

Ref. 3



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Memorandum

Date December 20, 2004
From Division of Petition Review (DPR), Toxicology Review Group (HFS-265)
Subject Comprehensive Final Toxicology Evaluation Memorandum: CAP 8C0257
To A. Orstan, Ph.D., Consumer Safety Officer, DPR

Through: Garfield N. Biddle, Ph.D. Garfield N. Biddle
Division Director, DPR

Through: Catherine Whiteside, Ph.D. Catherine Whiteside
Group Supervisor, DPR

CAP 8C0257

Related Petition: CAP 8C0262

EM Industries, Inc.

7 Skyline Drive, Hawthorne, NY 10532

Background:

EM Industries, Inc. has submitted CAP 8C0257 for the use of pearlescent pigments as a color additive in tableting applications and other pharmaceutical preparations. Pearlescent pigments comprise a group of compounds which consist of 1) mica coated with iron oxide, 2) mica coated with titanium dioxide, or 3) mica coated with both iron oxide and titanium dioxide.¹ Pearlescent pigments that consist of three components: mica, iron oxide, and titanium dioxide may also contain pseudobrookite which is formed during the calcining step of the manufacturing process.² A summary of the currently regulated uses of mica, titanium dioxide, and iron oxide is detailed in DPR Chemistry memoranda for CAP 8C0257.^{3,4} Mica-based pearlescent pigments (composed of either iron oxide coated mica or titanium dioxide coated mica) are currently approved for use in contact lenses under §73.3128.

An additional color additive petition for the use of pearlescent pigments as a color additive in various food preparations has also been submitted by the Petitioner (CAP 8C0262). The safety of this requested use in various food preparations is the subject of an ongoing evaluation.

This comprehensive final toxicology review memorandum will evaluate the safety of the use of pearlescent pigments as a color additive in tableting applications and pharmaceutical preparations as proposed in CAP 8C0257. In this memorandum we will: 1) address any remaining safety questions or issues pertaining to CAP 8C0257, 2) evaluate the safety of titanium

¹ E. Jensen, Chemistry Memorandum, 01/21/1999, CAP 8C0257

² E. Jensen, Chemistry Memorandum, 05/05/2000, CAP 8C0257

³ H. Lee, Chemistry Memorandum, 04/16/2003, CAP 8C0257

⁴ H. Lee, Chemistry Memorandum, 11/24/2004, CAP 8C0257

dioxide coated mica pearlescent pigments, and 3) evaluate the safety of iron oxide containing pearlescent pigments.

DPR Toxicology notes that this final toxicology review and its conclusions supersede those contained in a previous DPR Toxicology memorandum dated 06/04/2003 and in related addendum memoranda identified as follows:

1. June 4, 2003, T. Taras, "Final Toxicology Memorandum: CAP 8C0257" (located in CAP 8C0257)
2. June 20, 2003, T. Taras, "Addendum to Final Toxicology Memorandum: CAP 8C0257" (located in CAP 8C0257)
3. July 23, 2003, T. Taras, "Addendum to Final Toxicology Memorandum: CAP 8C0257" (located in CAP 8C0257)
4. August 27, 2003, T. Taras, "Addendum to Final Toxicology Memorandum: CAP 8C0257, Addendum No. III" (located in CAP 8C0257)
5. September 12, 2003, T. Taras, "CAP 8C0257: MEMO FOR THE RECORD" (located in CAP 8C0257)
6. November 25, 2003, T. Taras, "Addendum to Final Toxicology Memorandum: CAP 8C0257, Addendum No. IV" (located in CAP 8C0257)
7. November 25, 2003, T. Taras, "Addendum to the Toxicology Review Memorandum for Study T 9051: Memorandum dated 05/31/2002" (located in CAP 8C0257 and CAP 8C0262).

1. Pearlescent Pigment Exposure Summary

Table 1 summarizes the mean and 90th percentile, eaters-only intake of the pearlescent pigments and their components resulting from the proposed use of pearlescent pigments as a color additive in tableting applications and other pharmaceutical preparations.⁴ DPR Chemistry noted that these are conservative estimates, as they are based on the assumptions that the entire population uses the intended pharmaceutical products, all pharmaceutical products contain the pigments at the maximum specified use level (i.e. 3%), and that each component (i.e., iron oxide, mica, titanium dioxide) of the pigment is present at the maximum specified content level within the pigment.

Table 1:

	Adults (20-70 years) (g/p/d)		Children (2-4 years) (g/p/d)	
	Mean	90 th Percentile	Mean	90 th Percentile
Pearlescent Pigments	0.05	0.1	0.04	0.08
Mica	0.05	0.1	0.04	0.08
Titanium dioxide	0.03	0.06	0.02	0.04
Iron Oxide	0.03	0.06	0.02	0.04

Pseudobrookite Exposure Summary

The mean per capita daily intake of pseudobrookite (Fe₂TiO₅) from the proposed use of pearlescent pigments in pharmaceuticals was estimated to be 15 mg/p/d (adults) and 12 mg/p/d (children). DPR Chemistry noted that these EDIs were based on the assumptions that: 1) the intake of pearlescent pigments from the proposed use in pharmaceuticals is 87 mg/p/d for adults and 70 mg/p/d for children, and 2) all of the pigment ingested is Candurin Honeygold, which contains a theoretical

maximum of 18% by weight of pseudobrookite. DPR Chemistry indicated that this exposure estimate is highly conservative, as it assumes that all pearlescent pigments contain pseudobrookite at the theoretical maximum level. DPR Chemistry further indicated that it is expected that "the probable intake of pseudobrookite from the proposed use of the pearlescent pigments in pharmaceuticals would be negligible."⁴

Elemental Iron

Based on the proposed exposure to iron oxide containing pearlescent pigments with a maximum iron oxide content of 55% in the pigment and a maximum pigment use level in ingested drugs of 3%, the 90th percentile, eaters-only exposure to elemental iron was calculated to be 40 mg/p/d and 30 mg/p/d for adults and children, respectively.⁴

Heavy Metal Exposure Summary

For the proposed use of pearlescent pigments, the Petitioner is requesting heavy metal specifications for mica based pearlescent pigments as follows: not more than 4 mg/kg lead, not more than 3 mg/kg arsenic, and not more than 1 mg/kg mercury. These specifications have been accepted by OCAC Chemistry.⁵ Based upon these specifications, DPR Chemistry has calculated exposure estimates to lead, arsenic and mercury from the proposed use of the pearlescent pigments in ingested drugs (see Table 2).

Table 2:

	Adults (20-70 years) (µg/p/d)		Children (2-4 years) (µg/p/d)	
	Mean	90 th Percentile	Mean	90 th Percentile
Lead	0.20	0.40	0.16	0.32
Arsenic	0.15	0.3	0.12	0.24
Mercury	0.05	0.1	0.04	0.08

2. Toxicology Data Package

Table 3 summarizes the toxicological data that were submitted to the agency in support of the safety of the use of the pearlescent pigments in tableting applications and other pharmaceutical preparations.

Table 3: Toxicological Studies/Reports Submitted in support of CAP 8C0257

Study/ Document	CAP 8C0257 Volume	Title
1	1	Iriodin ^R Trial for acute toxicity in rats after oral administration and for primary skin and mucosal irritation in rabbits

⁵ N. Hepp, OCAC Chemistry Memoranda dated 06/02/1999, 02/01/2002, 03/08/2001, and 07/14/2003, CAP 8C0257

2	1	Nacreous pigment Iriodin ^R Colibri reddish-brown 04502 K. Trial for acute toxicity in rats after oral administration and for primary skin and mucosal irritation in rabbits
3	1	Iriodin Colibri Light Blue. Trial for acute toxicity in rats after oral administration and for primary skin and mucosal irritation in rabbits
4	1	Iriodin ^R Colibri Bluish Green 81006 K. Trial for acute toxicity in rats after oral administration and for primary skin and mucosal irritation in rabbits
5	1	Iriodin ^R Ti 100K. Trial for acute toxicity in dogs after oral administration
6	1	Iriodin 502 C 63. Acute toxicity study in rats after oral administration
7	1	4-hour, acute inhalation toxicity study with Iriobronze ^R Aurum in rats
8	1	Select Committee on GRAS Substances. Evaluation of the Health Aspects of Certain Silicates as Food Ingredients: PB301402
9	2, 3, 11-12	Study T 9051: Investigation of subchronic toxicity in rats in a 3-month feeding study with a 2-month treatment-free follow-up phase
10	4, 13	Study T 14771: Iriodin Ti 100K Trial for subchronic toxicity in the 3-month feed test in rats
11	5, 8-10, 13, 14	HLA Study No. 2164-100: Combined oral toxicity and oncogenicity study in rats with titanium dioxide coated mica
12	6	Study No. T 13368 Pseudobrookite - Acute toxicity study in rats after oral administration
13	6	Study No. T 13369 Pseudobrookite – Primary skin and eye irritation tests in rabbits
14	6	Study No. T 13352 Pseudobrookite - Test for skin sensitizing activity in guinea pigs in the Open Epicutaneous Test (OET)
15	6, 13	Art. 120608 (Candurin Honeygold) Micronucleus test in rats after oral administration
16	13	Scientific Judgment: 1) Bioavailability of pearlescent pigments 2) Irritation potential of pearlescent pigments on the gastrointestinal tract 3) Subchronic toxicity studies/Pseudobrookite
17	6	Behavior of Iriodin pearlescent pigments in artificial gastric and intestinal juices, Test Report Date 21.07.1999
18	14	Determination of iron in pearlescent pigments by Flame-AAS in artificial gastric and intestinal juices, Test Report Date 08/20/2003, Additional data submission dated 10/15/2003

OFAS Toxicologists have previously evaluated Studies 1 through 7⁶, Study 9⁷, and Study 10⁸. DPR Toxicology performed only cursory evaluations of Report 8⁹, Studies 12 through 14⁹, and Study

⁶ Reviewed by contract reviewers (Studies Contract No. 223-96-2302, Work Assignment Number 98-8, 01/15/1999 TDER, CAP 8C0257), Additional review comments included in A. Mattia, Toxicology Memorandum dated 05/31/2000

⁷ Reviewed by OFAS Toxicology Reviewers (I. Chen, Toxicology Memorandum, 01/05/00, T. Taras, Toxicology Memorandum, 05/31/02, and T. Taras addendum memo 10/13/2004)

⁸ Reviewed by OFAS Toxicologists (R. Chanderbhan, Toxicology Memorandum, 11/30/99, T. Taras, Toxicology Memorandum, 04/09/02, and T. Taras Addendum memo, 10/13/2004)

⁹ Reviewed previously by OFAS Toxicology, A. Mattia, Toxicology Memorandum, 05/31/2000

17.¹⁰ Based upon our evaluation of studies 1-7, 9, 10, 12-14, and 17, we have determined that these studies provide little useful information from which to evaluate the safety of the proposed pearlescent pigments because of their short duration, routes of administration, inadequate experimental designs, and/or deficiencies in data reporting. Therefore, we do not consider these studies to be pivotal to our evaluation of the safety of the proposed use of the pearlescent pigments and they will not be discussed in this memorandum. In addition, the utility of the SCOGS report (Report 8) to support the safety of the current petition is limited in that the report did not specifically address mica. Furthermore, Toxicology has previously concluded that “the only value of the SCOGS report is that it supports the general idea that insoluble silicates are inert and not of toxicological concern when ingested in lower mg amounts.”⁹

While we have determined that the overall toxicology database on the pearlescent pigments is adequate to evaluate the safety of the use of pearlescent pigments as proposed in CAP 8C0257, we note that the database did not include reproductive or developmental toxicity studies on the pearlescent pigments. During our review of this petition, OFAS Toxicologists addressed the issue of whether reproductive and development studies on pearlescent pigments are needed for our safety evaluation of these pigments (J. Welsh, Toxicology Memorandum, CAP 8C0257, 10/07/99, A. Mattia, Toxicology Memorandum, 05/31/00⁹, and Internal OFAS/DPR meeting on 09/05/01, Attendees: T. Taras, C. Johnson, K. Biddle, E. Jensen, S. Varner, R. Martin). Based on decisions from these evaluations and toxicology discussions, OFAS Toxicology concludes that reproductive and developmental toxicity studies are not necessary because the pearlescent pigments are generally expected to be highly insoluble and to have low bioavailability. Furthermore, based upon the composition of the pearlescent pigments, there is no current evidence to suggest that the pearlescent pigments present significant concerns as reproductive or developmental toxicants.

3. Safety Conclusions Regarding the Titanium Dioxide coated Mica Pearlescent Pigments

Based upon our review of the toxicology data package for the pearlescent pigments, we have selected “HLA Study No. 2164-100: Combined oral toxicity and oncogenicity study in rats with titanium dioxide coated mica” as the pivotal study for use in evaluating the safety of pearlescent pigments composed of titanium dioxide and mica (designated as Study No.11 in Table 3 of this memorandum). The selection of this study as the pivotal study is based on the following: 1) This study was performed in accordance to our U.S. GLP regulations (Note that the GLP compliance of this study was confirmed during a CFSAN Bioresearch Monitoring (BIMO) data audit and GLP inspection conducted June 16 – 21, 2002), 2) This study provided adequate chronic oral (52 and 130 weeks) toxicity testing of titanium dioxide coated mica in rats, and 3) It tested the carcinogenicity of titanium dioxide coated mica in rats.

HLA Study No. 2164-100¹¹ investigated the oral toxicity and carcinogenicity of 0, 1, 2, or 5% titanium dioxide coated mica in the diet of Fischer 344 rats for 52 weeks (chronic oral toxicity testing phase) or 130 weeks (carcinogenicity testing phase).

¹⁰ T. Taras “CAP 8C0257: Evaluation of the safety of iron oxide as a component of iron oxide containing pearlescent pigments, and other relevant data and information on iron oxide” Memorandum dated 12/17/2004

¹¹ Reviewed for CFSAN/OFAS by contract reviewers from Sciences International, Inc. (Contract 223-96-2303, Work Assignment No. 20-00, Dec. 2000 TDER, CAP 8C0257). In addition, this study was the subject of an Interim Toxicology Memorandum (T. Taras, Toxicology Memorandum, 06/11/2002) and two subsequent addenda to the T. Taras 06/11/2002 Interim Toxicology Memorandum (T. Taras, Addendum 1 dated 10/12/2004 and Addendum 2 dated 10/13/2004, CAP 8C0257)

The test compound evaluated in this study (a 1:1 blend of two titanium dioxide coated mica pigments, with the final blend containing 28% titanium dioxide and 72% mica) was reported to have been in the form of flat platelets with the longest dimensions ranging from 10 to 35 μm . Toxicology notes that the pearlescent pigments proposed for use in CAP 8C0257 vary in composition with mica levels ranging from 36 - 88% and titanium dioxide levels ranging from 12 - 52%.¹ Furthermore, the particle size of the pearlescent pigments containing titanium dioxide and mica also varies. In general, Toxicology considers the titanium dioxide coated mica tested in this study to be representative of the titanium dioxide coated mica pearlescent pigments.

Upon review of Study HLA 2164-100, the Center's Cancer Assessment Committee (CAC) concluded that the administration of diets containing up to 5% titanium dioxide-coated mica daily for 130 weeks did not induce any compound-related tumors in Fischer 344 rats.^{11,12,13} Furthermore, no apparent toxicologically-significant, compound-related effects were noted for titanium dioxide coated mica when fed to rats at test doses of 1, 2, or 5% (highest test dose) in the diet. Based upon the data in this chronic toxicity and carcinogenicity study, Toxicology has concluded that the 5% dose level can be considered as a NOEL for this study.¹¹ In addition, given the currently regulated uses of titanium dioxide and mica, available toxicological data for these compounds, and the overall chemical nature of these compounds (i.e. insoluble), we have no concerns regarding the presence of these components in the proposed pigments up to the maximum levels specified. Therefore, based upon the results of this study, the conservative exposure estimates calculated by DPR Chemistry, and the expected low bioavailability of titanium dioxide coated mica based on its overall chemical nature, DPR Toxicology concludes that we have no safety concerns for the use of titanium dioxide coated mica pearlescent pigments as proposed in CAP 8C0257.

4. Safety Conclusions Regarding Iron Oxide containing Pearlescent Pigments

In our safety evaluation of iron oxide as a component of the iron oxide containing pearlescent pigments proposed for use in CAP 8C0257, DPR Toxicology reviewed available data and information regarding the absorption and bioavailability of iron oxide,^{10,14} and in vitro data on the solubility of iron from iron oxide containing pearlescent pigments.^{10,15} We also consulted with a CFSAN Expert on iron compounds (Dr. Paul Whittaker, CFSAN, ONPLDS, HFS-840) regarding issues related to the solubility and bioavailability of iron from iron oxide. In addition, the 2001 established IOM tolerable upper intake levels and recommended daily allowances for iron¹⁶ were considered in our review of the safety of iron oxide containing pigments. Finally, we reviewed data from an in vivo micronucleus study which tested an iron oxide containing pearlescent pigment.¹⁷

¹² CFSAN Cancer Assessment Committee (CAC) memorandum dated 06/26/02, CAP 8C0257, Volume 14

¹³ S. Francke-Carroll, "Titanium Dioxide Coated Mica: Review of selected pathology findings from the two year bioassay in Fisher-344 rats" Memorandum, 09/08/2004, T. Taras cover memorandum entitled "CAP 8C0257: Addendum No. 1 to T. Taras "Interim toxicology review of the carcinogenicity of titanium dioxide coated mica in rats" Memorandum dated 06/11/2002", 10/12/2004

¹⁴ Document 16 discussed the bioavailability of iron oxide and was reviewed in a T. Taras Toxicology Memorandum dated 10/07/02, and two subsequent addenda to the T. Taras 10/07/02 Memorandum (T. Taras, CAP 8C0257, Addendum dated 10/16/03 and Addendum 2 dated 10/14/04).

¹⁵ Study 18 was reviewed by DPR Chemistry (H. Lee, Chemistry Memorandum, 11/19/2003).

¹⁶ Institute of Medicine. DRI: Dietary Reference Intakes for vitamin A, vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium, and zinc. National Academy Press, Washington D.C., 2001

¹⁷ Study 15 was reviewed by OFAS Toxicology (T. Taras, Y. Gu, Toxicology Memorandum, 01/23/2002).

Detailed discussions of our review and safety evaluation of the data pertaining to iron oxide and iron oxide containing pearlescent pigments are contained in the DPR Toxicology memorandum dated 12/17/2004.¹⁰

In our safety evaluation of the iron oxide containing pearlescent pigments, we utilized DPR Chemistry's "worst-case" dietary exposure estimates for the iron oxide containing pearlescent pigments. Various conservatisms were factored into these exposure estimates (e.g. that all ingested drugs would contain pearlescent pigments containing the maximum level of iron oxide (55% iron oxide) and that all of the pearlescent pigments would be used maximally in ingested drugs at levels of 3%). This 3% level represents the proposed upper limit of typical use for the pearlescent pigments. We also considered available relevant information regarding the absorption and bioavailability of iron oxide, and solubility data on the iron oxide containing pearlescent pigments. Based upon our review of this information, DPR Toxicology concludes that the solubility and bioavailability of iron from the iron oxide component of pearlescent pigments are expected to be low. Additionally, no evidence of genotoxicity was observed for the iron oxide containing pearlescent pigment, Candurin Honeygold, which was tested in an in vivo micronucleus assay in male rats. Therefore, based upon the conservatisms used in estimating the exposure to iron oxide containing pearlescent pigments and the available safety information on iron oxide and the iron oxide containing pearlescent pigments, DPR Toxicology concludes that that the proposed use of pearlescent pigments containing a maximum iron oxide content of 55% to color ingested drugs at a level not to exceed 3% does not raise any significant toxicological concerns.

5. Safety Conclusions Regarding Pearlescent Pigments which may contain Pseudobrookite

DPR Toxicology notes that pseudobrookite (Fe_2TiO_5) is a component of pearlescent pigments that contain iron oxide, titanium dioxide, and mica. In support of the safety of pearlescent pigments containing pseudobrookite, the Petitioner submitted an in vivo micronucleus test in male rats following oral administration of Candurin Honeygold (a pearlescent pigment which contains up to 18% pseudobrookite) (designated as Study 15 in Table 3 of this memorandum). This study was reviewed by DPR Toxicology and it was concluded that the test results for Candurin Honeygold were negative under the conditions of this study.¹⁷

Based on its chemical properties, pseudobrookite as a component of pigments containing iron oxide, titanium dioxide, and mica, is expected to be highly insoluble and inert.^{4,14} Data in Study 18 (see Table 3 of this memorandum) also lend support to such a conclusion. Although this study was determined to be of limited utility because it was not conducted in full compliance with GLP regulations, this study measured soluble iron released from a pearlescent pigment containing pseudobrookite (Candurin Corngold which contains up to 13.5% pseudobrookite) following incubation in artificial gastric and intestinal juices.^{10,15} This study indicated that the iron component of this pigment was highly insoluble under the testing conditions of the study. DPR notes that any soluble iron released from the test pigment in this study would have been released primarily from either the iron oxide and/or pseudobrookite components of the pigment.

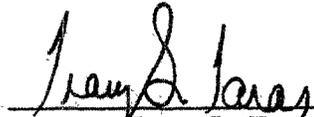
Overall, based on the chemical properties of pseudobrookite, its expected low bioavailability, and the lack of observed genotoxicity of a pearlescent pigment containing pseudobrookite tested in the submitted in vivo micronucleus study, DPR Toxicology concludes that exposure to pseudobrookite as a component of pearlescent pigments in tableting applications and pharmaceutical preparations does not pose a safety concern.

6. Safety of the heavy metals, lead, arsenic, and mercury, as potential contaminants in the pearlescent pigments

In our review of the safety of exposure to lead, arsenic, and mercury as potential contaminants in the pearlescent pigments, we compared DPR's calculated EDIs for these heavy metals resulting from the proposed use of the pearlescent pigments in tableting applications and pharmaceutical preparations to current tolerance levels. Tolerance levels used in our evaluation were the following: 1) FDA's Provisional Tolerable Total Intake Levels for lead in children, pregnant women, and adults¹⁸, 2) JECFA's Provisional Tolerable Weekly Intake for inorganic arsenic¹⁹, and 3) JECFA's Provisional Tolerable Weekly Intake (PTWI) for total mercury²⁰. DPR Toxicology has no safety concerns for the estimated exposures to lead, arsenic, and mercury resulting from the use of the pearlescent pigments to color ingested drugs.

Overall Safety Conclusions for CAP 8C0257

DPR Toxicology has evaluated the safety of the proposed use of pearlescent pigments in ingested drugs relative to the conservative exposure estimates calculated by DPR Chemistry. Based upon our above review, we conclude that the proposed use of pearlescent pigments with a maximum iron oxide content of 55% to color ingested drugs at a level not to exceed 3% is safe. However, if there is any significant increase in the ingestion of these pearlescent pigments, additional toxicity data will be required.


Tracy L. Taras, Ph.D.

HFS-265 (Biddle, Varner, Whiteside, Wallwork, Orstan, Carberry, Lee)

¹⁸ Guidance Document for Lead in Shellfish, FDA/CFSAN, August 1993, <http://www.cfsan.fda.gov/~frf/guid-pb.html#sV>; C.D. Carrington and P. M. Bolger, An assessment of the hazards of lead in food. *Regulatory Toxicology and Pharmacology*, 16, 265-272 (1992)

¹⁹ TRS 776-JECFA 33/27, FAS 24-JECFA 33/155, 1988,
<http://jecfa.ilsa.org/evaluation.cfm?chemical=ARSENIC&keyword=ARSENIC>

²⁰ TRS 631-JECFA 22/26, FAS 13-JECFA 22/43, 1978,
<http://jecfa.ilsa.org/evaluation.cfm?chemical=MERCURY&keyword=MERCURY>