Personal Care Products Council
Committed to Safety, Quality & Innovation
Formerly CTFA

May 4, 2009

Cynthia Oshita
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Proposition 65 Implementation
P.O. Box 4010 1001 I Street, 19th floor
Sacramento, California 95812-4010

RE: Prioritization: Chemicals for Consultation by the Carcinogen Identification Committee (03/05/09)

Dear Ms. Oshita:

The Personal Care Products Council[1] (the Council) appreciates the opportunity to provide comments on the above referenced topic. There are several chemicals used within the cosmetic and personal care product industries on the list of 38 chemicals for which the Carcinogen Identification Committee (CIC) has been asked to provide advice on prioritization. Thus, the assignment of priority is of significant interest to Council members. This document provides comments on several of these chemicals, all of which should be considered low/no priority based on the available scientific data.

The comments here will address **diethanolamine**; **triethanolamine**; and **D&C Yellow No. 11**. Further, we reference and second the comments submitted by the Consumer Healthcare Products Association regarding **fluoride and its salts**.

Diethanolamine (DEA)

Diethanolamine (DEA) does not meet the Proposition 65 standard for listing "known to the State to cause cancer". Therefore, DEA should be considered low/no priority for review by the CIC.

DEA is infrequently used in personal care products, but is found as a component/contaminant in DEA condensate ingredients such as cocamide DEA (coconut fatty acid diethanolamide) and

[1]Based in Washington, D.C., the Personal Care Products Council (formerly CTFA) is the leading national trade association representing the $250 billion global cosmetic and personal care products industry. Founded in 1894, the Council's more than 600 member companies manufacture, distribute, and supply the vast majority of finished personal care products marketed in the United States. As the makers of a diverse range of products millions of consumers rely on everyday, from sunscreens, toothpaste and shampoo to moisturizer, lipstick and fragrance, personal care products companies are global leaders committed to product safety, quality and innovation.

lauramide DEA (lauric acid diethanolamide). DEA condensates function as surfactants and viscosity increasing agents. DEA is present in condensates at levels generally ranging from 0.2% to 10%, and is also found in triethanolamine as a contaminant at levels which do not exceed 0.4%.

There are positive carcinogenicity findings for DEA in one study carried out by the National Toxicology Program (NTP) in B6C3F1 mice. DEA tested negative ("no evidence of carcinogenic activity") in a chronic bioassay in F344/N rats conducted by NTP, was negative in a transgenic mouse model, and is not genotoxic, as will be discussed further below. Thus, the evidence for DEA carcinogenicity is from one study in one species, with DEA exposure occurring via one route of exposure (dermal).

In the NTP mouse study[2], an increased incidence of tumors was seen in the livers of male and female mice. There was a marginal increase in renal tubule adenomas in males (only), which did not rise to the level of statistical significance until an extended analysis (step sectioning) was performed. No treatment-related increase was seen in kidney carcinomas, with or without step sectioning.

Mouse liver tumors are common spontaneous tumors, and B6C3F1 mice are particularly susceptible. The historical background liver tumor rate in B6C3F1 mice in 72 studies conducted for NTP during the years 1981-1986 ranged from 2-70% in females, and 10% to 81% in males,[3] and in dermal studies conducted by NTP, the background rate for liver adenomas ranged from 56%-78%.[4] The incidence of adenomas in control animals in the DEA bioassay was 64% and 62% in females and males, respectively; and the incidence of adenomas and carcinomas combined was 66% and 78% in females and males, respectively. The mouse liver is the most common target site in rodent bioassays run by the NTP.[5] Kidney adenomas are also known to occur spontaneously in B6C3F1 mice, and were seen in the concurrent controls. Thus, the effects seen in the mice were increases in tumors that occur spontaneously as a consequence of the B6C3F1 mouse genotype.

<u>DEA was negative in chronic bioassays in F344/N rats, and was negative in transgenic mouse studies. DEA is non-genotoxic.</u>

As noted above, a chronic bioassay was carried out by NTP with DEA in F344/N rats. The results of this study showed "no evidence" of carcinogenic activity in either males or females.[2]

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[2] NTP (1999) Toxicology and Carcinogenesis Studies of Diethanolamine (CAS No. 111-42-2) in F344/N Rats and $B6C3F_1$ Mice (Dermal Studies). NTP Technical Report Series No. 478.

[3]Haseman, J.K., Bourbina, J., and Eustis, S.L. <u>Fundam. Appl. Toxicol</u>. (1994) Vol. 23(1), pp. 44-52.

[4]See reference 2, p. 147.

[5]Huff, J., Cirvello, J., Haseman, J., and Bucher, J. (1991) <u>Environ. Health Perspect</u>. Vol. 93, pp. 247-270.

DEA was also negative in the Tg.AC transgenic mouse model.[6] It has been suggested that the negative transgenic result, in contrast to the positive outcome of the chronic bioassay, "is not necessarily representative of a 'false-negative' result but rather, an indication that the conventional bioassay has given a false positive result. Thus, the response in transgenic animals may provide a more accurate assessment of potential human risk."[6] This statement was based on evidence of a species-specific response to DEA, which will be discussed further below.

DEA is non-genotoxic in a battery of assays, which included *Salmonella typhimurium* and mouse lymphoma gene mutation assays, tests for sister chromatid exchange and chromosomal aberrations in Chinese hamster ovary cells *in vitro*, and a mouse micronucleus assay *in vivo*.[7]

Mechanistic work has identified choline deficiency as the mechanism of action of tumorigenesis for DEA in the B6C3F1 mouse, a highly susceptible species and strain. In contrast, humans are much less sensitive, and thus the outcome of the NTP study is not relevant to carcinogenicity in humans.

Extensive research has been conducted to elucidate the mechanism of action of liver tumor formation in B6C3F1 mice exposed to DEA. Choline deficiency, a recognized cause of liver tumor formation in rodents,[8] has been investigated, based on DEA's ability to disrupt phospholipid metabolism by inhibiting the incorporation of ethanolamine and choline into phospholipids.[9] It has been shown that mice treated with DEA demonstrate changes in choline metabolites that are consistent with choline deficiency.[10] [11] These effects were seen at all dose levels used in the mouse bioassay with severity that increased in relation to dose. The changes were not seen in rats which did not develop tumors in the chronic bioassay. *In vitro* studies have shown that DEA can block choline uptake into cells, alter the utilization of choline into phospholipid biosynthesis, and become incorporated in phospholipids directly.[12] These effects are competitive and reversible, and thus a critical dose must be exceeded in order to elicit the adverse effects. The mechanistic work has also demonstrated the lack of formation of nitrosamines from DEA under conditions designed to favor their formation.[10]

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[6] Spalding, J.W., French, J.E., Stasiewicx, S. Furedi-Machacek, M. Conner, F., Tice, R.R., and Tennant, R.W. (2000) Toxicol. Sci. Vol. 53(2), pp. 213-223.

[7]See reference 2, p. 6 and Appendix E.

[8]Newberne, P.M., DeCarmargo, J.L.V., and Clark, A.M. (1992) Toxicol. Path., Vol. 10, pp. 95-109.

[9]Barbee, S.J. and Hartung, R. (1979) Toxicol.Appl. Pharm. Vol. 47, pp. 431-440.

[10]Stott, W.T., Bartels, M.J., Brzak, K.A., Mar, M-H., Markham, D.A., Thornton, C.M., and Zeisel, S.L. (2000) Toxico. Lett., Vol. 14(1-3), pp. 67-75.

[11]Lehman-McKeeman, L.D., Gamsky, E.A., Hicks, S.M., Vassallo, J.D., Mar, M.H., and Zeisel, S.H. (2002) Toxicol Sci. Vol. 67(1), pp. 38-45.

[12]Lehman-McKeeman, L.D. and Gamsky, E.A. Biochem Biophys. Res. Commun. (1999) Vol. 262, pp. 600-604.

The B6C3F1 mouse is relatively lacking in capacity to maintain methylation status, which is thought to contribute to its susceptibility to hepatocarcinogenesis.[13] Altered DNA methylation can result from changes in S-adenosylmethionone (SAM) levels. Studies looking at alteration of SAM levels by DEA showed greater sensitivity in the B6C3F1 mouse strain compared to C57Bl/6 mice, a strain which is relatively resistant to liver tumor formation.[11] Data have also been developed showing that DEA does not effect SAM levels in rat liver, again demonstrating species differences.[11]

Humans differ markedly from rats and mice with respect to choline metabolism and with choline requirements. Rodents oxidize choline more rapidly than humans, a fact that is thought to contribute to species differences in susceptibility to choline deficiency.[14] Rodents require more methionine (part of the choline biosynthetic pathway) than humans do because of a greater demand for cysteine needed for hair growth.[15] In rodents, de novo synthesis of choline cannot keep up with the body demand for choline, and as such choline is a required dietary nutrient. In contrast, choline deficiency can be induced in humans only under extraordinary circumstances.[16]

Rats are also known to be sensitive to choline deficiency; however, the F344 rats exposed to DEA did not develop tumors. The dose levels used in the rat study were less than those used in the mouse study, and it is known that DEA penetrates mouse skin more readily than rat skin.[17] Furthermore, rats do not exhibit the extensive grooming behavior seen in mice, which would have effectively increased the dose received by the mice in this dermal study. The use of higher DEA doses in the chronic rat study was precluded by effects seen in skin in a subchronic rat study conducted by NTP; a higher dose would have exceeded the MTD. However, the dose of DEA that the rats received is still far in excess of a dose that humans would encounter in any realistic exposure scenario, and yet this sensitive species did not develop tumors. Dermal penetration studies conducted by both CTFA[18] and the U.S. FDA using human skin and realistic exposure conditions for cosmetics and personal care products showed very low absorption of DEA through human skin.[19] [20] For example, in the CTFA study, permeation over 24 hours from

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[13]Counts, J.L., Sarmiento, J.I., Harbison, M.L., Downing, J.C., McClain, R.M. and Goodman, J. (1996) Carcinogenesis, Vol. 17(6), pp. 1251-1257.

[14]Sidransky, H. and Farber, E. (1960) Arch. Biochem. Biophys. Vol. 87, pp. 129-133.

[15] Zeisel, S.H. and Blusztajn, J.K. (1994) Ann. Rev. Nutr. Vol. 14, pp. 269-296.

[16]Savendahl, L., Mar, M.-H., Underwood, L.E., and Zeisel, S.H. (1997) Am. J. Clin. Nutr., Vol. 66, pp. 622-625.

[17]Sun, J.D., Beskitt, J.L., Tallant, M.J., and Frantz, S.W. (1996) J. Toxicol.-Cut. & Ocular Toxicol., Vol. 15(2), pp. 131-146.

[18] CTFA (Cosmetics, Toiletry and Fragrance Association) is the former name of the Personal Care Products Council.

[19] Brain K.R., Walters K.A., Green D.M., Brain S., Loretz L.J., Sharma R.K., and Dressler W.E. (2005). Food Chem Toxicol 43(5):681-690.

formulations representing several product types ranged from 0.011% - 0.605% of the applied dose; flux values ranged from 1-48 ng/cm^2. It is reasonable to conclude that the carcinogenic risk from DEA to humans, with a much lower sensitivity to choline deficiency, is theoretically nonexistent.

The International Agency for Research on Cancer (IARC) conducted a weight of the evidence review of DEA carcinogenicity and concluded that DEA was "not classifiable as to human carcinogenicity."

DEA underwent evaluation by IARC in 2000. The IARC review considered all of the available evidence on DEA in reaching a conclusion on its carcinogenicity. The outcome of that review was that there was "inadequate evidence in humans for the carcinogenicity of diethanolamine", and "limited evidence in experimental animals for the carcinogenicity of diethanolamine." DEA was classified as Group 3, "not classifiable as to its carcinogenicity to humans."[21] There are no data developed since the time of the IARC review that would bring that conclusion into question.

The National Toxicology Program (NTP) conducted a weight of the evidence review of DEA carcinogenicity and concluded that DEA does not meet the NTP standard for listing in the Report on Carcinogens as "reasonably anticipated to be a human carcinogen".

DEA underwent evaluation by NTP in 2002 for possible listing in the 11th *Report on Carcinogens*. The review considered all of the available evidence on DEA in reaching a conclusion on its carcinogenicity. The outcome of that review was that DEA did not meet the NTP standard for listing in the *Report on Carcinogens* as "reasonably anticipated to be a human carcinogen."[22] There are no data developed since the time of the NTP review that would bring that conclusion into question.

Summary

The Council strongly believes that DEA should be of low/no priority for review by the CIC. An increased incidence of a common tumor type was seen in one species in a chronic bioassay. A second study in rats gave negative results, as did a study in transgenic mice. Mechanistic work has identified choline deficiency as the mechanism of action in B6C3F1 mice, a uniquely susceptible species and strain. This mechanism would not be relevant to humans under realistic exposure conditions. Lastly, both IARC and NTP, two authoritative bodies recognized under Proposition 65, have conducted reviews of DEA. IARC concluded that DEA was "not classifiable as to its carcinogenicity to humans." NTP concluded that DEA did **not** meet the

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[20] Kraeling M.E., Yourick J.J., Bronaugh R.L. (2004) Food Chem Toxicol 42(10):1553-1561.

[21] IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. (2000) Diethanolamine, Vol. 77, p. 349.

[22] http://ntp.niehs.nih.gov/ntp/htdocs/Liaison/111902.pdf

standard for listing in the *Report on Carcinogens*. Furthermore, OEHHA previously considered[23] listing DEA under Proposition 65 using the authoritative bodies mechanism, but concluded "(b)ecause it is not clear that the scientific criteria for listing under the authoritative bodies mechanism have been met, OEHHA has decided not to proceed with the administrative listing of diethanolamine under Proposition 65."

Triethanolamine (TEA)

Triethanolamine (TEA) does not meet the Proposition 65 standard for listing "known to the State to cause cancer". Therefore, TEA should be considered low/no priority for review by the CIC.

Triethanolamine is widely used in cosmetic and personal care product categories as an emulsifier and pH adjuster.

TEA has been tested for carcinogenicity by NTP, and findings of "some evidence" of carcinogenicity were reported in a study carried out in B6C3F1 mice. TEA tested negative ("no evidence of carcinogenic activity") in a chronic bioassay in F344/N rats conducted by NTP and was negative in a transgenic mouse model (TgAC), as will be discussed further below. Other chronic bioassays of TEA in rodents were negative for carcinogenicity with the exception of one study with serious limitations. TEA is not genotoxic. A brief review of each of the studies follows.

Hoshino and Tanooka [24](1978) of the National Cancer Research Institute of Japan studied ICR-JCL mice fed diets containing either 0.03 or 0.3% TEA. The only statistically significant increase in tumors was the incidence of lymphomas in females (Control 1/36; low dose 7/37; high dose 9/36). However, no historical control data for this tumor type was presented. It should also be noted that the TEA was heated during the formulation process for the diets which may have produced unknown byproducts.

In 1992 Konishi[25] et al. reported on the administration TEA in the drinking water of male and female B6C3F1 mice at 1% and 2% for 82 weeks. In this study there was no increase in tumor incidence in either sex.

In 1986 Maekawa[26] et al. reported on the administration of TEA in the drinking water of male and female F344 rats. At the initiation of the study both males and females received TEA at

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[23] http://www.oehha.ca.gov/prop65/CRNR_Notices/admin_listing/process_procedures/DEAnog.html

[24] Hoshino, H. and Tanooka, H. (1978) Cancer Research, Vol. 38, pp. 3918-3921.

[25] Konishi, Y., Denda, A., Uchida, K., Emi, Y., Ura, H., Yokose, Y., Shiraiwa, K., and Tsutsumi, M. (1992) Fund. Appl. Toxicol. Vol. 18, pp. 25-29.

[26] Maekawa, A., Onodera, H., Tanigawa, H., Furuta, K., Kanno, J., Matsuoka, C., Ogiu, T., and Hayashi, Y. (1986) J. Toxicol. Environ. Health Vol. 19, pp. 345-357.

either 1% or 2%. The males were maintained at this dose level for 104 weeks. In the females the dose levels were reduced by half after 69 weeks due to increased mortality and decreased body weights in the high dose group. In this study there was no increase in tumor incidence in either sex.

TEA was the subject of two dermal studies in $B6C3F_1$ mice conducted by NTP. The first mouse study[27] was deemed inadequate due to infection with *Helicobacter hepaticus.* The second study[28] yielded a conclusion of "equivocal" evidence of carcinogenicity in males based on a non dose-dependent increase in hemangiosarcoma incidence and "some" evidence of carcinogenicity in females based on dose-dependent increases in hepatocellular adenoma, multiple hepatocellular adenoma and hepatocellular carcinoma incidence. As noted above [see diethanolamine], mouse liver tumors are common spontaneous tumors. The mouse liver is the most common target site in rodent bioassays run by the NTP, and B6C3F1 mice are known to be particularly susceptible.

After publication of the 2004 NTP study, researchers considered two potential mechanisms for the observed increase in liver tumor incidence in mice, including depletion of hepatic choline levels[29] and *in vivo* formation of N-nitrosodiethanolamine (NDELA). NDELA formation as a mechanism of action for the formation of liver tumors was rejected by NTP in their follow-up study in 2004.[28] This was supported by the work of Saghir et al.[30] in which they concluded that their "findings in toto confirm the lack of any significant formation of NDELA from TEA in vivo".

However, the work of Stott et al. (2004) does support the depletion of hepatic choline as a mechanism of action for liver tumor formation in female mice. Choline is an essential nutrient for both humans[31] and mice[29]. Choline deficiencies can lead to fatty liver and muscle damage in humans[31]. In mice, chronic choline deficiency is associated with a well-characterized sequence of biochemical reactions leading to tumorigenesis[29]. Significantly, as discussed earlier in these comments [see diethanolamine], sensitivity to this effect appears to be species-specific, with female mice the most sensitive, hence the lack of an association between dermal TEA exposure and liver tumorigenesis in rats. DEA is a much more potent initiator of this reaction sequence than TEA, perhaps due to its higher chemical reactivity[29]. Higher mammals including man seem to be refractory to tumor induction by choline deficiency.

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[27] NTP (1999) Toxicology and Carcinogenesis Studies of Triethanolamine (CAS No. 102-71-6) in F344/N Rats and $B6C3F_1$ Mice (Dermal Study). NTP Technical Report Series No. 449.

[28] NTP (2004) Toxicology and Carcinogenesis Studies of Triethanolamine in $B6C3F_1$ Mice (Dermal Study). NTP Technical Report Series No. 518.

[29] Stott W.T., Radtke B.J., Linscombe V.A., Mar M.H., Zeisel S.H.. (2004) Toxicol. Sci. Vol. 79(2), pp. 242-7.

[30] Saghir, S.A., Brzak K.A., Markham D.A., Bartels M.J., and Stott W.T. (2005) Regul. Toxicol. Pharmacol. Vol. 43(1), pp. 10-18.

[31] Fischer, L.M., daCosta, K.A., Kwock, L., Stewart, P.W., Lu, T.S., Stabler, S.P., Allen, R.H., Zeisel, S.H. (2007) Am. J. Clin. Nutr. Vol. 85(5), pp. 1275-85.

TEA was negative/equivocal in a chronic bioassay in F344/N rats, and was negative in a transgenic mouse study. TEA is non-genotoxic.

NTP tested TEA in a dermal 2-year carcinogenicity study in Fischer 344/N rats.[27] The study yielded "equivocal" evidence of carcinogenicity based on a "marginal" increase in renal tubule adenomas in male rats, and "no evidence" of carcinogenicity in female rats.

TEA exhibited no activity in a transgenic mouse model for carcinogenesis.[32]

TEA was negative in all *in vivo* and *in vitro* genetic toxicology tests conducted by NTP,[27] including *Salmonella typhimurium* reverse mutation, sister chromosome exchange, *in vitro* micronucleus, sex-linked recessive lethal mutations and mouse peripheral blood micronucleus tests.

The International Agency for Research on Cancer (IARC) conducted a weight of the evidence review of TEA carcinogenicity and concluded that TEA was "not classifiable as to human carcinogenicity."

TEA underwent evaluation by IARC in 2000. The IARC review considered all of the available evidence on TEA in reaching a conclusion on its carcinogenicity. The outcome of that review was that there was "inadequate evidence in humans for the carcinogenicity of triethanolamine", and "inadequate evidence in experimental animals for the carcinogenicity of triethanolamine." TEA was classified as Group 3, "not classifiable as to its carcinogenicity to humans."[33] The 2004 NTP study and the subsequent work on TEA mechanism of action would not be expected to change this conclusion.

Summary

The Council strongly believes that TEA should be of low/no priority for review by the CIC. The NTP bioassay in mice resulted in "some evidence" of a common tumor type in females, and "equivocal evidence" in males. Other rodent bioassays were negative, or, in one case, lacking in historical data by which to judge the results. Negative/equivocal results were seen in an NTP rat bioassay; a study in transgenic mice was negative; and TEA is not genotoxic. IARC has conducted a review of TEA and concluded that TEA is "not classifiable as to its carcinogenicity to humans."

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[32]Spalding, J.W., French, J.E., Tice, R.R., Furedi-Machacek, Haseman, J.K., and Tennant, R.W. (1999) Toxicol. Sci. Vol. 49 pp. 241-254.

[33]IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. (2000) Triethanolamine, Vol. 77, p. 381-401.

OEHHA previously (2003) made available a draft data summary and priority for TEA with respect to its potential to cause cancer. At that time OEHHA assigned a draft priority of "not high carcinogenicity concern" to TEA. The Council believes that that conclusion remains valid today. Based upon the carcinogenicity, genotoxicity, and mechanistic work, review of TEA by the CIC for potential listing under Proposition 65 should **not** be a priority.

D&C Yellow No. 11

D&C Yellow No. 11 does not meet the Proposition 65 standard for listing "known to the State to cause cancer". Therefore, D&C Yellow No. 11 should be considered low/no priority for review by the CIC.

D&C Yellow No. 11 is a colorant approved by the U.S. FDA for use in cosmetics and drugs which are externally applied ("applied only to external parts of the body and not to the lips or any body surface covered by mucous membrane" (21 CFR 70.3(v)).

The database relevant to the carcinogenicity of D&C Yellow No. 11 is limited to a single chronic feeding study in F344/N rats conducted by the NTP, and genotoxicity data with mixed results. No cancer epidemiology studies have been identified. The lack of data justifies a conclusion of low/no priority for review of this chemical.

In the NTP D&C Yellow No. 11 2-year dosed feed study, conclusions for both sexes were "some evidence of carcinogenicity"[34]. In males, the conclusion was based on findings of increased incidences of hepatocellular adenoma, renal tubule neoplasms, and squamous cell neoplasms of the oral cavity. The oral cavity tumors are likely related to the oral route of exposure, while D&C Yellow No. 11 is approved for external use only and not allowed for ingestion. In females, the conclusion of "some evidence" was based on increased incidences of hepatocellular neoplasms. Incidences of uncommon squamous cell carcinomas of the oral cavity in females may have been related to chemical treatment.

Results of genetic toxicity testing for D&C Yellow No. 11 were mixed.[34] In *Salmonella typhimurium*, results were equivocal in one study, based on responses observed in strain TA100 in the presence of metabolic activation, and weakly positive in a second study, based on responses observed in stains TA98 and TA100 in the presence of metabolic activation. D&C Yellow No. 11 induced sister chromatid exchanges and chromosomal aberrations in cultured Chinese hamster ovary cells, with and without metabolic activation. However, in an *in vivo* study, no increase was observed in the frequency of micronucleated normochromatic erythrocytes in peripheral blood samples from male and female B6C3F1 mice administered D&C Yellow No. 11 in feed for 13 weeks.

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[34] NTP (1997) Toxicology and Carcinogenesis Studies of D&C Yellow No. 11 (CAS No. 8003-22-3) in F344/N Rats (Feed Studies). NTP Technical Report Series No. 463.

Summary

The inclusion of D&C Yellow No. 11 in the list of chemicals to be considered for prioritization by OEHHA's CIC is based on the mutagenicity and carcinogenicity data reported by NTP. The available *in vitro* mutagenicity data are inconclusive while the *in vivo* micronucleus data were negative. Regarding the carcinogenicity data, it is important to note that data reported by NTP were from a study in rats that were administered D&C Yellow No. 11 orally via the diet. However, D&C Yellow No. 11 is approved for use in the United States and Europe only for products intended for external use and not for oral or eye contact applications. As such, dermal carcinogenicity data, which apparently are not available, would be the appropriate endpoint on which to judge the carcinogenic potential of this color additive when used as intended.

Fluoride and its Salts

The Personal Care Products Council agrees with and seconds the comments submitted by the Consumer Healthcare Products Association (CHPA) regarding a "no priority" designation for review of fluoride and its salts by the CIC. The public health benefits of fluoride are well-recognized. As discussed in the CHPA comments, neither the epidemiology data nor the animal data provide convincing evidence of an association between fluoride exposure and increased cancer incidence. Further, the genotoxicity data are inconsistent and therefore do not add to the weight of the evidence for carcinogenicity. It is not our intention to discuss those data here as they are well-described and referenced in the CHPA comments. We would simply reiterate that the existing database does not support a priority review of fluoride, and the benefits of fluoride further argue against review by the CIC.

Thank you for your attention to these issues.

Sincerely,

John E. Bailey, Ph.D.
Executive Vice President - Science