the classification of "Known Carcinogen". Alternatively, as stated in our comments of June 2, 2000, the classification of nickel should be qualified to exclude products which do not produce a significant bioavailable exposure.

In this regard, since our comments of June 2, 2000, we have had an opportunity to briefly review the NTP background report entitled "Report on Carcinogens, Background Document for Metallic Nickel and Certain Nickel Alloys". The draft was prepared by the Technology Planning and Management Corporation for the December 13-14, 2000 meeting of the NTP Board of Scientific Counselors, Report on Carcinogens Subcommittee.

The draft report states that, "The ability of divalent nickel ions, Ni(II) or Ni^{2+}, to interact with nucleo proteins appears to be the major determinant of the carcinogenic effect of nickel." (Sunderman 1989a). The release of Ni^{2+} from inhaled metallic nickel or nickel alloy particles depends on oxidation of the elemental nickel by endogenous oxidants rather than the solubility of the elemental nickel. p.61. The report goes on to state that, "The absorption, distribution and elimination of nickel compounds depend upon solubility, concentration, and, in inhalation exposures, the particle sizes of various nickel compounds." (Ni DI 1997), p.63. The report concludes:

> "Absorption, distribution, and excretion of nickel compounds depend on solubility, concentration, and surface area. Once absorbed the ionic form of nickel acts as the ultimate carcinogenic species, with a variety of biokinetic factors dictating the carcinogenic potential of the soluble or insoluble nickel compounds." p.65.

We believe these statements reflect accurately that the carcinogenic potential of nickel compounds is contingent on the nickel ion being available from the inhaled or ingested particle. Since nickel is not available from complex inorganic color pigments containing nickel, these pigments should be excluded from the defined compounds or alloys.

At a minimum, we would request that the statements cited above from the NTP background document (p.65) be incorporated into the abstract for nickel which is published in the next Report on Carcinogens.

Thank you in advance for your attention to this matter. Please call me at the number provided above if there are any questions or further comments.

Sincerely yours,

[redacted]

J. Lawrence Robinson
President

CPMA
COLOR PIGMENTS
MANUFACTURERS
ASSOCIATION, INC.

June 2, 2000

Dr. C.W. Jameson
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The primary commercial pigment compound of concern here is Nickel Antimony Titanium, Yellow Rutile or Nickel Antimony Titanate ("NAT"). These pigment compounds are produced by a high temperature calcining process which fuses metal oxide components into extremely stable crystalline compounds at temperatures of approximately 1000 degrees centigrade.

Due to the broad review of Nickel compounds proposed by the NTP, we must assume that complex inorganic pigments such as NAT are included, since Nickel is within the structure of these pigments. The following discussion will address NAT pigments as an example. All complex inorganic color pigments share similar manufacturing methods and stability in the final product. Nickel as a component comprises generally less than thirty percent of these pigments. Nickel is also used as a modifier to change the color properties of many complex inorganic color pigments which do not contain Nickel as a significant ingredient. Some of these pigments will contain less than one percent Nickel. Since the Nickel present within complex inorganic pigments is not bioavailable, these products should not be labeled carcinogenic in a catch-all classification.

NAT is by far the most commercially important and tested example of the complex inorganic pigments containing Nickel. NAT is a crystalline rutile pigment based on titanium dioxide. Nickel Oxide is absorbed by the rutile lattice of titanium dioxide and thereby imparts a color to the otherwise white titanium dioxide. The incorporated oxides lose completely their original chemical, physical and physiological properties since they no longer exist as chemical individuals in the rutile lattice.

It is important that toxicological evaluation of these pigments be based on the extremely stable crystalline compound and not the individual metal used in the preparation of these pigments.

Anaerobic transformations of these pigments have not been observed. Metal oxide stability depends on the ambient temperature and oxygen partial pressure.[2] However, anaerobic decomposition (reduction) of metal oxides requires high temperatures (ca. 700 °F or higher), very low oxygen pressures (vacuum conditions, inert atmosphere blankets, or reducing atmospheres), or a combination of the two. Such conditions are not reasonably expected to occur in the terrestrial environment, and anaerobic transformation of complex inorganic pigments such as NAT is not therefore possible. As a result, a significant exposure to Nickel within NAT and other Nickel containing pigments is unlikely at best.

The Availability of Nickel from NAT

The level of Nickel extractable from NAT has recently been measured. Under strongly acidic conditions (hydrochloric acid solution, pH = 1.15) the extractable Nickel in NAT is 170 PPM (or g/g). Extractions performed using higher pH solutions (pH = 7 and pH = 10) yielded substantially less extractable Nickel in each case.

NAT is inert and its constituent elements are not readily bioavailable. NAT contains approximately 4% or 40,000 PPM Nickel total. The Nickel within NAT remains tightly held in the crystalline lattice and is unable to migrate into the environment. This Nickel, contained within the pigment structure and is incorporated in a mineral lattice, is inert and has no toxicological significance.[3]

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[2] Kingery, W. D., et al ., Introduction to Ceramics, Second Ed., John Wiley & Sons, New York, p. 393-397.

[3] Toxicological Profile for Nickel, U.S. Department of Health & Human Services, Washington, D.C., 1993, p. 81, Agency for Toxic Substances and Disease Registry.

When using the LD_{50} value as a judge of acute toxicity, NAT is non-toxic via oral ingestion. A Duke University Laboratories study on NAT revealed that NAT was relatively harmless by oral ingestion, having an LD-50 value in excess of 10,000 mg/Kg.[6] Another study also found NAT to have an LD_{50} in excess of 10,000 mg/kg.[7] In comparison, common table salt, NaCl, has an LD_{50} of only 4,000 mg/kg.[8] Feeding studies have confirmed the low acute toxicity of NAT pigments.

In a subchronic assay, Wistar rats were fed up to 1% or 10,000 PPM (parts per million) NAT in their diets for three months.[9] Hematological, clinical, and biochemical tests were conducted at the end of the study. No adverse effects on food consumption or body weight gain were observed during the testing. No mortalities or overt signs of reaction to the treatment were observed. Elevated liver Nickel levels related to the treatment could not be determined. The conclusion by the authors was that,

> "....neither the pigments (NAT) themselves nor the bioavailable traces of metals are considered to have toxicological significance even after extremely high oral exposure".

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[6] Duke Laboratories, Examination of Ferro Corporation Inorganic Pigment Samples for Rat LD-50, 1977, p.1.

[7] Acute Oral toxicity tests of NAT yellow pigments, by Hilltop Labs for The Shepard Color Company, 1979 and 1987.

[8] Fisher Scientific, NaCl MSDS, 1988.

[9] Bomhard, E., Loser, E., Dornemann, A., *Toxicology Letters*, 1982, 14, 189-194.

Carcinogenic/Chronic Toxicity Issues for Nickel Antimony Titanate

The International Agency for Research on Cancer (IARC) has classified Nickel compounds as Group 1, carcinogenic to humans.[13] However, these assessments were made without direct testing of most Nickel compounds. A literature search found no evidence for carcinogenic or chronic hazards directly associated with NAT.[14]

NAT has recently been tested for evidence of its carcinogenicity with negative results. Direct testing of NAT, which contains 4 % Nickel, reveals an absence of carcinogenic behavior. Ames testing showed no evidence of carcinogenic activity from exposure to NAT.[15] In Mouse Lymphoma forward mutation assays, conducted using EPA approved protocols, no signs of cell line mutations were observed upon exposure to NAT.[16] This direct testing of NAT pigments suggests that this particular Nickel compound is neither a mutagen nor a carcinogen.

The nature of the Nickel compound has a determining influence on the ecotoxicity and biotoxicity of the Nickel bearing material. Materials where the suspected carcinogen is sequestered in a mineral lattice and therefore unavailable for interaction with its environment will behave differently from chemicals in which the suspected agent is readily bioavailable. NAT is a Nickel compound in which the Nickel is tightly bound in the mineral lattice. The Nickel in NAT is incorporated in the pigment's lattice and has no ecological and biological significance.

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[13] IARC Monograph on the Evaluation of Carcinogenic risks to Humans: Chromium, Nickel, and Welding, Vol. 49, 1990, World Health Organization, Lyon, France.

[14] Literature search on Chromium Antimony Titanium buff Rutile and Nickel Antimony Titanate, 1997.

[15] Corning Hazleton Labs, Ames testing for CPMA, 1995.

[16] Corning Hazleton Labs, mouse lymphoma testing for CPMA, 1995.

As a result of its unique properties, NAT is now used as an indirect food additive for use in coloring food packaging materials. Recently NAT was approved by the Food and Drug Administration ("FDA") for use as a colorant in all polymers intended to contact food, 21 CFR 178.3297. The FDA's approval is based on evaluation of migration testing of NAT out of a polymer and into a simulated food matrix. The requirements for approval are quite strict; a colorant must exhibit less than 0.5 parts per billion migration to be approved. Because of its extreme insolubility and chemical inertness, no migration of NAT out of the polymer could be observed down to the detection limits of the test.

Therefore, we strongly believe that complex inorganic color pigments containing Nickel such as NAT are not suitable for listing as "Known Carcinogens" by the Board in the 10th Report on Carcinogens.

Conclusion

Complex inorganic color pigments containing Nickel should not be elevated with all Nickel compounds to the classification "Known Carcinogen". Exemptions for products which do not produce bioavailable Nickel should be considered. Alternatively, the classifications of Nickel should be qualified to exclude products which do not produce a significant bioavailable exposure. The addition of all Nickel compounds to the Report on Carcinogens as "Known Carcinogens" is unjustified, since this action would cause insoluble pigments with little or no bioavailable Nickel to be classified as carcinogens. Over classification such as this can also be detrimental, since the utility of the report and public respect for its conclusions are called into question.