

Ref 8



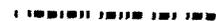
Memorandum

Date July 15, 1999

From Research Biologist, Office of Cosmetics and Colors, HFS-128

Subject Review of Petition CAP 7C0208, Carbon Black For Use As A Color Additive In Cosmetics (Including Eye Area Use).

To Martha Peiperl, HFS-215
Through: Director, DSAT, OCAC, HFS-125 *S. Bell for D. A. Dennis*



A toxicology and reference review was conducted by Cosmetic Toxicology Branch (CTXB) for the December 18, 1997 amendment to Color Additive Petition 7C0208, submitted by the Cosmetic, Toiletry, and Fragrance Association (CTFA).

I. Identity Of Carbon Black Pigment That Is Subject Of Petition

The 12/18/97 amendment indicates that CAP 7C0208 covers only high purity carbon black made by the furnace process or high purity furnace black (HPFB).

II. Exposure To Carbon Black From Proposed Cosmetic Uses

In CTFA's November 19, 1986 petition submission, the estimated exposure to carbon black from all proposed cosmetic uses was less than 1 mg/kg body weight/day. This included possible exposures from soaps, temporary hair color rinses, creams and lotions. In the amended petition of 12/18/97, CTFA indicates the total exposure to carbon black from all cosmetic uses remains at 0.87 mg/kg body weight/day, and that approval for carbon black would be for the following cosmetic uses: eye liner, brush-on-brow, eye shadow, mascara, lipstick, blushers and rouge, makeup and foundation, and nail enamel. Although CTFA states that the primary use of carbon black would be in products for use in the area of the eye, in their risk assessment they state that additional use in toiletries (soaps, temporary hair color rinses, creams and lotions) would increase carbon black exposure to a total of 1.0 mg/kg body weight/day. There is no information provided to us from industry regarding exposure to carbon black from use in soaps, temporary hair color rinses, creams and lotions. CTFA may either remove from requested approval the use of carbon black in toiletries (soaps, temporary hair color rinses, creams and lotions) or provide data indicating the expected exposure from these additional uses.

The Chemistry Review Team (CRT) evaluated CTFA's exposure estimates to HPFB from cosmetic products (eye liner, brush-on-brow, eye shadow, mascara, lipstick,

001619

blushers and rouge, makeup and foundation, and nail enamel).¹ An exposure estimate was developed using product information from cosmetic industry and color exposure scenarios developed by the Hart Panel². CRT assumes that the color available for absorption is 50% and states that total exposure likely falls between 1 and 10 mg/p/d. Based on the average body weight of 60 kg, this exposure range is equivalent to 0.017 to 0.17 mg/kg-bw/d.

III. Specifications For Carbon Black Pigment

Table 1 in the Appendix summarizes proposed specifications, standard methods, and previous recommendations by FDA for the analysis of carbon blacks. The manufacturer of HPFB, Cabot proposes to manufacture two grades of HPFB, BP 4750 "high jet" material and BP 4350 "low jet" material.

A. Surface Area by Nitrogen BET

Because the surface area of carbon black determines bioavailability of polycyclic aromatic hydrocarbons (PAH's) from carbon black, surface area determination is an important specification from a toxicological standpoint. An increase in surface area increases the ability of carbon black to tightly bind PAH's. Since Cabot proposes to supply two products, BP 4750 "high jet" material and BP 4350 "low jet" material, the surface area by nitrogen should be measured, particularly for the "low jet" material that has a lower surface area where PAHs may be more available for extraction. Cabot initially specified a surface area of ≥ 150 m²/g, however, on 2/3/99 they requested that the proposed specification be changed to ≥ 90 m²/g to include the lower grade carbon black.

CTXB concurs with the Colors Technology Branch (CTB) review³ in requesting (1) data from the determination of the surface area of five representative samples of each grade of HPFB and (2) a copy of the method used.

B. Volatile matter

CTXB agrees with the CTB review.

Memorandum from Elke Jensen, Chemistry Review Team, HFS-246, March 23, 1998

Hart, et al., Risk Anal. 6(2) 117-154 (1986)

Memorandum from Alan Scher, Color Technology Branch, HFS-126, June 1, 1999

C. Total tinting strength

CTXB agrees with the CTB review.

D. Toluene extractable impurities

It is specified in CAP 7C0208 that the allowable content of toluene extracted impurities should be $\leq 0.02\%$, however, the identity and major components of these impurities was not stated. CTXB would like to know the identity of the unknown toluene extractable impurities and whether these impurities are consistent with each lot of carbon black. CTXB agrees with the CTB review and requested information.

E. Ash

No toxicology comments.

F. Heavy metals

No toxicology comments.

G. Sulfur and Sulfur PAHs

CTXB agrees with the CTB review and requested information.

H. PAHs

CTXB agrees with the CTB review and requested information.

IV. Correlation Of Proposed Product Specification With Toxicology Data.

The carbon blacks described in the toxicology review are for the most part, described in terms of an ASTM notation, which refers to particle size. CTFA states that those blacks showing no PAH bioavailability have a surface area comparable to the surface area put forward in the specifications indicated in the petition. Examples of carbon blacks used in some bioavailability studies were ASTM N-234 with a N₂ surface area 128 m²/g, ASTM N-351 with a N₂ surface area 70m²/g, and ASTM N-375 with a N₂ surface area 101 m²/g (Buddingh et al., 1981)

V. Summary Of Relevant Toxicological Literature

A review of all references submitted in the December 18, 1997 amendment to Color

Additive Petition 7C0208 was conducted. A summary of the pertinent references are given:

A. Routes Of Exposure

In CAP 7C0208, CTFA lists the major uses of carbon black in cosmetics, including those for use in the area of the eye: eye liner, brush-on-brow, eye shadow, mascara, lipstick, blushers and rouge, makeup and foundation, and nail enamel. The use of the word "major", however, implies that there are other minor uses. Again, CTFA may either remove from requested approval the use of carbon black in toiletries (soaps; temporary hair color rinses, creams and lotions) or provide data indicating the expected exposure from these additional uses. Relevant routes of exposure from the use of cosmetics containing carbon black were determined to be dermal, ocular, and oral. Inhalation was not considered relevant for the current toxicological assessment.

1. Subcutaneous

The study by Steiner (1954) demonstrates that the physical/chemical properties of a particular carbon black is a critical determinant in the content and bioavailability of PAH byproducts.

The study demonstrated that coarse furnace black (surface area of 15 m²/g) contained 300 ppm benzene-extractable benzo[a]pyrene that was bioavailable with a subcutaneous sarcoma tumor yield of 39%. No sarcomas were reported in mice treated with channel black (surface area of 380 m²/g), channel black with exogenously added 300 ppm benzo[a]pyrene, or a combination of furnace black and channel black. This study suggests the strong capacity of carbon black with a high surface area to tightly adsorb PAHs.

2. Ocular

A case study by Sugar and Kobernick (1966) reported that four patients showed pigmentation on the conjunctival surface of their eyelids and all had used liquid eye liner containing carbon black for at least two years. The authors attempted to associate the use of mascara with the pigmentation of the conjunctival surface by application of the liquid eye liner to rabbit eyes (unspecified age, number, no controls) followed by surgically sewing the eyes shut. After one month, pigmentation was found in a lymphatic nodule including a number of lymphocytes and polymorphonuclear cells. CTFA claimed that there were no clinical signs of inflammation associated with exposure to mascara containing carbon black. However, in two of the four patients, inflammatory cells found around the pigment, the mild folliculosis and symptom of itching suggested an allergic secondary factor. A third patient also complained of

itching and puffiness. In this study, the concentration of carbon black is unknown, and there are probably some formulation differences between eye liner and mascara that one may not be substituted for another. It was noted that very few people who use cosmetics containing carbon black show pigment deposition. However, it is stated in this petition that in eye cosmetics, carbon black produces black pigmentation of the conjunctiva and there is lymphatic infiltration and phagocytosis of the pigment by macrophages. Although there is a claim of no adverse symptoms associated with this, Sugar and Kobernick (1966) also conclude that "discontinuance of the use of the eye liner cosmetics in those who show subconjunctival pigment deposition is not necessarily recommended...it is not expected that discontinuance of its use would result in disappearance of the pigment any more than after tattooing of the skin with carbon black pigment".

The repeated eye irritation study of a 5% dispersion of 1 mg carbon black was conducted in 20 rabbits and 5 Rhesus monkeys (Color Additive Master File No. 9, Entry No. 300). It was concluded that the study demonstrated no particle embedding nor significant irritation (CAP7C0208, page 10 of 19, November 19, 1986),(Gittes to McCowin internal memorandum dated Dec. 29 1975). There was no direct information given on the particle size of the carbon black used in this study, however, from information in CMF 9, Entry No. 301, it is assumed that the particle size of the channel black used in the eye study is 28 nm.⁴

Grant W.M. (1986)-review Carbon. Toxicology of the Eye. The review indicates that carbon black has produced black pigmentation of the palpebral conjunctiva at the upper tarsal border after regular application to the lid margins for at least two years. There is lymphocytic infiltration and the pigment is taken up by macrophages. CTFA claims that the deposits cause essentially no symptoms.

3. Oral

Pence and Buddingh (1985; CTFA, 1986) demonstrated that carbon black (ASTM N-375) when administered to rats and mice for 2 years, was not a carcinogen nor a co-carcinogen with dimethylhydrazine.

Pence and Buddingh (1987) demonstrated that colon tumor incidence in rats was significantly increased by the chronic ingestion of industrial carbon black in the context of a high fat diet. The 20% corn oil enhanced the metabolism of carcinogen adsorbed to carbon black, or increased elution of carcinogen in the GI tract. This study raises the possibility of lipophilic extraction of the PAH from the carbon black as

Memorandum from M. Peiperl, drafted 5/24/99.

demonstrated by the apparent synergism occurring between a high fat diet and the concomitant oral intake of carbon black .

4. Intraperitoneal

Specific information on carbon black "Corax L" is contained in the IARC monograph, vol. 65, p. 201. Twenty mg furnace black "Corax L" suspended in 2 ml saline [1.2% volatiles; toluene extract, <0.1% ; primary particle size, 23 nm; surface area, 150 m²/g] was injected intraperitoneally once per week for four weeks into female Wistar rats. After 132 weeks, only 1 out of 35 animals examined histopathologically had a sarcoma in the abdominal cavity. Although no control was reported, because of low tumor incidence, "Corax L" is not considered a carcinogen (Pott et al., 1991).

B. Bioavailability

1. Affinity of Carbon Black for PAH's

Reference (Cabot; FAP5B4464) does discuss analytical techniques used to extract PAH's from carbon black. In order to detect ppm levels of PAH's, 10 g of dried carbon black is extracted.

2. Extraction from Biological Systems

Steiner (1954) noted that PAH was extracted from the highly loaded coarse furnace black (surface area of 15 m²/g) by the vehicle tricaprylin. Mice exposed to this formulation had a higher cancer incidence (39%) due to the bioavailability of the PAH in the tricaprylin vehicle. Tricaprylin (glyceryl trioctanate) is used in cosmetics and can increase skin penetration. Because the vehicle used in this study was able to extract PAH from the carbon black, it is important to determine what potential PAH extraction can occur using other lipophilic cosmetic vehicles. Also, mice exposed to the same dose of carbon black in pellet form (without tricaprylin) had a low tumor incidence (2%), but the material was fairly well retained and became quickly encapsulated by fibrous connective tissue.

Exogenously added B[a]P to carbon black (ASTM N-375: N2 surface area 101 m²/g) was not extracted by rat liver microsomes (Lakowicz and Bevan, 1979, 1980) or model phospholipid vesicles of dipalmitoyl L- α -phosphatidylcholine (Lakowicz et al., 1980). B[a]P added on asbestos, silica, and other particles were extracted by microsomes and phospholipid vesicles. The particulate examined could adsorb up to 300 ppm exogenous BP, but the specific loading capacity for each particle was not provided. Carbon black with adsorbed B[a]P was less carcinogenic than B[a]P alone.

Bevan and Worel (1984; CAP 7C0208, March 10, 1989) using rubber grade carbon blacks: N-234, N-339, N-351, and N-375, carbon black had a 70-fold (N-375) and 200 to 500-fold greater affinity for benz[a]pyrene than dimyristoyl L- α -phosphatidylcholine and dipalmitoyl L- α -phosphatidylcholine vesicles. However, the authors bring up two good points: 1) adsorption of B[a]P at concentrations higher than normal association with carbon black may result in binding to sites other than those of highest affinity, and 2) carbon black contains numerous PAHs in addition to B[a]P, with total endogenous PAH contents in the range of 500-1000 ppm. The presence of these other endogenous PAHs at high concentrations could alter the affinity of carbon black for endogenous B[a]P.

The most compelling toxicology study to support the position of limited PAH bioavailability was the study by Buddingh et al., (1981) using swine lung, swine serum, and human plasma to evaluate the bioavailability of B[a]P from three rubber-grade oil furnace blacks (ASTM N-351; N2 surface area 70m²/g, N-375; N2 surface area 101 m²/g, and N-234; N2 surface area 128 m²/g) as compared to their extractability with toluene. It was determined that less than 0.005% of the toluene-extractable B[a]P was extracted by the serum, plasma, or tissue homogenates. Moreover, in the same report, liver and lung homogenates were taken from F0, F1 and F2 generations of outbred ICR mice exposed to carbon black in their bedding and diet with a total consumption of 0, 4, 100 or 998 g carbon black/kg body wt, and analyzed for aryl hydrocarbon hydroxylase (AHH) activity as a marker of internal exposure to B[a]P. There was no detectable AHH induction.

C. A Summary of the Risk Assessments For Exposure To Carbon Black and PAHs.

The color additive petition (CAP 7C0208, pp. 12-13 of 19, November 19, 1986) provides details that show the total expected daily exposure to carbon black from cosmetic uses to be 0.87 mg/kg body weight/day. In the December 18, 1997 amendment to the petition again it is stated that additional use in toiletries would increase carbon black exposure to a total of 1.0 mg/kg body weight/day. CTFA has previously stated that carbon black would not be used in soaps, temporary hair color rinses, creams and lotions. For total expected daily exposure to carbon black, CTFA continues to use the exposure value of 1.0 mg/kg body weight/day. For a 50-kg woman, this would be equivalent to a total daily intake of 50 mg.

Chemistry Review Team evaluated CTFA's exposure estimates to HPFB from cosmetic products. An exposure estimate was developed using product information from the cosmetic industry and color exposure scenarios developed by the Hart Panel. CRT assumes that the color available for absorption is 50% and states that total exposure likely falls between 1 and 10 mg/p/d. Based on the average body weight of 60 kg, this exposure range is equivalent to the conservative estimate exposure range of 0.017 to

0.17 mg/kg-bw/d. However, CRT states further that the conservatism underlying their exposure will cover the unspecified uses in lotions, hair rinses, and creams. **If carbon black is to be used in soaps, temporary hair color rinses, creams and lotions, CTXB requests another exposure and risk assessment be performed, due to the different exposure from creams and lotions which are leave on products that cover a larger surface area of the body.**

To estimate the worst-case potential risk due to exposure to PAHs present in HPFB, CTFA assumed that all of the PAHs present on the carbon black would desorb from the pigment. The exposure level based on the bioavailability data was 0.005%. If carbon black routinely contains the maximum proposed PAH level of 0.5 ppm (5×10^{-7} mg/mg), the maximum potential exposure to PAHs resulting from the use of 1.0 mg/kg body weight/day of carbon black would be 5×10^{-7} mg/kg body weight/day.

However, a total of 22 distinct PAHs may be present on carbon black at varying levels, including the potent carcinogens benzo[a]pyrene and dibenz[a,h]anthracene. For their risk assessment, CTFA uses a toxic equivalency factor (TEF)-based method that scales the relative carcinogenicity of each PAH in relation to the most potent carcinogen, benzo[a]pyrene, to estimate exposure from the PAHs contained on the carbon black. CTFA cites a precedent for this type of analysis using the FDA risk assessment for consumption of fish after the Exxon Valdez oil spill.⁵ TEF values were either obtained from this reference or derived from information previously submitted to FDA by Cabot Corporation in support of the food additive petition (FAP 5B4464) for high-purity furnace black.

A regulation based on FAP 5B4464 set purity specifications for indirect uses of carbon black limiting total PAH content to 0.5 ppm and the benzo[a]pyrene and dibenz[a,h]anthracene content to 5 ppb (0.005 ppm). Multiplying the average concentration of each compound present in the carbon black grade found to contain the highest total PAH content by the respective TEF values yields the B[a]P-equivalent level of each compound. Adding the products together for all 22 species, the total B[a]P equivalent PAH content is about 43 ppb. Under the TEF approach, the toxicity-weighted PAH content of the carbon black (43 ppb) is a ten-fold reduction of the maximum total PAH content specified in the current petition of 0.5 ppm (500 ppb).

CTFA used the worst-case assumption of 100% desorption of the PAHs from the carbon black with 100% bioavailability, the exposure to PAHs was calculated to be 4.3×10^{-8} mg B[a]PE PAH/kg body weight/day. Multiplying this exposure by the FDA

derived unit risk factor (URF) for benzo[a]pyrene of 1.75 (mg/kg body weight/d)⁻¹

(QRAC, 1990)⁵ resulted in a lifetime cancer risk of 7.5×10^{-8} .

CRT also uses the TEF-based approach, however, assumes that benzo[a]pyrene and benzo[a,h]anthracene were both present at 0.005 ppm, the proposed limit. The 20 other PAHs would be present in equal amounts, with a total PAH concentration of 0.5 ppm. This resulted in a concentration of 0.0245 ppm for each other PAH. Multiplying these concentrations by the TEFs and summing the products resulted in a total B[a]P-weighted concentration of 44 ppb, which is about the same value that CTFA obtained. Combining the color additive exposure of 10 mg/p/d (0.17 mg/kg-bw/d), with the PAH concentration results in a B[a]P-equivalent PAH exposure of 0.43 ng/p/d (4.3×10^{-7} mg/p/d, 7.2×10^{-9} mg PAH/kg-bw/d). CRT assumes that 10% of the total PAHs can be absorbed into the body from carbon black, to obtain an exposure to the B[a]P-equivalent PAHs of 4.3×10^{-8} mg/p/d (7.2×10^{-10} mg/kg-bw/d). Multiplying this exposure by the FDA derived unit risk factor resulted in CRT obtaining a lifetime cancer risk of 1.25×10^{-9} .

D. Safety Summary

The primary remaining concern in evaluating the safety of carbon black is the bioavailability of PAHs that are formed during the manufacturing process. CTFA concludes and CTXB concurs that exposure to carbon blacks containing PAHs does not result in adverse effects by subcutaneous, oral, or intraperitoneal routes of administration except where a high PAH load is placed on carbon black in excess of the ability of the pigment to adsorb the PAHs on the carbon black surface.

In order to complete its safety summary for color additive petition CAP 7C0208, CTXB requests that the following information and data be provided:

1. Because the bioavailability of the PAHs depend on the surface area (particle size) of the HPFB, CTXB concurs with the Colors Technology Branch (CTB) review in requesting (1) data from the determination of the surface area of five representative samples of each grade of HPFB and (2) a copy of the method used.

2. It is specified in CAP 7C0208 that the allowable content of toluene extracted impurities should be $\leq 0.02\%$, however, the identity and major components of these impurities was not stated. CTXB would like to know the identity of the unknown toluene extractable impurities and whether these impurities are consistent with each lot of carbon black. CTXB agrees with the CTB review and requested information.

QRAC memorandum of August 9, 1990.

3. Because the vehicle tricaprylin was able to extract PAH from carbon black, it is important to determine what potential PAH extraction can occur using lipophilic cosmetic vehicles. CTXB requests that a short study be conducted to determine PAH transfer from carbon black to an o/w emulsion. The carbon black should be from a batch of the "low jet" material, using five samples. The oil-in water emulsion formulation should be a commercially available formulation in a product category that typically might contain carbon black - such as foundation. The length of the study should be at least one week.⁶

4. The safety review of this petition can be done on the proposed use of high-purity carbon black as a color additive in cosmetics for the following uses: eye liner, brush-on-brow, eye shadow, mascara, lipstick, blushers and rouge, makeup and foundation, and nail enamel. However, a safety review of CAP 7C0208 cannot be done on soaps, temporary hair color rinses, creams and lotions, because there is no information provided to us from industry regarding exposure to carbon black from these products. The petitioner should either remove from requested approval the use of carbon black in toiletries (soaps, temporary hair color rinses, creams and lotions) or provide data indicating the expected exposure from these additional uses. If carbon black is to be used in soaps, temporary hair color rinses, creams and lotions, CTXB requests another exposure and risk assessment be performed, due to the different exposure from creams and lotions which are leave on products that cover a larger surface area of the body.

By using a toxicity-equivalency based approach, CTFA estimates a lifetime cancer risk of approximately 7.5×10^{-8} and CRT estimates a lifetime cancer risk of 1.25×10^{-9} . Both estimates demonstrate an acceptable risk. However, the Quantitative Risk Assessment Committee should review this approach with the calculation of estimated cancer risk performed by CTFA and CRT.

Sandra Bell for

Margaret E.K. Kraeling
Cosmetic Toxicology Branch, HFS-128

Memorandum from B. Bronaugh to M. Peiperl, June 8, 1999.

cc: HFS-126 (Bell)
HFS-126 (Scher)
HFS-215 (Lipman)
HFS-225 (Johnson)
HFS-246 (Jensen)

REFERENCES

Bevan, D.R. and Worrel, W.J. (1984). The bioavailability of benzo(a)pyrene adsorbed to carbon black. In: Polynuclear Aromatic Hydrocarbon: Mechanisms, Methods and metabolism, 8th International Symposium, Cooke, M and Dennis, A.J. (Eds.), Battelle Press.

Buddingh, F., Bailey, M.J., Wells, B., and Haesemeyer, J. (1981). Physiological significance of benzo(α)pyrene adsorbed to carbon black: Elution studies, AHH determination. Amer. Indust. Hyg. Assoc. J. 42:503-509.

Cabot Corporation. High-purity furnace black [Chemical Abstracts Registry No. 1333-86-4] for use as a colorant for polymers intended for contact with food. FAP 5B4464. Submitted May 18, 1995

Federal Register notice of final rule. 62 FR 25475, May 9, 1997. § 178.3297, Colorant for polymers to provide for the safe use of the color additive in polymers intended for use in contact with food.

FDA August 9, 1990 Report on the Quantitative Risk Assessment Committee on the "Estimation of Risk Associated with Consumption of Oil-Contaminated Fish and Shellfish by Alaskan Subsistence Fisherman Using a Benzo[a]pyrene Equivalency Approach."

Grant, W.M.. (1986). Carbon. Toxicology of the Eye. Charles C. Thomas Publishers, Springfield, IL, pp. 178.

IARC (1996). Printing Processes and Printing Inks, Carbon Black and Some Nitro Compounds. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, World Health Organization, Lyon. pp. 149-262.

Lakowicz, J.R. and Bevan, D.R. (1979). Effects of asbestos, iron oxide, silica, and carbon black on the microsomal availability of benzo(a)pyrene. Biochemistry 18:5170-5176.

Lakowicz, J.R. and Bevan, D.R. (1980). Benzo[a]pyrene uptake into rat liver microsomes: Effects of adsorption of benzo[a]pyrene to asbestos and non-fibrous mineral particulates. Chem.-Biol. Interact. 29:129-138.

Lakowicz, J.R., Bevan, D.R. and Riemer, S.C. (1980). Transport of a carcinogen, benzo[a]pyrene, from particles to lipid bilayers. Biochim. Biophys. Acta 629:243-258.

Pence, B.C. and Buddingh, F. (1985). The effect of carbon black ingestion on 1,2-dimethylhydrazine-induced colon carcinogenesis in rats and mice. *Toxicol. Lett.* 25:273-277.

Pence, B.C. and Buddingh, F. (1987). Co-carcinogen effect of carbon black ingestion with dietary fat on the development of colon tumors in rats. *Toxicol. Lett.* 37:177-182.

Pott, F., Roller, M., Rippe, R.M., Germann, P.G. and Bellmann, B. (1991). Tumours by the intraperitoneal and intrapleural routes and their significance for the classification of mineral fibers. *Mechanisms in Fibre Carcinogenesis*, Brown, R.C., et al. (Eds.), Plenum Press, New York, pp. 547-565.

Steiner, P.E. (1954). The Conditional Biological Activity of the Carcinogens in Carbon Blacks, and Its Elimination. *Cancer Research* 14:103-110.

Sugar, H.S. and Kobernick, S. (1966). Subconjunctival pigmentation associated with the use of eye cosmetics containing carbon black. *Amer. J. Ophthal.* 62:146-149.