CPMA
COLOR PIGMENTS MANUFACTURERS ASSOCIATION, INC.

June 2, 2000

Dr. C.W. Jameson
National Toxicology Program
Report on Carcinogens
MD EC-14
79 Alexander Drive (East Campus)
P.O. Box 12233
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. 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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Based on a review on the NTP publication Update (March 2000), it is our understanding that the NTP will publish the 10th Report on Carcinogens in 2002. The NTP review will include analysis of Nickel and Nickel compounds including metallic Nickel and Nickel alloys. It is not clear how the current review of Nickel compounds differs from the earlier assessment of Nickel compounds in 1998. We believe strongly that the extremely stable compounds manufactured by our members do not represent the toxicological concerns posed by bioavailable forms of Nickel. Since color pigments do not exhibit the toxicity characteristics of bioavailable Nickel, we believe that color pigments should not be represented by the classification, "Known Carcinogen", in the 10th edition.

COMPLEX INORGANIC PIGMENTS CONTAINING NICKEL

The NTP review of Nickel compounds in the 10th edition includes all forms of Nickel. Members of the CPMA Complex Inorganic Color Pigments Committee manufacture specific complex inorganic color pigments, many of which contain Nickel.

These pigments include:

Nickel Silicate Green Olivine
Cobalt Nickel Gray Periclase
Nickel Barium Titanium Primrose Priderite
Nickel Antimony Titanium Yellow Rutile
Nickel Niobium Titanium Yellow Rutile
Nickel Tungsten Yellow Rutile
Nickel Ferrite Brown Spinel
Chrome Iron Nickel Black Spinel
Cobalt Titanate

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.

The Stability of NAT Pigments in the Environment

NAT pigments are 75 % or more titania (TiO_2) by weight. They have the same crystal structure as rutile titania, and share many of its physical properties. These materials are resistant to chemical attack, air oxidation, photolysis, heat, including combustion, and biotransformation.

Because of their resistance toward heat, sunlight, and chemical attack, NAT is used in exterior durable paints, coatings, and vinyl siding. Warranties of up to 30 years against color fade can be offered for these products, because NAT will not decompose and will not change color. They are also used for coloring decorative ceramic glazes, since the pigments are insoluble and do not react with molten glass. Many engineering plastics are colored with NAT, because it does not decompose under processing conditions nor react with the polymers as do less durable pigments. When plastics colored with NAT are incinerated, the pigments can be recovered unchanged. [1]

Biotransformation are not observed with NAT pigments. They contain metal ions in stable oxidation states surrounded by a lattice of oxide (O^{2-}) ions. These materials are not prone to biological attack, since there is no metabolic energy to be gained by their metabolism. The lattice oxide ions are in a very stable state. They cannot be further reduced, and their conversion to higher oxidation states (such as peroxides or molecular oxygen) requires a large amount of energy. Consequently, NAT is not prone to biotransformation, and the constituent metal ions are not released by microorganism attack.

During its formation, NAT pigments are strongly heated in the presence of atmospheric oxygen. As a result, they are not prone to further aerobic reactions.

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[1] Endriss, H. "Titanium Nickel Yellow and Titanium Chrome Yellow Pigments", Toxicological and Ecological Aspects, Farbe + Lack, 95, January, 1989, p. 494, Translation and Follow up study available on request.

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.

The Nickel in NAT is, therefore, tightly bound in a mineral lattice. In application, NAT is further immobilized in a paint, plastic, or glass enamel glaze making it even more environmentally and toxicologically inaccessible.

Acute Toxicity of NAT

Nickel is poorly absorbed in the gastrointestinal tract, especially when administered with food. Tests on non-fasting human volunteers given a single dose of 5,600 g soluble Nickel indicated that only 1 to 5 % of the dose was intestinally absorbed. The balance is eliminated without absorption, mainly fecaly. Bodily absorbed Nickel has an elimination half-time measured to be 28 $\pm$ 9 hours.[4] The combination of poor absorption and rapid elimination from the body results in a relatively low acute toxicity of orally ingested Nickel. Workers accidentally ingesting soluble Nickel doses as high as 2,500,000 g of soluble Nickel developed various temporary effects, but were asymptomatic within three days of exposure.[5]

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[4] Environmental Health Criteria 108: Nickel, International Program on Chemical Safety, 1991, p. 139, World Health Organization, Geneva.

[5] Sunderman, F.W. Jr., Dingle, B., Hopfer, S.M., Swift, T., Am. J. Ind. Med., 1988, 14, 257-266.

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.

In a study for the Sherwin-Williams Company, ten male Sprague-Dawley albino rats were fed a single dose of 5,000 PPM NAT in aqueous suspension.[10] No significant gross pathology was observed after 14 days. Additional acute oral toxicity studies by Duke Laboratories for the Ferro Corporation[11] and by Ciba-Geigy Ltd. confirm the low acute toxicity of NAT.

Another subchronic feeding study of rats using 1,000 mg/kg NAT in the rat's diet for 90 days was performed by the Tokyo Medical College.[12] In addition, the same study conducted oral feeding studies of dogs and kittens, exposed fish to large concentrations in an aqueous environment, and examined the effect of NAT on plant germination. Comparison of control rats to those exposed at the end of the study showed no abnormalities upon pathological examination. No toxic action on kittens or dogs were observed. No differences between exposed fish and the control group was observed. The overall conclusion of the study was that,

> "Titani yellow [NAT] did not show any toxic symptoms when given to rats orally for a prolonged test period...the rats administered with the test chemical showed no difference from the control rats, and there was no inhibition in growth. Furthermore, (NAT) had no effect on small fish, and did not inhibit the growth of plant seed. ...this substance does not show any toxic symptoms at all. Therefore, it was predicted that this substance could be safely used as a coloring agent, particularly for paint, printing ink, and for coloring of synthetic resins, packaging papers, and containers for food."

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[10] Study by Rosner-Hixson laboratories for the Sherwin-Williams Company of Chicago, IL, 1963.

[11] Acute oral toxicity study of NAT by Duke Laboratories for Ferro Corporation, March 1977.

[12] Hara, S., Shibuya, T., Tokizaki, K., Yakazu, K., Kobayashi, T., Takahashi, R., Pharmacological studies of Titani Yellow with regards to its toxicity, Department of Pharmacology, Tokyo Medical College. Translated from Japanese by Terng T. Su, Ph.D., March 1972, The Franklin institute Research laboratories, Science information Services Department, Philadelphia, PA.

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 an inhalation hazard, NAT resembles TiO_2, because it is predominantly comprised of titanium dioxide (approximately 80%), and shares its physical characteristics of insolubility and inertness. Titanium dioxide is widely regarded as a negative control for a dusty material due to its absence of chronic toxicity.[17]

The form of a Nickel containing compound is very important when determining its susceptibility to phagocytosis. A recent study on Nickel toxicity in the lung supports the concept that most Nickel toxicity is due to the solubility of the Nickel.[18] This work states that,

> "It has been postulated that the cytotoxicities of some forms of Nickel are related to the ability of cells to phagocytize or internalize the material, thereby increasing the actual dose to cell and allowing solubilization of the compounds to $Nickel^{2+}$ within the cell".

Normally insoluble Nickel compounds, such as Nickel Sulfide, Ni_2S_3, can be metabolized inside the cell to yield soluble Nickel ions upon phagocytosis.

NAT is insoluble at the pH of biological fluids, and is not prone to biological attack. NAT could not, therefore, provide soluble Nickel upon phagocytosis in the lungs. NAT has not shown evidence of chronic toxicity in laboratory testing. Because of its chemical inertness, NAT would not be expected to be carcinogenic via phagocytosis upon inhalation.

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[17] Driscoll, K.E., *Inhal. Toxicol.*, 1996, 8, 139-154.

[18] Nickel and Human Health, Nieboer, E. and Nriagu, J.O. ed., 1992, John Wiley & Sons, New York, "Biological Utilization of Nickel", Hausinger, R.P., p. 328.

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.

We hope these comments are helpful to you and the Board in reviewing the available data for these important color pigment products. Please call me at the number provided above if there are any further questions, comments or references which we may be able to assist you with.

Sincerely,

[redacted]

J. Lawrence Robinson
President

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