



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration  
Rockville MD 20857

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Perry M. Gottesfeld, M.P.H.  
Executive Director  
Occupational Knowledge International  
1255 Post Street, Suite 437  
San Francisco, California 94109

Re: Docket No. 00P-1210  
Comments No. CP1, C1, and C2

Dear Mr. Gottesfeld:

This letter responds to a citizen petition (CP1) submitted by Occupational Knowledge International dated March 6, 2000, and filed on March 22, 2000, under Docket No. 00P-1210 in the Food and Drug Administration's (FDA) Dockets Management Branch. The petition requested the agency to: (1) Initiate a formal review of the use, sale, and distribution of coal tar shampoo, soap, and ointments, (2) restrict the sale and distribution of coal tar products to prescription sales, and (3) require additional warning language to protect public health.

The grounds for your petition were primarily based upon: (1) Results from a dermal carcinogenicity bioassay conducted in mice at the Fraunhofer Institute of Toxicology (the Fraunhofer study), (2) a quantitative risk assessment of the Fraunhofer data, and (3) a list of published articles in the scientific literature referencing coal tar. On June 6 and July 26, 2000, amendments to your petition (C1 and C2, respectively) were filed in the public docket and provided additional references plus information on the European Union's assessment of coal tar.

Background

In 1982, the FDA Advisory Review Panel on Over-the-Counter (OTC) Miscellaneous External Drug Products (the Panel) found that coal tar preparations are safe and effective for OTC use as shampoos for controlling dandruff, seborrheic dermatitis, and psoriasis of the scalp. The Panel recognized the concern regarding the carcinogenic potential of topically applied coal tar preparations, but stated that the contact time of a shampoo is of such short duration that this concern should not prevent the use of coal tar on the scalp (47 FR 54646 at 54656 to 54660, December 3, 1982).

Comments submitted in response to the Panel's report objected to the limitation that coal tar products not be used on the body. Comments provided two 25-year retrospective studies on coal tar for psoriasis that were published in the literature after the Panel made its recommendation. The patients in these studies were treated with coal tar and ultraviolet radiation. In neither study was the number of patients in whom skin cancer developed significantly different from the

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expected incidence for selected populations of the United States. Comments also argued that the benefits of using coal tar in treating psoriasis far outweigh any theoretical risk or the risks associated with currently available alternative therapies. The agency used these studies and other information presented to it to propose reclassifying coal tar for use on the body from Category III (insufficient data to determine whether generally recognized as safe and effective) to Category I (generally recognized as safe and effective)(51 FR 27346 at 27348 to 27349, July 30, 1986). The agency received no objections to this proposal and coal tar products formulated to be applied and left on the skin or scalp were included in the final monograph for OTC dandruff, seborrheic dermatitis, and psoriasis drug products (56 FR 63554, December 4, 1991).

The agency has reviewed the information contained in your petition and in comments submitted to the public docket by interested persons. Based upon our review, the agency concludes that there is not sufficient new information to reverse the findings of our prior review of coal tar-containing OTC drug products. We find that the petition does not demonstrate that pharmaceutical coal tar increases the risk of cancer under the conditions of use described in the final monograph for OTC dandruff, seborrheic dermatitis, and psoriasis drug products. The following specific comments concern the information reviewed.

#### Fraunhofer Dermal Carcinogenicity Study

We do not agree that data from the Fraunhofer study may be used to calculate a "No Significant Risk Level" (NSRL) under conditions of OTC use because of several confounding factors in the study. This study measured the incidence of skin tumors in male CD-1 mice from direct dermal application of coal tar in doses from 0 to 9 milligrams of coal tar per treatment. Doses were applied twice weekly for 78 weeks. The study evaluated two different coal tar substances in a toluene vehicle. One contained approximately 10 micrograms of benzo[a]pyrene per gram of coal tar. Mice treated with this preparation did not show a statistically significant deviation in dermal tumor incidence from the control. The second preparation contained approximately 275 micrograms of benzo[a]pyrene per gram of coal tar. This group showed statistical increases in tumor incidence with increasing coal tar doses and these data were used in the human dermal cancer potency factor calculation submitted with your petition.

The agency believes that a quantitative risk assessment cannot be reasonably conducted using data from this study because of the presence of skin lesions, which likely changed the exposure to target sites and would confound extrapolation to humans. Analysis of systemic effects was confounded by secondary effects of skin infections and the entire study was confounded by the use of toluene due to its destructive effect on the skin of the mice in the study. Also, the study was of insufficient duration to detect carcinogenic systemic effects; systemic histologic evaluation was not performed; and the study utilized only one gender of one species. In addition, it is not clear how the type of coal tar used in this study relates chemically to the types used in OTC drug products, which must meet the monograph and compendial (United States Pharmacopeia) standards. Therefore, we find that the Fraunhofer dermal study in mice adds nothing to what is already known about carcinogenic liability of coal tar under conditions of OTC use and should not be used to estimate an NSRL.

Published Scientific Articles

The agency considered articles in the scientific literature provided by your petition and other comments to the docket. We focused our review on studies of topical applications of medicinal coal tar in humans and studies of background incidence of skin cancer in psoriasis patients. We excluded studies that looked at occupational exposure because these did not involve medicinal grade coal tar. Coal tar, at some exposures, has already been acknowledged to be carcinogenic. It would not be appropriate to extrapolate occupational data to humans using products under the conditions of use specified in the OTC drug product monograph.

Of eleven studies reviewed, five investigated the risk of skin cancer in patients treated with coal tar over a period of time ranging from 5 to 25 years. One study involved patients with atopic dermatitis while the other four studies were conducted with patients having psoriasis. These studies did not show an increased risk of cutaneous or non-cutaneous malignancies in psoriatic patients exposed to coal tar products.

Four other studies investigated the risk of skin cancer in patients with psoriasis. Two of the four found no statistically significant increase in risk, while one found a statistically significant risk of developing basal cell carcinomas. The results of the study with statistical significance, however, could have been explained by other factors not fully examined in the study, including skin type, surveillance bias, and exposure to other agents. In the fourth study, the incidence of skin cancer in the psoriasis group not treated with psoralen plus ultraviolet A radiation (PUVA) was three times higher than in a control group of diabetic patients (statistically significant). The difference can be explained by the fact that these non-PUVA treated psoriasis patients had received known carcinogenic agents (ultraviolet B (UVB) radiation, tar, ionizing radiation, arsenic, and nitrogen mustard). Thus, the independent risk of cancer from coal tar in these patients is not known.

The remaining two studies examined the association between tar and/or ultraviolet radiation exposure and the development of skin cancer. One study found a significantly increased risk of skin cancer. In this study, the effects of tar and ultraviolet radiation were not investigated separately. Thus, the effects of ultraviolet radiation, a known carcinogen, can explain the difference. In the other study, there was no statistically significant difference between the prevalence of malignant and pre-malignant skin lesions in psoriasis patients and population matched controls in spite of increased exposure to UVB and other treatments, including tar.

While there are animal and human occupational exposure data to show that coal tar is carcinogenic, the data does not support that therapeutic use of coal tar in concentrations and formulations used in OTC drug products poses a risk of carcinogenicity. Upon reviewing the published studies, the agency does not find that there is evidence to implicate the use of OTC coal tar-containing drug products as an independent risk factor for the development of skin cancer. Therefore, we conclude that, at this time, there is no evidence that topical treatment of dermatological disorders with OTC coal tar shampoo, soap, or ointment drug products increases the risk of skin cancers.

Adverse Event Reporting System

The agency has reviewed all adverse event reports in our Adverse Event Reporting System associated with coal tar-containing products. A total of 27 reports were retrieved (one report was not legible and one report was a duplicate). Of the 25 cases, most adverse events involved the skin or scalp (e.g., itching or burning) with a few allergic-type reactions. There were no reports of carcinogenicity found in the database.

Conclusions

While we have granted your first request and conducted a formal review of the use of coal tar, the agency concludes that the petition has failed to provide sufficient basis for the agency to grant your other requests. Our review of information in your petition, comments submitted to the docket, and reports in FDA's Adverse Event Reporting System did not disclose new evidence that the risk of cancer is greater in consumers who regularly use OTC drug products containing coal tar than in consumers who do not. Therefore, at this time, we do not find adequate basis to change the status of coal tar-containing drug products for the treatment of dandruff, seborrheic dermatitis, and psoriasis from OTC to prescription or to require additional warning statements on product labeling.

For the foregoing reasons, the first request in your petition (for a formal review) is granted while the second and third requests (for prescription status and additional labeling) are denied. If you have any questions regarding this matter, please refer to the docket and comment numbers noted above and submit all inquiries in triplicate to the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, Maryland 20852.

Sincerely yours,



Dennis E. Baker  
Associate Commissioner  
for Regulatory Affairs