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October 24, 2000

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Jennifer Butler
Docket Management Branch
Food and Drug Administration
Room 1061
5630 Fishers Lane
Rockville, MD 20852

Re: FDA Docket 00P-1210/CP1: Comments Concerning the Occupational Knowledge International's Petition to Restrict Coal Tar-Containing Shampoos, Soaps and Ointments to Prescription Sales

Dear Ms. Butler:

Neutrogena Corporation ("Neutrogena") provides these comments to the United States Food and Drug Administration ("FDA") regarding the above-referenced citizen petition submitted by Perry Gottesfeld on behalf of Occupational Knowledge International on March 14, 2000 (the "Petition"). The FDA acknowledged receipt of the Petition by letter dated March 22, 2000, assigning it docket number OOP-1210/CP 1. The Petition requests that the FDA restrict over-the-counter ("OTC") shampoos, soaps and ointments for the treatment of certain scalp conditions to prescription sales, due to the presence of coal tar in these products. However, the Petition fails to cite any new scientific, clinical or other developments which warrant or justify a change in the position of the FDA regarding the above-mentioned category of products for a simple reason -- there are no new scientific, clinical or other developments. Neutrogena markets several shampoo products which treat dandruff, seborrhea and psoriasis, and which may be affected by the outcome of this citizen petition. These comments are submitted for inclusion in the docket file. 21 CFR § 10.30(d). These comments do not address any procedural issues which may arise from the content of the Petition. Neutrogena reserves the right to provide comments on any procedural or other issues at a later date.

The products at issue for Neutrogena are T/Gel® Shampoo and T/Gel® Conditioner (each containing 2.0% "Neutar® Solubilized Coal Tar Extract" (equivalent to 0.5% Coal Tar)) and T/Gel® Extra Strength Shampoo (containing 4.0% "Neutar®

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Solubilized Coal Tar Extract" (equivalent to 1.0% Coal Tar)) and other T/Gel® coal tar-containing hair care products, which products are used to treat dandruff, seborrhea and psoriasis, and are regulated as over-the-counter drugs. The "Neutar® Solubilized Coal Tar Extract" contained within the T/Gel® products is the single active ingredient.

"Dandruff, Seborrheic Dermatitis, and Psoriasis Drug Products for Over-the-Counter Human Use" are the subject of a final monograph resulting from the OTC Drug Review process, located at 56 Fed. Reg. 63554 (December 4, 1991), which became effective on December 4, 1992. The legal function of the monograph is to establish conditions under which these products "are generally recognized as safe and effective and not misbranded." 56 Fed. Reg. at 63554. These products contain coal tar. 21 CFR §§ 358.701-358.750. A final FDA determination that a drug is generally recognized as safe and effective (GRASE) removes a product, definitionally, from "new drug" status. 21 U.S.C. § 321(p); 21 CFR § 330.10(a)(6)(i). Hence, coal tar is not eligible to be regulated as a "new drug" for treatment of dandruff, seborrhea or psoriasis.

The FDA's responses to comments numbers 17, and 19-22 in the final monograph are instructive with respect to the Petition. These are comments directed at the sufficiency of the warnings required to be placed on these products. Part of the required warning advises consumers to consult a doctor if the condition does not improve after using the product as directed, and that the product should not be used for "prolonged periods without consulting a doctor." The warning does not say how soon the doctor should be consulted. In response to comments that, without a specified time period, these warnings were not sufficient in light of the presence of coal tar, the FDA states "the agency is aware that coal tar has been associated with skin cancer but is not aware of any well-defined, long-term studies that show specifically how long coal tar products can be used without significant side effects." 56 Fed. Reg. at 63565.¹ The agency goes on to state:

As discussed in the tentative final monograph for these products (51 FR 27346 at 27348 and 27349), two long-term studies using coal tar for the treatment of psoriasis showed no significant difference in development of skin cancer in the test group when compared to the expected incidence in selected populations of the United States. The length of time for use of coal tar products after initial treatment, in one of these studies, varied from no use up to as much as 26 years. The agency is not aware of any well defined, long-term studies that show specifically how long these products can be used without significant side effects. Therefore, the agency has no basis to specify a definite time period over which to use these products before consulting a doctor.

¹ To Neutrogena's knowledge, there have been no peer reviewed journal articles or studies published showing a positive correlation between use of coal tar containing shampoo products and skin cancer in humans.

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Id. at 63565-63566. Clearly the FDA gave lengthy consideration to the same issue that is raised by the Petition, during the notice and comment phase of the rulemaking and the issuance of the monograph. The studies referred to in the quote above were two 25-year-long retrospective human studies. In the tentative final monograph, six studies were evaluated by the agency which studied the possibility of a relationship between coal tar use and cancer. 51 Fed.Reg. at 27348-49. The FDA determined that the reports contained in these studies "are sporadic and are complicated by the fact that the patients were often exposed to multiple treatments including ionizing radiation, arsenic, and ultraviolet radiation, as well as coal tar." 51 Fed. Reg. at 27348. The FDA found the 25-year studies to be more reliable, concluding that "the benefits to be derived from the use of coal tar outweigh the potential risks." 51 Fed.Reg. at 27349. However, because of the potential risk and the uncertainty, the FDA promulgated the required warning labeling.

The T/Gel[®] hair care products manufactured and sold by Neutrogena are in compliance with the OTC drug monograph for dandruff, seborrheic dermatitis and psoriasis. The Petition is flawed as it is based on the Newfields report, which, in turn, is based on the Fraunhofer animal study. The Fraunhofer study is not suitable for assessing the carcinogenic potential of coal tar-containing hair care products in humans because the studies were performed with coal tar oil, not coal tar, and they were done using an animal model that has not been validated for predicting cancer in humans. In fact, there are no reliable published studies that show a positive correlation between the use of coal tar-containing hair care products and cancer. It is Neutrogena's considered opinion that T/Gel[®] products are not carcinogenic, that no new information has been presented to suggest that additional warning is needed, and that the safety of these products does not suggest a need to change them to prescription drugs.

Neutrogena asserts that the FDA's action in the final monograph was, and remains, protective of the public health. While the Petition relies on a new assessment of the carcinogenicity of coal tar oil applied to mice (and an extrapolation to humans therefrom) -- the Newfields report-- that assessment is still not the 'well defined long-term' study that the agency was looking for when the final monograph was issued. (See Neutrogena Corporation's Comments on Scientific Issues Raised by the Occupational Knowledge International Petition, attached hereto under Tab "A"). In addition, because the Newfields report cannot be viewed as a 'well-defined long-term study,' it does not support changing a safe OTC product to a prescription-only product. There simply is no new scientific basis for revisiting the conclusions reached by the FDA in the final monograph.

A prescription drug is a "drug intended for use by man which (A) because of its toxicity or other potentiality for harmful effect, or the method of its use, or the collateral measures necessary to its use, is not safe for use except under the supervision of a practitioner licensed by law to administer such drug; or (B) is limited by an approved application under section 355 of this title [a new drug] to use under the professional supervision of a practitioner licensed by law to administer such drug." 21 U.S.C. § 353(b)(1); see also 21 CFR § 330.10(a)(4)(vi) ("A drug shall be permitted for OTC sale and use by the laity unless, because of its toxicity or other potential for harmful effect or because of the method or collateral measures necessary to its use, it may safely be sold and used only under the supervision of a practitioner licensed by law to administer such drugs.").

The FDA has thoroughly studied the drug coal tar, for the proposed use, and has issued a final monograph. During an OTC Drug Review the drug is evaluated for safety.

Safety means a low incidence of adverse reactions or significant side effect under adequate directions for use and warnings against unsafe use as well as low potential for harm which may result from abuse under conditions of widespread availability. Proof of safety shall consist of adequate tests by methods reasonably applicable to show the drug is safe under the prescribed, recommended, or suggested conditions of use. This proof shall include results of significant human experience during marketing. General recognition of safety shall ordinarily be based upon published studies which may be corroborated by unpublished studies and other data.

21 CFR § 330.10(a)(4)(i).

An important factor to consider in deciding whether a prescription must be required is the seriousness of the harm which could occur from an unsupervised layperson's use of the product. U.S. v. Article of Drug . . . Labeled . . . Decholin, 264 F.Supp. 473 (E.D. Mich. 1967). Years of successful marketing of coal tar-containing shampoos have shown that the unsupervised layperson is well-equipped to use the product properly. Another factor to consider is whether a layman can safely self-diagnose the condition for which the OTC drug is claimed to be effective. U.S. v. 62 Packages . . . Marmola Prescription Tablets, 48 F.Supp. 878, 887 (W.D. Wis. 1943), aff'd, 142 F.2d 107 (7th Cir. 1944), cert. denied, 323 U.S. 731 (1944) (treatment for hypothyroidism). This concern is unlikely to apply to the scalp problems at issue in this Petition.

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When the administrative record shows that the FDA has considered the scientific materials submitted by a petitioner or plaintiff during the notice and comment phase of a rulemaking on an OTC drug or a prescription drug, and the FDA has made a decision based upon the scientific evidence, the agency's decision must stand. National Nutritional Foods Assoc. v. Weinberger, 366 F.Supp. 1341, 1345 (S.D.N.Y. 1973), aff'd, 491 F.2d 845 (2d Cir. 1973). Interpreting the definition of prescription drug, the court in this case stated,

Plaintiffs' quarrel with the Commissioner is over the dosage point at which some restrictions would become prudent. . . . The Commissioner's judgments about safety levels (in the admittedly uncertain and debated state of knowledge) and consumer habits are solidly grounded. If the question were for de novo decision, the court would probably decide as he did. But it is enough to say his determinations are reasonable and rational.

Id. at 1346-47. Congress left it to the FDA to decide whether medical supervision is necessary to ensure patient compliance with the labeling restrictions needed for safe use of a drug. Thus, safety is considered in the context of use directions and labeling. 21 U.S.C. § 355(d). The FDA's determination of what labeling best reflects current scientific information regarding the risks and benefits of a drug involves a high degree of expert scientific analysis, and is entitled to deference. Henley v. Food and Drug Admin., 873 F.Supp. 776, 782 (E.D.N.Y. 1995), aff'd, 77 F.3d 616 (2d Cir. 1996) (FDA was not arbitrary and capricious in concluding that animal studies were not of value in predicting the consequences of human use of oral contraceptives); Truth in Labeling Campaign v. Shalala, 999 F.Supp. 1289 (E.D. Mo. 1998) (FDA action was not arbitrary and capricious where the FDA compiled an administrative record containing the conflicting scientific evidence and weighed that evidence). "Mere differences in the weight or credence given to particular scientific studies are an insufficient basis upon which to overrule an agency's decision on a matter within its expertise." Id. As the tentative and final monographs show, the FDA has analyzed studies evaluating the possibility of a link between the use of coal tar and cancer, and has addressed the margin of risk involved in use of the drug through appropriate warning requirements.

Neutrogena submits that FDA's decision regarding the safety of coal tar in products sold for the treatment of dandruff, seborrhea and psoriasis is well within the FDA's expertise, and the agency cannot, and should not, be expected to reassess a final monograph each time that a new study is performed on the drug that is regulated by the monograph; especially in the situation where the agency has already assessed the particular risk in issue, and the new study is one that does not rely on studies on humans. See, e.g., Henley, 873 F.Supp. at 782. The monograph sets the safe concentrations and uses for this drug, and sets the required standards for warnings. See 21 CFR §§ 358.701-

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358.750. Any product sold for treatment of these conditions that does not conform to the final monograph is misbranded, and is subject to enforcement action. Neutrogena contends that the OTC monograph for "Dandruff, Seborrheic Dermatitis, and Psoriasis Drug Products for Over-the-Counter Human Use," in its present form, should stand. In Neutrogena's considered opinion, the T/Gel® products are not carcinogenic, do not need to be changed to a prescription drug, nor is any additional warning needed.

For all the reasons set forth above and in the attachment to this letter, Neutrogena urges FDA to deny the Petition. In addition, in order to provide the consuming public and the regulated community with the maximum clarity on the issue presented by the Petition, Neutrogena requests that the FDA take the following actions in response to the Petition: (1) find that the Newfields assessment and Fraunhofer study (those collectively being the purported scientific support for the petitioner's request), do not constitute an adequate basis for evaluating the human cancer risk from coal tar-containing hair care products; (2) find that no additional warnings beyond those set out in the final OTC monograph are necessary or appropriate to protect users of coal tar-containing hair care products which comply with the OTC monograph (and may be counterproductive to the user); and (3) find that no change in status from OTC drug to prescription drug is warranted for these products. Furthermore, Neutrogena requests that FDA find that no limits on individual poly-aromatic hydrocarbons are necessary or appropriate to ensure the safety of users of coal tar-containing hair care products which comply with the OTC monograph.

Neutrogena thanks the FDA for this opportunity to comment on the Petition and looks forward to working with the agency on these issues.

Very Truly Yours,



Donald S. Orth, Ph.D.
Director of Technical Services
Neutrogena Corporation

EXHIBIT A

**Neutrogena Corporation's Comments on Scientific Issues Raised by the
Occupational Knowledge International Petition, FDA Docket No. OOP-1210/CP 1**

This document comments on the Occupational Knowledge International Petition ("Petition"), FDA Docket No. OOP-1210/CP 1, and summarizes a review of scientific information relating to the continued use of coal tar in topical OTC-drug products.

A. Introduction

In 1991, The Food and Drug Administration (FDA) issued a final rule in the form of a final monograph that established conditions under which over-the-counter (OTC) dandruff, seborrheic dermatitis, and psoriasis drug products are generally recognized as safe and effective and not misbranded (1). This monograph, which is part of the ongoing review of OTC drug products conducted by the FDA, established that these products are safe and effective for human use if they contain 0.5–5.0% coal tar (active ingredient) and are labeled in accordance with provisions of the monograph. T/Gel® Shampoo and related OTC drugs manufactured by Neutrogena are in compliance with this monograph. Furthermore, the concentration of coal tar used in T/Gel® Shampoo is 0.5% -- the *lowest* level of coal tar that can be used for products that are in compliance with the monograph. All other T/Gel® anti-dandruff hair care products contain 0.5% coal tar, except for T/Gel® Extra Strength Shampoo, which contains 1.0% coal tar.

The Petition is based on a report prepared by Newfields, a consultant to an individual associated with the entity that filed the Petition. That individual is also a plaintiff in litigation in California under California's Proposition 65 concerning coal tar containing products. The Newfields report is, in turn, based primarily on an unpublished study performed by the Fraunhofer Institute of Technology. The conclusions reached by the Newfields report are not supported by the human epidemiology of treatment of skin conditions by coal tar application and coal tar – containing shampoo application. In addition, a concern is presented by Newfields' use of the Fraunhofer data, in that the Fraunhofer study: (i) did not test coal tar material of the type used in coal tar – containing hair care products; (ii) did not test coal tar – containing hair care products themselves; and (iii) used an animal test model that was not validated for predicting human cancer from the use of these products.

B. Epidemiology

In 1982 an expert panel reviewed coal tar as a treatment for seborrheic dermatitis, psoriasis and atopy (eczema) for the U.S. Food and Drug Administration. The Advanced Notice of Proposed Rule Making (ANPR) included a review of the then available epidemiological data (2-4). Only one of these references, reference 3, was peer reviewed, the others being information garnered from a symposium (2) and a bulletin (4).

Since the publication of the 1982 ANPR, five additional peer reviewed epidemiology studies have been reported in the medical literature (5-9). These have been reviewed and summarized (10).

Taken as a group of six epidemiological studies, 1,924 patients treated with 100% crude coal tar for psoriasis or atopy applied to large areas of their bodies and left on for periods up to 24 hours were evaluated against non-treated controls.

These studies (2 from Denmark, 2 from the United States, 1 from Sweden and 1 from the United Kingdom) included follow up periods on the 1,924 patients from between 25 and 60 years post treatment.

In addition, over 15,000 psoriasis patients' medical histories were examined for any increased incidence of cancer (6). These medical histories showed no increased risk of skin cancer due to the use of coal tar.

The weight of epidemiological evidence clearly demonstrates that there is no increased risk from cancer when crude coal tar is applied to patients suffering from the pathological skin conditions of psoriasis or atopy.

C. The Fraunhofer Study is not an Appropriate Basis for the Petition

- 1. The Fraunhofer study does not, and does not purport to, provide an adequate basis for estimating the risk of cancer from therapeutic application of coal tar or coal tar – containing hair care products.***

Cancer potency estimates may be derived from either human or animal data. Various risk assessments of coal tar have been performed using data from human epidemiological studies or cancer bioassay studies in animals. A carcinogenicity study of coal tar oil in male mice, which was reported by the Fraunhofer Institute of Toxicology in 1997 (hereafter, the "Fraunhofer study"), was used by Newfields to estimate a cancer potency factor for coal tar. The Fraunhofer study was selected for cancer potency estimates because it is a study of a substance described as coal tar oil that was tested at multiple dose levels. In order to perform a cancer potency estimate, a study with multiple dose levels is required.

Unfortunately, the Fraunhofer study does not provide an adequate basis for Newfields' estimate of the cancer potency for the coal tar used in coal tar – containing hair care products for, among other things, the reasons set forth below. These reasons include:

- Failure to conform to standard guidelines for carcinogenicity testing;
- Failure to use the same coal tar materials in the study as are used in the coal tar – containing hair care products;
- Use in the test material of a solvent that enhances absorption of the test material;
- A study result for the test material most closely resembling the coal tar in coal tar-containing hair care products that shows no increased cancer risk;
- The existence of test conditions that confound the study results; and
- The use of an unvalidated animal test model.

2. *The Fraunhofer study did not conform to standard guidelines for carcinogenicity testing.*

The Fraunhofer study did not meet standard OECD and EPA guidelines for carcinogenicity testing. The authors of the Fraunhofer study summarized many of these exceptions to the guidelines on page 20 of the study report. The authors explained, “These exceptions were justified and accepted by the sponsor, since the objective of the study was to evaluate possible carcinogenic effects of CTP on the skin of male CD-1 mice.” While the study sponsors may have decided that these “exceptions” may be justified and acceptable for the purposes of the sponsor, that does not make those exceptions appropriate for using this study for purposes of quantitative risk assessment of coal tar shampoos. Further, no studies known to Neutrogena seeking to replicate the Fraunhofer study have been performed on other species.

The Fraunhofer study failed to meet standard guidelines in many respects. The study was conducted in male mice only. Standard guidelines generally require that carcinogenicity testing be performed in both male and female animals in order to evaluate the consistency of the results. Many of the standard endpoints of toxicity were not evaluated in the Fraunhofer study. The significance of this “exception” is that it is difficult to assess the effects of systemic toxicity on the overall findings of the study. Food consumption was not measured in the Fraunhofer study, a generally accepted principle in cancer bioassays. One purpose of measuring food consumption is to determine whether the animals are healthy and eating normally. Since there was clear evidence of infections in this study, the lack of food consumption data and other measures of toxicity is a serious omission. No histopathology was performed on any organs except for the skin. The site of application was not covered after administration of the test material, as required by standard guidelines. The study indicated no precautions to prevent animals from licking the applied coal tar oil off of themselves, which would have caused them to ingest the coal tar oil orally. And the stability of the test material was performed in acetone, but the test material was given in toluene, not acetone. And finally, because the mice at the high

dose CTP-2 “unexpectedly” exhibited suppurative ulceration of the skin, treatment was terminated on “nominal days 269-274.”¹ As a result, one new control group and three new dosed groups were added to the study toward the end of the first year. Therefore, all of the control groups and the coal tar oil exposed groups were not concurrent. As a result, reliance on the Fraunhofer study for quantitative risk assessment would require relying on the results of different dose levels tested at different times. In summary, the Fraunhofer study does not comply with standard guidelines, and it does not meet “generally accepted scientific principles.”

3. *The test material that produced cancer in mice in the Fraunhofer study is not the same material as the coal tar in coal tar-containing hair care products.*

The Fraunhofer study evaluated two coal tar oils for potential carcinogenicity. Only one produced cancer. The first test material (CTP-1) was described as “coal tar oil with low benzo[a]pyrene content” (approximately 10 ppm). This test material did not produce a significant increase in the incidence of cancer in mice at any dose level. As noted below in Table 1, this concentration is 4 to 8 times higher than the concentration of coal tar present in T/Gel® and most other coal tar shampoos. An even starker contrast is presented by the second test material (CTP-2), described in the Fraunhofer study as “coal tar oil with medium benzo[a]pyrene content” (approximately 275 ppm) that was carcinogenic in mice. CTP-2 contains 22.6 to 45.2 times as much coal tar as is found in T/Gel® shampoos and over four times as much coal tar as the highest FDA monograph-approved percentage of coal tar for these types of products.²

The chemical composition of the test materials in the Fraunhofer study differed from that of the T/Gel shampoos and hair care products in several ways, some of which are set forth in the following paragraphs.³ (See Table 2)

First, as indicated above, the concentration of coal tar in the test materials in the Fraunhofer study was much higher than the coal tar concentration of most OTC coal tar – containing hair care products, including T/Gel® shampoos. Table 1 summarizes the percentage of coal tar in the Fraunhofer test materials and in representative products.

¹ Fraunhofer Report (1997) p. 13.

² Furthermore, the Fraunhofer Study involved applications of test materials that were not washed off the skin, an additional dissimilarity to coal tar – containing hair care products.

³ Also of importance is the fact that the coal tar used in Neutrogena's® T/Gel® coal tar – containing hair care products undergoes an additional step of refinement/processing in which certain impurities/particulates are filtered out.

**Table 1.
Comparison of Coal Tar Content of Fraunhofer Test
Materials and REPRESENTATIVE COAL TAR-CONTAINING Shampoos**

Parameter	Fraunhofer CTP-2 (High BaP)	Fraunhofer CTP-1 (Low BaP)	1% Coal Tar-Containing Shampoo (1.0% Coal Tar)	0.5% Coal Tar – Containing Shampoo (0.5% Coal Tar)
Coal tar (%)	22.6	4.1	1.0	0.5
Carcinogenic in Fraunhofer study?	Yes	No	[None Reported in the Literature]	[None Reported in the Literature]

Second, the reliability of the Fraunhofer study is further compromised by its use of an analytical report of materials that purported to be the Fraunhofer test materials. That analytical report, by a Dr. Grimmer, was dated March 9, 1993, prior to the start of the Fraunhofer study. Therefore, there is no evidence that the test material actually used during the course of the study was analyzed chemically. In addition, the test material analyzed by Dr. Grimmer prior to the start of the study was dissolved in acetone. This was different from the test material actually used during the study since the test material used for the study was dissolved in toluene. See section C. 4 below.

Third, based on Dr. Grimmer's 1993 report, the coal tar oils used in the Fraunhofer study presented a profile of individual chemicals and PAHs that were different from those in coal tar – containing shampoos. Table 2 compares the chemical composition of the Fraunhofer coal tar oils to the chemical profile of the representative coal tar-containing shampoo. Many of the same chemical constituents were found in the Fraunhofer coal tar oils and in the shampoo. However, the concentrations and ratios varied widely. The Fraunhofer study indicates that its test material was "coal tar oil," not the FDA – approved coal tar used in coal tar containing hair care products. This difference is highlighted by the fact that the IARC monograph does not equate coal tar oil with coal tar. See IARC Monograph, p. 90 (Reference 11). Thus, the coal tar in coal tar – containing shampoo is not the same as the coal tar oils evaluated in the Fraunhofer study.

Table 2.
Comparison of the Chemical Profile of Fraunhofer Test Materials and T/Gel Shampoos

Substance	Fraunhofer CTP-2 (High BaP)	Fraunhofer CTP-1 (Low BaP)	Example of 0.5% coal tar shampoo ^a
Coal tar	226,000	41,000	5,000
Naphthalene	25,314	126,000	60
Acenaphthylene	--	--	<9
Acenaphthene	--	--	275
Fluorene	--	--	105
Phenanthrene	126,286	32,355	500
Anthracene	4,886	3,454	160
Fluoranthene	42,114	3,857	455
Pyrene	23,771	1,243	355
Benzo[a]anthracene	--	--	60
Chrysene	--	--	65
Benzo[b]fluoranthene	--	--	29
Benzo[k]fluoranthene	--	--	16
Benzo[a]pyrene (BaP)	275	10	35
Dibenzo[a,h]anthracene	25	1	5
Benzo[g,h,i]perylene	107	4	17.5
Indeno[1,2,3-cd]pyrene	57	4	15
Benzo[e]pyrene	249	8	115

All Table Values are in parts per million (ppm).

^a Based on "Koppers Industries, Inc. Polynuclear Aromatic Hydrocarbon Analysis - K 1535 Refined Tar" dated March 24, 1993.

Even if the Fraunhofer study were flawless (which it is not), it would not be an appropriate study for the quantitative risk assessment of coal tar-containing shampoos, since the Fraunhofer test materials were distinctly different from the coal tar used in shampoos. It is not appropriate to estimate the potential cancer risks of coal tar-containing shampoos based on the Fraunhofer study of coal tar oils. Merely because coal tar oils and coal tar shampoos both contain PAHs does not mean one can be used to predict the cancer risk of the other. Diesel exhaust and charcoal-broiled hamburgers both contain PAHs, but it would be inappropriate to estimate the potential risk of eating a hamburger based on the results of a study of diesel exhaust.

4. *The test material was administered in toluene, a solvent that would enhance the absorption of coal tar oil.*

In the Fraunhofer study, both test materials were dissolved in the solvent toluene. The test materials were placed on the mouse skin in toluene. Toluene would be expected to enhance the dermal absorption of coal tar oil, because it is known that many organic solvents, including toluene, affect percutaneous absorption. For example, King and Monteiro-Riviere (12) found that toluene increased the delivery of test materials into skin. Therefore, the responses in the Fraunhofer study may have been heavily influenced by the choice of toluene as a vehicle. However, even when using toluene as a solvent, the CTP-1 did not produce cancers in the sensitive mouse model (CTP-1 group).

Coal tar – containing hair care products do not contain toluene. A mouse cancer bioassay of coal tar oils given in toluene would not represent a reliable basis for quantitative risk assessment of coal tar –containing shampoos that are rinsed off the skin.

5. *The test material that most closely resembled the concentration of coal tar in hair care products did not cause cancer in the Fraunhofer study.*

As noted above, it is not appropriate to use the Fraunhofer study to estimate the potential cancer risks of coal tar – containing shampoos. But, even if we assume that the Fraunhofer study is an appropriate basis for risk assessment, the Fraunhofer study suggests that coal tar-containing shampoos would not cause cancer in mice. Of the two test materials evaluated in the Fraunhofer study, the composition of these shampoos more closely resembles CTP-1, the test material that did not cause cancer, than CTP-2. (See Tables 1 and 2 above.) Based on an assumption that the Fraunhofer study is relevant, one could predict that coal tar – containing shampoos would not cause cancer in mice, much less in humans. Again, it is worth noting that at least six epidemiological studies (3, 5-10) corroborated the absence of positive correlation between use of these shampoos and human skin cancer.

6. *Ulcerations, infections, and shaving in mice in all dosed groups confound the results of the Fraunhofer study.*

a. *The presence of ulcerations of the skin represents a significant flaw in the Fraunhofer study.*

All dose levels of coal tar oils produced serious ulcerations of the skin in the Fraunhofer study. These skin lesions were so serious that the investigators had to temporarily interrupt treatment at all dose levels. With CTP-1, treatment had to be interrupted due to skin ulcers in 19/62, 23/62, and 25/62 of the low, middle, and high dose mice, respectively. With CTP-2, treatment was interrupted in 25/62 and 45/62 low and middle

dose mice, respectively. The high dose level of CTP-2 had to be terminated altogether because the mice developed serious skin ulcers; the authors reported the complete focal loss of the epidermis. As such, the mice had no protective skin barrier to prevent rapid dermal absorption of the test material. Importantly, this ulceration may have contributed significantly to the production of skin tumors in the test mice.

In comparison, coal tar shampoos do not cause ulcerations of the skin or the loss of the epidermal skin layer. The Fraunhofer test evaluated the carcinogenicity of coal tar oils under conditions that caused severe ulcerations of the skin. It is not appropriate to quantitatively extrapolate from the results of studies of coal tar oils in mice under conditions that caused skin ulcers to humans exposed to coal tar in rinse-off shampoos.

b. The presence of infections in mice in all dosed groups confounds the results of the Fraunhofer study.

The authors of the Fraunhofer study observed “an increase in dead or moribund animals with enlarged spleen and enlarged lymph nodes in all treated groups of the main study compared to control group.”⁴ An enlarged spleen and enlarged lymph nodes are typical symptoms of a systemic infection. The authors attributed these infections to the open ulcerations of the skin. The authors stated: “These effects were obviously due to infections subsequent to skin ulcerations.”⁵ The presence of infections, particularly skin infections due to ulceration, may have confounded the results of this skin cancer study. It is not clear what the results of a study of coal tar oils would have been without the presence of infections in the animals. It is clear, however, that it is not a “generally accepted scientific principle” of animal bioassays that the test animals exhibit serious infections and ulcerations. The investigators recognized the serious nature of this problem when they terminated exposure of the high dose group. While this study may be adequate for *qualitatively* determining whether coal tar oils are potentially carcinogenic in mice, the study is not adequate for purposes of *quantitative* risk assessment for coal tar – containing hair care product use in humans.

c. Shaving the skin of mice in order to apply the test material may have caused skin damage, another confounding factor.

In the Fraunhofer study, it was necessary to repeatedly shave off the fur of the mice in order to apply the test materials. This is usually done with electric clippers. Clipping the skin can cause minor cuts and abrasions in the case of normal, healthy skin. In the Fraunhofer study, many of the mice did not have normal healthy skin. The mice in the Fraunhofer study suffered from ulcerative skin lesions, and clipping the skin in the presence of such serious ulcerations could have created even more serious skin damage

⁴ Fraunhofer Report (1997) p. 11.

⁵ Fraunhofer Report (1997) p. 11.

and infections. Such conditions may have altered the capacity of the skin to absorb components of the test materials, affecting the results of the skin painting study.

It is not certain to what extent shaving the skin of mice presents an additional confounding factor in the Fraunhofer study. However, in humans, hair is not usually shaved prior to application of coal tar shampoo. To be meaningful, animal bioassay studies for quantitative risk assessment must meet generally accepted scientific principles, including the degree to which dosing resembles the expected manner of human exposure. In humans, coal tar shampoos are applied dermally, but they are not applied in a manner that causes serious ulcerations of the skin and infections that require people to stop using the shampoo. Also, coal tar shampoos are rinsed off shortly after they are applied, whereas in the Fraunhofer study, the coal tar oils were never removed from the skin. Therefore, the dosing of the test material in the Fraunhofer study did not resemble the expected manner of human exposure.

7. *Use of the CD-1 Mouse for Carcinogenicity Testing is not Validated for this Purpose.*

Until recently, we relied on animal studies to determine toxicological end points of test materials. Often, doses higher than those to which humans would be exposed were used to produce a response in the test animals. Although we have been able to use data from animal studies to predict many toxicity end points, it is recognized that there are interspecies differences and that the results from some animal studies may not be relevant to humans. As noted above, laboratory strains of mice readily develop cancers when exposed topically to PAHs, but epidemiological data in humans exposed to medicinal coal tar or coal tar-containing antidandruff shampoos does not corroborate these findings. As with chemical analyses, animal models must be validated for use in predicting end points in humans. Without such validation, the studies are of limited value.

There is no documentation to indicate that the CD-1 mouse model has been validated for extrapolating findings on the carcinogenicity of topically-applied coal tar oil to the carcinogenicity of coal tar in rinse-off shampoos used on humans.

The strain of mouse used in the Fraunhofer study has not been validated for predicting cancer in humans as a result of using coal tar-containing shampoos. Pickering (13) noted that the mouse appears to be the most sensitive test animal, so it is likely that it will provide a cancer slope factor/NSRL value that is unrealistically low (or in error).⁶ Dr.

⁶ Pickering (13) reported that BAP is carcinogenic when administered to some experimental animals and that the mouse appears to be the most susceptible animal. He observed that PAHs are ubiquitous – they are present in air, soil, water, foods, cosmetics and medicines; consequently, they are inhaled, ingested and applied topically. He stated that “Considering that they are such powerful mutagens and carcinogens under laboratory conditions, it is surprising that the human species is not riddled with PAH-induced tumors. This may be due to a significant interspecies difference in the absorption and metabolism of the chemicals in question.”

Shull, author of the Newfields report, noted this potential for error in the last few paragraphs of the Newfields report. Thus, a mouse cancer bioassay of coal tar oils applied in toluene would not represent a reliable basis for quantitative risk assessment of coal tar-containing shampoos that are applied in the shower and rinsed off.

8. *The Fraunhofer study is seriously flawed for purposes of quantitative risk assessment of coal tar in shampoos, and does not adequately support the Petition.*

As discussed above, there are a number of important reasons why the Fraunhofer study should not be used for quantitative risk assessment to support the Petition. To reiterate, these reasons include:

- Failure to conform to standard guidelines for carcinogenicity testing;
- Failure to use the same coal tar materials in the study as are used in the coal tar – containing hair care products;
- Use in the test material of a solvent that enhances absorption of the test material;
- A study result for the test material most closely resembling the coal tar in coal tar-containing hair care products that shows no increased cancer risk;
- The existence of test conditions that confound the study results; and
- The use of an unvalidated animal test model.

Thus, the Petition and the Newfields report are not adequately supported by the Fraunhofer Study.

D. *Determination of NSRL for Coal Tar by Newfields.*

1. *Objective of the Newfield Report*

Newfields used the Fraunhofer study to determine a NSRL for coal tar use in shampoo. Newfields calculated a NSRL of 0.02 $\mu\text{g}/\text{day}$ for coal tar using the incidence of skin tumors in male CD-1 mice following the direct dermal application of different concentrations of coal tar oil in toluene.

2. *Problems with the Newfields Approach*

In addition to relying inappropriately on the Fraunhofer study, the Newfields report has several other flaws that render it inadequate to support the Petition.

a. *Determination of the NSRL for coal tar*

A major problem with the Newfields exposure assessment for coal tar shampoo use is that the proposed NSRL of 0.02 $\mu\text{g}/\text{day}$ for *coal tar* is below the California Prop. 65 NSRLs of many of the individual components of coal tar. This is illustrated by reviewing the following:

- Benzo(a)anthracene NSRL = 0.04 $\mu\text{g}/\text{day}$
- Chrysene NSRL = 0.2 $\mu\text{g}/\text{day}$
- Benzo[b]fluoranthene NSRL = 0.04 $\mu\text{g}/\text{day}$
- Benzo(a)pyrene NSRL = 0.06 $\mu\text{g}/\text{day}$

The primary reasons for the unrealistically low proposed NSRL for coal tar are: 1) use of data from the Fraunhofer study in which coal tar oil (not coal tar) in toluene was applied to the shaved backs of male CD-1 mice; 2) use of the Prop. 65 default assumptions for product use for 70 years; and 3) use of LMS model extrapolations that are highly conservative and overestimate carcinogenic potency. As noted above, the CD-1 mouse model is not a validated test system for demonstrating carcinogenicity of coal tar – containing hair care products in humans. Clearly, recent reports in the literature bring into question the applicability of animals for predicting carcinogenicity (14).

In the discussion of the potency factor in the Newfield document, Dr. Shull noted that “the systemic distribution of absorbed doses is not relevant.” This is not consistent with the 3/22/00 Gottesfeld petition in which Mr. Gottesfeld stated that “epidemiological studies have demonstrated that coal tar can cause skin and other systematic [systemic] cancers.” It should also be noted that Dr. Shull stated that the California Office of Environmental Health Hazard Assessment method for risk assessment uses systemic distribution of a dose (using body weight scaling). This suggests that Dr. Shull’s data were generated using different assumptions than were used for other California Prop. 65 NSRLs.

b. *Residue factor*

In the Newfields report, Dr. Shull noted that the calculations used two different residue factors. These residues were 2% (“the OEHHA assumption for the applied dose in a shampoo that remains as a persistent residue”) and 10% (the “European Community Scientific Committee assumption for rinse off products”). As it turns out, Dr. Shull used

these 2% and 10% residue factors as *absorption factors* (p. 4 of the Newfields risk assessment). It is common knowledge in dermatology that the stratum corneum provides a barrier to topically applied materials. Thus, it would be appropriate to use only a percentage of the residue for the amount actually absorbed into the epidermis -- the outermost living portion the skin.

c. *Exposure duration and study design*

In discussing the Exposure Duration, Dr. Shull notes that the California Prop. 65 default assumptions of product use constantly and consistently for 70 years (the lifespan of an individual) "is very conservative and results in estimating a lower NSRL... than if shorter exposure durations were used." Use of the default assumptions is unrealistic because people do not use coal tar -- containing hair care products for their entire life.

In discussing the Animal Study Design, Dr. Shull noted that "use of the mouse provides the most conservative cancer potency results for determining a NSRL." Data from studies using the CD-1 mouse are of questionable value in this type of exposure assessment because the CD-1 mouse model has not been validated for predicting cancer to topically applied antidandruff shampoos in humans.

d. *Risk determined by use of the LMS model*

In discussing the Carcinogenic Toxicity Criteria, Dr. Shull noted that "The LMS model assumes that there is no threshold for carcinogenic substances; that is, exposure to even one molecule of a carcinogen is sufficient to cause cancer. This is a highly conservative and questionable assumption because the body has several mechanisms to protect against cancer." Furthermore, he stated that "An animal bioassay can't determine what happens at low levels of exposure, however, which are generally typical of human exposure levels." Unfortunately, use of the LMS model resulted in an unrealistically low proposed NSRL for coal tar in antidandruff shampoos. This low NSRL would lead one to think that there may be a problem with coal tar-containing shampoos when, in fact, antidandruff shampoos have never been reported to cause cancer in humans. Dr. Shull recognizes this on the last page when he stated that "Several factors in the LMS [model]... can greatly overestimate risk."

3. *Perspective on the Newfields Report*

Any risk assessment is only as good as the underlying assumptions on which it is based. The Newfields report appears unrealistically biased because: (i) it used such conservative and questionable assumptions that the proposed NSRL for coal tar is *below* the California Prop. 65 NSRLs for many of the PAHs in coal tar; (ii) it used data from an animal model that has not been validated; and (iii) it failed to take into account relevant epidemiological data.

E. Conclusions

The Petition fails to establish the existence of any new scientific, clinical or other developments that warrant or justify a change in the status of coal tar – containing hair care products. The Newfields report that forms the basis for the Petition inappropriately relies on the Fraunhofer study despite the fact that the Fraunhofer study is seriously flawed and did not even test the type of coal tar material used in coal tar – containing hair care products. The Newfields report uses an excessively conservative and questionable approach to generate an NSRL for coal tar that is lower than the California NSRLs for individual coal tar constituents, a result that is unjustifiable.

Further, the Petition takes a position that is entirely inconsistent with the epidemiological data base. The data base has grown since the time the FDA monograph for these products was finalized, and continues to demonstrate that even application of one-hundred percent crude coal tar to large areas of the body for continuous periods up to twenty four hours does not increase the risk of cancer. Thus, use of rinse – off coal tar – containing hair care products continues to be a safe use of these products.

The scientific evidence leads Neutrogena to conclude that T/Gel® coal tar – containing hair care products are not carcinogenic. The Petition provides no adequate scientific basis for any action by FDA. Therefore, there is no reason for the FDA to alter the final monograph on coal tar – containing hair care products, no reason for any additional warnings for these products, and no reason for FDA to alter the status of these products.

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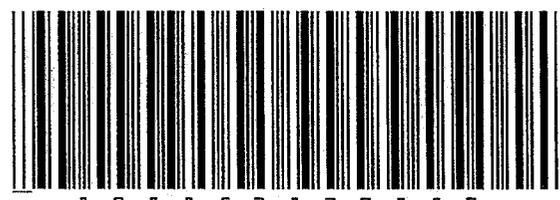
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