CPMA
COLOR PIGMENTS
MANUFACTURERS
ASSOCIATION, INC.

November 18, 1998

Dr. Larry Hart
Report on Carcinogens
National Toxicology Program
Building 101, South Campus
National Institute of Environmental Health Sciences (NIEHS)
111 T.W. Alexander Drive
Research Triangle Park, NC 27709

Re: Comments of the Color Pigments Manufacturers Association, Inc. on the 9th Report on Carcinogens Concerning on the Status Change for Nickel and Cadmium

Dear Dr. Hart:

I am writing on behalf of the Color Pigments Manufacturers Association, Inc. ("CPMA"), with respect to the changes proposed by the National Toxicology Program ("NTP") for the 9th edition of the "Report on Carcinogens" with respect to the elements nickel and cadmium. 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 , it is our understanding that the NTP Board of Scientific Counselors (the "Board") will meet in early December to review, among other things, the elevation of cadmium and nickel to the status of "Known Carcinogens". It is further our understanding that these "Known Carcinogen" classifications will apply to all compounds of nickel compounds and cadmium without regard to bioavailability. We believe strongly that the extremely stable compounds manufactured by our members do not represent the toxicological concerns posed by bioavailable forms of nickel and cadmium. Since color pigments do not exhibit the toxicity characteristics of bioavailable nickel and cadmium, we believe that color pigments should not be elevated to the classification, "Known Carcinogen", proposed for the 9th edition.

COMPLEX INORGANIC PIGMENTS CONTAINING NICKEL

The elevation of nickel compounds to Known Carcinogens in the 9th edition includes all compounds of nickel. Members of the CPMA Complex Inorganic Color Pigments Committee manufacture specific complex inorganic color pigments, several 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

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 listing of nickel compounds proposed by the NTP, we must assume that complex inorganic pigments such as NAT are included, since nickel oxide is used in the structure of these pigments. Please inform us if NAT and other similar compounds are not included in the proposed classification or if an exemption based on characteristics is available.

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. NAT is by far the most commercially important and tested example of the complex inorganic pigments containing nickel.

NAT is a mixed phase 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 completely lose their original chemical, physical and physiological properties since they no longer exist as chemical individuals in the mixed phase.

It is important that toxicological evaluation of these pigments be based on the extremely stable mixed phased crystalline compound and not the individual metal oxides incorporated in the crystal structures.

The Stability of NAT Pigments in the Environment

NAT pigments are 75 % or more titanium dioxide 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, 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]

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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.

Biotransformation is 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. Anaerobic transformations of these pigments have not been observed, but might unreasonably be expected to occur based on the principles of solid state chemistry. 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 anticipated. As a result, a significant exposure to the metal oxides ingredients within NAT is unlikely at best.

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

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 mg/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 4 % or 40,000 PPM Nickel total. The bulk of the Nickel in NAT remains tightly held in the crystalline lattice and is unable to migrate into the environment. Nickel that is incorporated in this mineral lattice is inert and has no toxicological significance.[3]

The Nickel in NAT is 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 mg 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

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[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.

to be 28 ± 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 mg of soluble Nickel developed various temporary effects, but were asymptomatic within three days of exposure.[5]

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.

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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.

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.

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".

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. Another 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.[11] 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

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

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

11 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.

exam. 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."

Additional acute oral toxicity studies by Duke Laboratories for the Ferro Corporation[12] and by Ciba-Geigy Ltd. confirms the low acute toxicity of NAT.

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]

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

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.

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 not 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.

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]

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

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

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

The form of the 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 $Nickel_2Sulfer_3$, 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. It would be unable, therefore, to 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.

Therefore, we strongly believe that complex inorganic color pigments containing nickel are not suitable or intended for listing as "Known Carcinogens" by the Board in the 9th Report on Carcinogens.

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[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.

CADMIUM COMPOUNDS

Cadmium pigments are highly insoluble compounds of cadmium used as colorants for artist's colors, specialty paints and inks, plastics, and aerospace coatings. These pigments all exist in a highly stable hexagonal crystal form and are classified as cadmium zinc sulfide, Color Index ("C. I.") Pigment Yellow 35, cadmium sulfide, C. I. Pigment Yellow 37, cadmium sulfoselenide, C. I. Pigment Orange 20 and cadmium selenide, C.I. Pigment Red 108. Like many other calcined inorganic compounds, the crystal structure of cadmium pigments imparts a stability and relative insolubility which distinguishes these products from other cadmium compounds.

Although cadmium pigments are included in the IARC classification of cadmium in all forms, the classification is based on chronic inhalation studies involving other more soluble cadmium compounds. Two chronic animal inhalation studies involving cadmium pigments have been reported. In the first, mice and hamsters were exposed to cadmium pigment at concentrations up to 1,000 micrograms per cubic meter of air (as Cd) for 44 weeks. No carcinogenic response was observed in the experiment. [19] In the second long-term inhalation study, rats were exposed to pigment at airborne concentrations up to 2,430 micrograms per cubic meter of air for up to 18 months. [20] These authors, for the first time, reported a carcinogenic

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[19] Heinrich, U., et al. "Long-term Inhalation Exposure of Syrian Golden Hamsters and NMRI Mice to Various Cadmium Compounds," presented at the 4th IUPAC Cadmium Workshop, Schmallenburg-Graftschaft, Germany, September 11-13, 1988.

[20] Glaser, U. et al. "Carcinogenicity and Toxicity of Four Cadmium Compounds Inhaled by Rats", presented at the 4th IUPAC Cadmium Workshop, Schmallenburg-Graftschaft, Germany, September 11-13, 1988.

response similar to the other more soluble cadmium compounds tested. This response was noted at very high dose levels far greater than the dose level tested for other, more soluble, cadmium compounds. Subsequent investigations by the original authors and others determined that the aerosol method used to expose the animals to cadmium pigment caused the cadmium pigment to breakdown into other, soluble, cadmium compounds. [21] [22] [23] Indeed, the original findings of this study, referred to as the Glaser, et al. study, can be attributed to the inadvertent exposure the animals received from other soluble forms of cadmium. [24]

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[21] Glaser, U. et al. "Cadmium Solubility in Suspensions During Long-Term Generation of Cadmium Sulfide Aerosols", presented at the Toxic Metal Compounds Workshop, Les Diablerets, Switzerland, March 1991.

[22] Konig, H.P. et al., "How Does the Solubility of Cadmium Sulphide (CdS) Affect the Results of Inhalation Studies with CdS Particles?", presented at Third European Meeting of Environmental Hygiene, Dusseldorf, F.R.G.

[23] Gagliardi, G. B. and Ulicny, L. J., "Photodecomposition of Dilute Cadmium Sulfide Slurries," presented at the XXIVth RETEC, Charlotte, North Carolina, October 1990.

[24] Ulicny, L. J. "What is the Evidence for the Carcinogenicity of Cadmium Sulfide Pigments?", presented at the 7th International Cadmium Conference, New Orleans. Louisiana, April 1992.

The proposed "blanket" classification of cadmium compounds by NTP contrasts strongly with the situation inside the European Community. Its chemical hazard classification system recognizes three levels of hazard from cadmium compounds:

Hazard Classification & Materials Affected	**Risk & Safety Phrases Required**
TOXIC: cadmium oxide cadmium sulfate cadmium sulphide (chemical)	·May cause cancer by inhalation. ·Harmful if swallowed. ·Toxic: danger of serious damage to health by prolonged exposure through inhalation and if swallowed. ·Avoid exposure - obtain special instructions before use. ·In case of accident or if you feel unwell, seek medical advice (show label where possible).
HARMFUL: All other cadmium compounds EXCEPT cadmium pigments.	·Harmful by inhalation, in contact with skin and if swallowed. ·Do not breathe dust.
CADMIUM PIGMENTS	·NO statutory risk or safety phrases required. Self-classify material on the basis of its physical and chemical properties. ·This self-classification leads to a "non-hazardous" result. All manufacturers do, however, use a voluntary "good practice" label including e.g. "do not breathe dust", as this should not be done with any chemical.

With respect to human studies involving carcinogenicity and cadmium sulfide generally, there are also new studies which cast doubt on the assumption that cadmium sulfide (or therefore, cadmium pigments which are far more stable) is a carcinogen. In one recent study, the authors concluded:

> "Conclusions-Hypotheses which are consistent with the study findings include: (a) cadmium oxide is the presence of arsenic trioxide is a human carcinogen, (b) cadmium oxide and arsenic trioxide are human lung carcinogens and cadmium sulphate and cadmium sulphide are not (or they are less potent carcinogens), or (c) arsenic trioxide is a human lung carcinogen and cadmium oxide, cadmium sulphate, and cadmium sulphide are not." [25]

The authors in this study were re-examining the data reviewed by Dr. Thun in the landmark study used by many organizations to establish the carcinogenicity of all cadmium compounds. [26] This additional data, at a minimum, calls the assumed carcinogenicity for cadmium pigments into question. Long term health studies of workers at cadmium pigment manufacturers have failed to show any evidence of carcinogenic activity from exposure to cadmium pigments alone. Negative health effects were only seen when there was also exposure to cadmium oxide, known for decades to be a highly-toxic material. These groups of workers, with much greater (certainly in

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[25] Sorahan, T., Lancashire, R.J., "Lung Cancer Mortality in a Cohort of Workers Employed at a Cadmium Recovery Plant in the United States: An Analysis with Detailed Job Histories", Occ. Env. Med. 54, pp. 194-201 (1997)

[26] Thun, M. et al. "Mortality Among a Cohort of US Cadmium Production Workers - An Update", J. Natl. Cancer Inst. 1985; 76, p. 825

the past) and more prolonged exposure than end-users of cadmium pigments, would be expected to show a clear positive effect if cadmium pigments had carcinogenic activity.

Additionally, cadmium pigments have been used by artists and industry for decades. If there were a discernable link between lung cancer and the use of cadmium pigments, evidence of that linkage would have been reported or known.

Cadmium pigments are important colorants which produce a unique, long-lasting, brilliant, light and heat stable, yellow to red color in the resins or coating matrix in which these colors are used. The effectiveness of cadmium pigments are unsurpassed in many high temperature plastic, ceramic and outdoor applications. By simply assuming, without evidence, that these valuable compounds are carcinogenic, NTP seriously harms and unnecessarily alarms the markets and users of these valuable products.

CONCLUSION

Complex inorganic color pigments containing nickel should not be elevated with all nickel compounds to the classification "Known Carcinogen", nor should cadmium pigments be elevated with all cadmium compounds to the classification of "Known Carcinogen". In both cases, these extremely stable color pigments have not been shown to exhibit the characteristics of bioavailable nickel, in the cases of complex inorganic pigments, or bioavailable cadmium, in the case of cadmium pigments. Exemptions for products which do not produce either bioavailable nickel or cadmium should be considered. Alternatively, the classifications of nickel and cadmium as "Known Carcinogens" should be qualified to exclude products which do not produce a siginificant bioavailable exposure.

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 or comments which we may be able to assist you with concerning either of these classifications.

Sincerely,

J. Lawrence Robinson
President

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