




Ref. 1

Memorandum

Date January 21, 1999 AD 

From Division of Product Manufacture and Use (HFS-246)
Chemistry Review Team

Subject CAP 8C0257 (MATS M2.0 & 2.1): EM Industries, Inc. (submissions of 21 April, 1998 and 27 May, 1998). Use of pearlescent pigments as a color additive in tablets and other pharmaceutical preparations.

To Color Additive Special Project Team
Attn.: Aydin Örstan, Ph.D., Division of Petition Control, HFS-215

EM Industries, Inc. has submitted a petition requesting the listing of "pearlescent pigments" for use in tablets and other pharmaceutical applications, including hard and soft gelatin tablets, and liquid dosage forms. The pigments are mixtures consisting of mica with iron oxide, titanium dioxide, or both.

Mica is regulated under 21 CFR 73.1496 (*Mica*) for use in dentifrices and externally applied drugs and §73.2496 (*Mica*) for general use in cosmetics. Iron oxide is currently listed for coloring sausage casings under §73.200 (*Synthetic iron oxide*),¹ §73.1200 (*Synthetic iron oxide*) for both ingested and topical drugs, such that the level of elemental iron consumed may not exceed 5 mg, and §73.2250 (*Synthetic iron oxide*) for general use in cosmetics. Titanium dioxide is permitted in food in general at levels up to 1% by weight under §73.575 (*Titanium dioxide*), and in drugs (§73.1575, *Titanium dioxide*) and cosmetics (§73.2575, *Titanium dioxide*) without restriction.

EM Industries seeks to expand §73.1496 to permit the use of mica in pearlescent pigment mixtures in tablets and ingested drugs, and seeks to raise the limit on elemental iron intakes from ingested drugs (§73.1200) to allow for pearlescent pigment mixtures that contain iron oxide. Another petition from EM Industries (CAP 8C0262) would permit the use of pearlescent pigments in foods. We will report the resulting exposures to estimate cumulative exposures to each component of the pigment.

1. Identity

The petitioned pearlescent pigments comprise a sheet of mica (muscovite) $[(K_2Al_6Si_6O_{20})(OH)_4]$ layered with a controlled thickness of titanium dioxide (TiO_2), iron oxide (Fe_2O_3), or both. The presence of multiple layers results in interference effects perceived as nacreous or pearlescent. Changing the thickness and identity of the layers results in a different color of the pigment.

¹ Iron oxides are also regulated for coloring pet foods, but as this application will not result in human exposure, it will not be considered here.

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The petitioners have provided analytical information on the composition of their pigment products that give the ranges of composition for the three constituents in each pigment. Considering all the different pigment formulations, the fraction of each component in the pearlescent pigments falls in the following ranges: mica, 36 to 88%, iron oxide, 3 to 56%, and titanium dioxide, 12 to 52%.²

Recent data submitted by the petitioner suggests that iron oxide and titanium dioxide react when the pigment is synthesized, and thus the color additive may not be a simple mixture. Until this issue is resolved, the exposure estimates will be made for the total pigment and for each component separately. If other data confirm the presence of another component, the exposure will be revisited.

2. Use, Use Level, and Technical Effect

EM Industries has requested a maximum use level of 5% by weight of pearlescent pigment in pharmaceutical applications. They state, however, that typical use levels would be 0.1 to 3% (p. 000008). For the exposure estimates (next section), we will assume that the pearlescent pigment mixture is used at the maximum requested level, 5%.

Based on the maximum use level of the mixture and the amounts of mica, titanium dioxide, and iron oxide in the pigments, we calculated the upper limit on the use level of each component:

Table 1. Maximum levels of components in pigments and products

Component	Max. Amt. in pigment	Max. level in products*
Mica	88%	4.4%
Iron oxide	56%	2.8%
Titanium dioxide	52%	2.6%

*Amount in pigment \times 0.05.

These levels may be used to provide an upper-bound estimate of exposure to any one component of the pigment.

3. Exposure Estimates to Pigmented Products

The petitioners request the use of pearlescent pigments in pharmaceutical applications, including tablets, liquid preparations, and dentifrices. They estimated exposure to the pigments

² These do not apply to a single pigment formulation. See appendices 2a-b.

using average component concentrations,³ and based their exposure estimates on different assumptions about product intake than are usually used by the agency. Because the petitioners used different assumptions than are normally used by the agency, and to maintain consistency with previous exposure calculations, we will present our own exposure estimates for the color additive. We will also estimate cumulative exposure.

Usually, the estimated daily intake (EDIs) for an additive is obtained by combining product use levels with the concentration of the additive in each product. We begin therefore, by discussing the intake levels of ingested pharmaceutical products, including tablets, liquids, and dentifrices. Exposure levels will be assessed for two populations of consumers: children (2-4 year age group) and adults (20-70 year age group).

Dentifrice Intake

Use levels of dentifrices were discussed in an earlier memorandum.⁴ There, average levels of ingested dentifrices were calculated for several age groups. Intakes are highest for children (0.3 g/p/d) because they tend to swallow toothpaste rather than spit it out. Exposure decreases rapidly with age, with the exposure for adults being about one tenth that for children (0.04 g/p/d). Dentifrice intakes by age are shown below:

Table 2. Dentifrice Intake by Age

Age group	Average dentifrice ingested
2-4	0.30 g/d
5-7	0.13 g/d
11-13	0.07 g/d
20-35	0.041 g/d

We will use the dentifrice intake for 20-35 year olds to model intake for adults aged 20 to 70 years.

Tablet Intake

Previous exposure estimates for ingredients used in tablets have relied on an average consumer intake of one tablet per day, and assumed that each tablet weighs 600 mg.⁵ In the past

³ Appendix 14 of the petition.

⁴ Memorandum from L. Borodinsky, HFF-415, to J. Ziyad, HFF-335, March 26, 1987.

⁵ Memorandum from S. Carberry, HFS-247, to F. Fields, HFS-207, January 27, 1994.

several years, however, changes to the Federal Food, Drug, and Cosmetic Act⁶ have made dietary supplements (most of which are in tablet form) much more commonly available, and consumers have become increasingly aware of such products. Therefore, assuming that average tablet intake for adults has increased to two tablets/person/day (1200 mg/p/d) seems reasonable at this time. We assume that tablet intake for children has not increased, remaining at one tablet/day, or 600 mg/d.

Intake of Liquid Pharmaceutical Preparations

Little information is available regarding the intake levels of liquid pharmaceutical preparations, such as cough syrups. A memorandum regarding exposure to Red 3 noted that "chronic exposure from drug syrups cannot be reliably estimated, but it seems reasonable to conclude that when short term daily doses are averaged over long periods they would be comparable to levels estimated for drugs ingested on a chronic basis."⁷ At the time, tablet intakes were estimated to be 600 mg/p/d. Unlike tablets, however, we do not have information to suggest that intakes of liquid pharmaceutical preparations have increased. On this basis, we estimate a long-term daily intake of syrups for both children and adults to be 0.5 g/p/d.

We now consider the probable exposures to the components of the pearlescent pigment from the proposed uses. Based on the above information, and EM Industries' request for a maximum use level of 5%, we can estimate the upper bound exposure to the pigment mixture from its use in pharmaceutical applications. Table 3 shows the product use levels and resulting pigment intakes for adults and children.

Table 3. Estimated exposure to pearlescent pigments from petitioned uses (mg/p/d)

Product category	Product intake level		Pigment exposure	
	Adults	Children	Adults	Children
tablets	1200	600	60	30
liquid formulations	500	500	25	25
dentifrices	41	300	2	15
Total:			87	70

EM Industries has also submitted a petition for pearlescent pigments to be used in various food applications (CAP 8C0262). Details of the exposure estimates from food uses of the

⁶ Dietary Supplement Health and Education Act (1994).

⁷ Memorandum from G. Cramer, HFF-458, to A. Dennis, HFF-334, December 11, 1986 (CAP 9C0096).

pigments are described elsewhere; we only summarize the results here.⁸ From food, mean per-capita intakes of the pigment would be 250 mg/p/d for adults, and 150 mg/p/d for children. The combined exposure to the pearlescent pigments obtained by adding the exposures from foods and pharmaceutical products is thus about 340 mg/p/d for adults and 220 mg/p/d for children.

Because the various components of the pigments are regulated independently, we will also estimate exposure to each component (e.g., mica, iron oxide, and titanium dioxide). For each component, we estimate the exposure from the proposed pharmaceutical uses, then report the calculated exposure from food use as estimated for CAP 8C0262, and finally consider the exposure from currently regulated applications. The cumulative exposure to each substance is obtained by summing the appropriate intakes from each source.

Mica exposure

Table 4 shows the estimated daily intakes (EDIs) for mica from the petitioned uses of pearlescent pigment. The exposure is calculated by multiplying the amount of the product ingested by 4.4% (0.044). Summing the individual exposures gives the total exposure:

Table 4. Exposure to mica from petitioned uses in pharmaceutical products (mg/p/d)

Product category	Product intake level		Mica exposure	
	Adults	Children	Adults	Children
tablets	1200	600	53	27
liquid formulations	500	500	22	22
dentifrices	41	300	2	13
Total:			77	62

For the petitioned food uses (CAP 8C0262), exposure to mica from food would be 132 mg/p/d for children, and 220 mg/p/d for adults.

Mica is currently regulated for use in products, including lipstick, dentifrices, and various packaging materials. Exposure to mica from these sources was previously estimated (note 4) and is presented in Table 5:

⁸ Memorandum from E. Jensen, HFS-246, to A. Orstan, HFS-215, of January 22, 1999 (CAP 8C0262).

Table 5. Exposure to mica from regulated sources (mg/p/d)

Product category	Adults	Children
lipstick	0.1	-
dentifrice	0.23	1.7
Total	0.33	1.7

Exposure from indirect applications was estimated to be 25.5 µg/p/d (0.0255 mg/p/d).⁹ This is negligible compared with the petitioned uses. Because the uses of mica and pearlescent pigments in dentifrices are substitutional (as both are coloring agents), our exposure calculation will rely on the mica exposure with the highest substitutional amount, which is that from the pearlescent pigment (2 mg/p/d for adult, 13 mg/p/d for children, Table 3). Based on these estimates, the cumulative exposure to mica from regulated and both petitioned uses would be approximately 300 mg/p/d for adults and 195 mg/p/d for children.

Iron oxide exposure

As above, exposure to iron oxide from the requested uses of pearlescent pigments is calculated by combining the product use level with the maximum use level of iron oxide in those products, 2.8% (0.028). Table 6 shows the resulting exposures:

Table 6. Iron oxide exposure from petitioned uses in pharmaceutical products (mg/p/d)

Product category	Product intake level		Iron oxide exposure	
	Adults	Children	Adults	Children
tablets	1200	600	34	17
liquid formulations	500	500	14	14
toothpaste	40	300	1	8
Total			49	39

Ingestion of pearlescent pigments in foods from the uses proposed in CAP 8C0262 would result in an additional iron oxide intake of 140 mg/p/d for adults, and 84 mg/p/d for children.

Iron oxide is currently regulated for food and drug use. Section 73.1200 (*Synthetic iron oxide*) for ingested and topical drugs limits its use such that the level of elemental iron consumed

⁹ Petition CAP 8C0076.

may not exceed 5 mg (corresponding to 7 mg/p/d iron oxide (as Fe₂O₃)). To estimate cumulative exposure, we assume that iron oxide intake from this source is at the regulatory limit.¹⁰

Table 7. Exposure to iron oxide from regulated sources (mg/p/d)

Regulation	Estimated Daily Intakes	
	Adult	Child
§73.200 (food)	6.5*	4.6
§73.1200 (drug)	7	7
Total from regulated sources	13.5	11.6

*Eaters-only intake for ages 2+.

The uses under §73.1200 (drugs) are subsumed under the uses requested in this petition. Since the petitioned levels would be higher, we use these numbers to estimate an upper bound on exposure. The cumulative exposure to iron oxide from regulated and petitioned uses is therefore 196 mg/p/d for adults and 128 mg/p/d for children. These iron oxide intakes correspond to elemental iron intakes of 140 mg/p/d and 90 mg/p/d, respectively. For comparison, typical dietary intakes of iron are 10 - 15 mg/p/d.¹¹

Titanium dioxide exposure

Exposure to TiO₂ from ingested cosmetic products, e.g., lipstick, is negligible (about one mg/p/d for adults) compared with the exposure from food use.¹² Table 8 shows the amounts of titanium dioxide that would be ingested as part of a pearlescent pigment mixture.

¹⁰ There is no limit on iron intake from food or cosmetic sources.

¹¹ Report from the Scientific Committee on GRAS Substances (SCOGS), number 35 (1973), LSRO/FASEB, Rockville, MD.

¹² Cosmetic, Toiletry, and Fragrance Association. Submission to CAMF 9, June 23, 1983. This submission provides the following data used to estimate exposure: (7 mg lipstick/application)(2.86 applications/day)(0.5 lipstick ingested). We assume that average lipsticks contain 10% titanium dioxide. This results in approximately 1 mg/p/d titanium dioxide ingested.

Table 8. Titanium dioxide exposure from petitioned uses in pharmaceutical products (mg/p/d)

Product type	Product use level		TiO ₂ exposure	
	Adult	Child	Adult	Child
tablets	1200	600	30	15
liquid	500	500	15	15
dentifrice	40	300	1	10
Total			46	50

Titanium dioxide is permitted for direct addition to food at levels up to 1%. The EDI for TiO₂ from direct addition to food could therefore be as high as 15 g/p/d (1%* 1500 g solid food intake/p/d). As noted above, because both titanium dioxide and the pearlescent pigments are coloring agents, their uses are likely to be substitutional. Therefore, the exposure to TiO₂ in pearlescent pigments used in food is unlikely to exceed that of the highest substitutional use, direct addition of TiO₂ as a pigment (15 g/p/d). The cumulative exposure to TiO₂ from both petitioned and regulated uses would not exceed 15.05 g/p/d for either adults or children.

For ease of reference, all the exposure data are summarized in a table at the conclusion of this memorandum.

4. Conclusion

Exposure to pearlescent pigments and their components, both from regulated and from petitioned uses, have been estimated for adults and children. The exposure estimates are summarized in Table 9. Cumulative exposures are given on a mean, per capita basis.

Table 9. Cumulative intakes of components of pearlescent pigments (mg/p/d)

	Mean intake (this petition)		Cumulative exposure*	
	Adults	Children	Adults	Children
Pigment	87	70	337	225
Mica	77	62	300	195
Iron oxide	49	39	200	135
TiO ₂	45	37	15045	15037

These are conservative estimates as they rely on maximizing assumptions, such as that consumers would select only items colored with the petitioned additive, that all products would contain the additive at the maximum requested level, and that each component of the pigment is present at the maximum amount within the pearlescent pigment mixture.



Elke Jensen, Ph.D.

cc: HFS-226; HFS-245; HFS-248 CAP 8C0257 (SPT)
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SUMMARY OF INGESTION-BASED EXPOSURES TO PEARLESCENT PIGMENTS AND THEIR COMPONENTS (MG/P/D)

	Product type	Adults		Children	
		Product usage	Exposure	Product usage	Exposure
Mica					
Petitioned uses					
Food (CAP 8C0262)		5000	220	3100	132
Drug (CAP 8C0257)	tablet	1200	53	600	27
	liquid	500	22	500	22
	dentifrice	41	1.8	300	13.2
Subtotal			296.8		194.2
Regulated uses					
§73.1496	dentifrice	41	0.23	300	1.7
§73.2496	lipstick		0.1		0
Total			296.9		194.2
Iron oxide					
Petitioned uses					
Food (CAP 8C0262)		5000	140	3100	84
Drug (CAP 8C0257)	tablet	1200	34	600	17
	liquid	500	14	500	14
	dentifrice	40	1.15	300	8.4
subtotal			189.15		123.4
Regulated uses					
§73.200	sausage casing		6.5		4.6
§73.1200*	ingested drugs		7*		7*
Total			202.65		135
Titanium dioxide					
Petitioned uses					
Food (CAP 8C0262)†		5000	130 †	3100	80 †
Drugs (CAP 8C0257)	tablet	1200	31	600	16
	liquid	500	13	500	13
	dentifrice	40	1.1	300	8
subtotal			175.1		45
Regulated uses					
§73.575	all food	1.5 kg	15 g		15 g
§73.2575	lipstick		1		0
Total			15.05 g		15.04 g

SUMMARY OF INGESTION-BASED EXPOSURES TO PEARLESCENT PIGMENTS AND THEIR COMPONENTS (MG/P/D)

Pigment	Product type	Adults		Children	
		Product usage	Exposure	Product usage	Exposure
Food			250		155
Drug			87		70
Total			337		225

*Since the uses in §73.1200 would be subsumed under the new requested uses e.g., the 5 mg limit would be changed, this amount is not included in the total.

†This use is subsumed under §73.575, and is not included in the calculated exposure.