December 20, 2007

Dockets Management Branch
Food and Drug Administration
Room 1061
5630 Fishers Lane
Rockville, MD 20852

Via Facsimile: 301.827.6870

Re: Supplement to Petition: 2007P-0438

Dear Dr. von Eschenbach:

The National Toxic Encephalopathy Foundation (NTEF), hereinafter referred to as the Petitioner, respectfully requests the following Code of Federal Regulations be incorporated as a supplement to the petition commonly referred to as 2007P-0438.

Under **Chapter I Subchapter A (Title 21 CFR-Food and Drug-Part 10 Subpart B Sec. 10.30 E (g)** a petitioner may supplement a petition in writing without agency approval.

Sec. 10.30 Citizen Petition
E. Certification
(g) "A petitioner may supplement, amend, or withdraw a petition in writing without agency approval and without prejudice to resubmission at anytime until the Commissioner rules on the petition…"

Benzophenone 2:

The thyroid gland is part of the endocrine system (glands that are primarily ductless that release hormones/chemical mediators directly into the blood stream), which is part of what is referred to as the hypothalamic-pituitary-adrenal axis. The thyroid's hormones (Triiodothyronine, Thyroxine/tetraiodothyronine, Calcitonin) control numerous physiological functions (metabolism, protein synthesis, calcium levels et al) which affect the entire body. The thyroid works on what is euphemistically referred to as a negative feedback system with the other 2 glands in this axis.

Any disruption from exogenous chemicals that elicit a dysfunctional response on this gland has a systemic response upon the body.

Benzophenone 2 (BP2) has been found to have potent thyroid function disruption. This has been noted to be severe in iodine deficient cells. Recently published studies showed that BP2 exerts estrogenic activity; thus, it is an endocrine active chemical. Absorption rates of BP2 transcutaneously in the human are likely to exceed any safe threshold values. Current data from research centers world wide have demonstrated alarming properties “see below” associated with the use BP2 in humans. Additional toxicological studies should be conducted to clarify possible adverse effects in the context of a still prevailing iodide deficiency in many parts of the world.

.BP2 is a endocrine disruptor, that affects the endocrine system by attaching itself to the receptor sites and mimicking hormonal activity. BP2 has an estrogen like affect, whereby estrogen is the primary female sex hormone that is involved with secondary sex characteristics along with stimulating endometrial and increased uterine growths. BP2 exerts uterotrophic effects from its binding to the estrogen receptors.

The ultraviolet filter benzophenone 2 interferes with the thyroid hormone axis in rats and is a potent in vitro inhibitor of human recombinant thyroid peroxidase. **“**Endocrine disrupting chemicals (EDCs)…may interfere with the thyroid hormone (TH) axis. Here, we examined whether selected EDCs inhibit the key reactions of TH biosynthesis catalyzed by thyroid peroxidase (TPO… BP2 is contained in numerous cosmetics of daily use and may be in regular contact with human skin. … serum total T(4) was significantly decreased and serum thyrotropin was significantly increased. Thus, EDCs, most potently BP2, may disturb TH homeostasis by inhibiting or inactivating TPO, effects that are even more pronounced in the absence of iodide. This new challenge for endocrine regulation must be considered in the context of a still prevailing iodide deficiency in many parts of the world.”[1]

Multi-organic endocrine disrupting activity of the UV screen benzophenone 2 (BP2) in ovariectomized adult rats after 5 days treatment. “The chemical industry has developed sun protection factor products, which contain a variety of so-called "UV screens"…benzophenones (BP). Based on the structure it can be assumed, that the variant BP2 may be a potent estrogenic endocrine disrupter (ED). Only very limited data are available in the literature … However, determination of ED activity in the uterus is only a restricted approach with the potential risk of missing undesirable actions. …. A dose dependent E2-agonistic activity was observed in the uterus (increased weight), vagina (increased IGF1 expression), pituitary (reduced LH synthesis), liver (increased IGF1 expression) and lipid parameters (reduction). A non-E2-like action of BP2 was observed on T4- and T3-levels, which were significantly reduced. Except for the action of BP2 on thyroid hormone levels where it may inhibit thyroid peroxidase, this UV screen exerts clear E2-agonistic actions. Application of BP2 for 5 days proved to be a

sufficient treatment period to unravel a multi-organic endocrine disrupting activity of this UV screen."[2]

A dose-response study on the estrogenic activity of benzophenone-2 on various endpoints in the serum, pituitary and uterus of female rats. "The tetrahydroxylated biphenyl-ketone 2,2',4,4'-tetrahydroxybenzophenone (BP2), one of twelve benzophenone-derived UV-filters, is used in cosmetic products …. Recently published studies showed that BP2 exerts estrogenic activity; thus, it is an endocrine active chemical. …The uterotrophic assay, proposed by the OECD, was modified to have a broader view on endocrine activity outside the urogenital tract to prevent that undesirable actions in other organs regulated by estrogens are missed. … If BP2 is transcutaneously absorbed in the human, the obtained threshold values would suggest refraining from the further use of BP2 as UV-filter in cosmetic products although additional toxicological studies should be conducted to clarify possible adverse effects."[3]

Thyroid-hormone-disrupting chemicals: evidence for dose-dependent additivity or synergism. "Endocrine disruption from environmental contaminants has been linked to a broad spectrum of adverse outcomes. One concern about endocrine-disrupting xenobiotics is the potential for additive or synergistic (i.e., greater-than-additive) effects of mixtures. A short-term dosing model to examine the effects of environmental mixtures on thyroid homeostasis has been developed. …. A mixture was custom synthesized with the ratio of chemicals based on environmental concentrations. ... Six serial dilutions of the mixture were tested in the same 4-day assay. Doses of individual chemicals that were associated with a 30% TH decrease from control (ED30)…interferes with the thyroid hormone axis in rats and is a potent in vitro inhibitor of human recombinant thyroid peroxidase…. most potently BP2, may disturb TH homeostasis by inhibiting or inactivating TPO, effects that are even more pronounced in the absence of iodide. This new challenge for endocrine regulation must be considered in the context of a still prevailing iodide deficiency in many parts of the world."[4]

Pure estrogenic effect of benzophenone-2 (BP2) but not of bisphenol A (BPA) and dibutylphtalate (DBP) in uterus, vagina and bone. "Contradictory results whether the endocrine disrupters (ED) benzophenone-2 (BP2)…) exert estrogenic effects …Selective estrogen receptor modulators (SERMs) exert estrogenic effects in some but not in all organs and ED may be SERMs..binding properties to recombinant ERalpha and ERbeta protein and their effects in the uterus, vagina and bone of ovariectomized rats. BP2 bound to both receptor subtypes, while BPA had a relatively high ERbeta selectivity... In the uterus, only E2 and BP2 increased uterine weight and the complement C3 but decreased ERbeta gene expression… In the vagina, BP2 but not …had clear estrogenic effects…BP2 had antiosteoporotic effects in the metaphysis of the tibia. The serum surrogate parameters of bone metabolism, i.e. osteocalcin and the cross (rat) laps were significantly reduced … effect shared with BP2 but not by the two other EDs. The conclusion: BP2 acts as ERalpha and ERbeta agonist mimicking effects of E2..."[5]

Multi-Organic Risk Assessment of Endocrine Disrupters. "The estrogen receptors (ERs) are members of a super family of ligand-activated transcription factors mediating estrogenic responses. A close functional kinship was found for the structurally related estrogen receptor-related receptorl (ERR1), a constitutively active transcription factor. The aryl hydrocarbon receptor (AhR) mediates the toxic and estrogenic effects of a wide variety of environmental contaminants and industrial pollutants. Both the ERR1 and the AhR are known to modulate the ER's signalling pathways in multiple ways. ..The UV-screens benzophenone-2 and benzophenone-3 (BP2, BP3), structurally related to known steroid receptor ligands, are used in cosmetics and plastics to improve product stability and durability…BP2…shown to exert uterotrophic effects and BP2 was shown to bind to the estrogen receptors. Whether such effects are also exerted in other organs is unknown…multi-organic risk assessment for these substances…measuring the gene-expression…receptors in the pituitary, the uterus and the thyroid after a five-day treatment in comparison to estradiol. Though BP2 seems to exert an estrogen-like effect … there are regulatory effects on receptor expression for both substances that indicate a kind of endocrine disruption that is not assessed by classical estrogenic markers."[6]

The ability of Benzophenone-2 to affect the thyroid and estrogen receptors while influencing the systemic regulation of these hormones clearly places the system in a precarious and hazardous situation with the direct introduction into the vascular system of Angel Parfum.

Chapter I Subchapter A (Title 21 CFR –Food and Drug –Subpart A Section 2.5 (a)(1)(2))

Sec. 2.5

"(a) Within the meaning of the Federal Food, Drug, and Cosmetic Act an imminent hazard to the public health is considered to exist when the evidence is sufficient to show that a product or practice, posing a significant threat of danger to health, creates a public health situation (1) that should be corrected immediately to prevent injury and (2) that should not be permitted to continue while a hearing or other formal proceeding is being held. The imminent hazard may be declared at any point in the chain of events which may ultimately result in harm to the public health. The occurrence of the final anticipated injury is not essential to establish that an imminent hazard of such occurrence exists."

Respectfully submitted by:

NATIONAL TOXIC ENCEPHALOPATHY FOUNDATION

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Angel De Fazio, B.S.A.T.

President

References

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2. Jarry H, Christoffel J, Rimoldi G, Koch L, Wuttke W. **Multi-organic endocrine disrupting activity of the UV screen benzophenone 2 (BP2) in ovariectomized adult rats after 5 days treatment.** Toxicology. 2004 Dec 1;205(1-2);87-93

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5. Siedlova-Wukke D, Harry H, Wuttke W. **Pure estrogenic effect of benzophenone-2 (BP2) but not of bisphenol A (BPA) and dibutylphtalate (DBP) in uterus, vagina and bone.** Toxicology. 2004 Dec 1;205(1-2):103-12

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