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JAN - 5 2004

DANIEL R. JOHNSON
Senior Vice President

December 30, 2003

VIA: CERTIFIED MAIL, RETURN RECEIPT REQUESTED

Dr. C. W. Jameson
National Toxicology Program
Report on Carcinogens, MD EC-14
P. O. Box 12233
Research Triangle Park, NC 27709

Dear Dr. Jameson:

Re: Comment on Nominations Reviewed in 2003 for Listing in Report on Carcinogens

This comment is submitted by Combe Incorporated with respect to lead and lead compounds under consideration with respect to the Report on Carcinogens. Combe Incorporated is the manufacturer of the leading hair dye that contains a small amount of lead acetate to color gray hair and, as such, is an interested party.

Combe wishes to call attention to Dr. James A. Swenberg's October 8, 2003 letter to you with respect to lead acetate used in hair dyes. As discussed in this letter, these products present no toxicological risk of dermal exposure and have been conclusively demonstrated to be completely safe. Dr. Swenberg reviewed this matter at our request. A copy of Dr. Swenberg's letter is enclosed for reference.

As noted by Dr. Swenberg, the section on dermal absorption in the ROC Background Document on Lead and Lead Compounds is incomplete with respect to dermal absorption of inorganic lead.

There are convincing, published data, accepted by the U.S. Food and Drug Administration and regulatory authorities around the world, that demonstrate the safety of these hair dye products because of the absence of dermal exposure to lead. These data are summarized by Dr. Swenberg in his letter. It is respectfully requested that the ROC be clarified in this regard, and that the absence of dermal exposure and carcinogenic risk from lead acetate-containing hair dyes be noted in the final ROC.

Thank you.

Very truly yours,

Daniel R. Johnson

DRJ/ar
Enclosure

OCT - 9 2003

THE UNIVERSITY OF NORTH CAROLINA
AT
CHAPEL HILL

Curriculum in Toxicology

The University of North Carolina at Chapel Hill
CB# 7270, 509 Faculty Laboratory Office Building
Chapel Hill, NC 27599-7270

October 8, 2003

C. W. Jameson, Ph.D.
Head, Report on Carcinogens
National Institute of Environmental Health Sciences
P.O. Box 12233
Research Triangle Park, NC 27709

Dear Bill:

I enjoyed talking with you yesterday and am following up with this letter to clarify a few concerns with the ROC Background Document on Lead and Lead Compounds. I read the document and some related papers over the weekend. Let me first say that I found the document to be well written and quite detailed for the epidemiology studies. As stated in the document, other issues had been reviewed in detail by IARC in 1987. For transparency, I should state that the document was brought to my attention by Combe, Inc., a manufacturer of a hair dye formulation that utilizes lead acetate and asked me to review the ROC document. I recognize that such a product contributes very little to overall human exposure. Nevertheless, my comments are aimed at improving and clarifying the ROC document so that even such products are assessed with the best science available.

It is clear that dermal exposure has not contributed to the carcinogenic hazard identification of lead acetate. First, nearly all of the positive animal studies utilized oral exposure and none used dermal exposure. Likewise, human cancer risks have been associated with inhalation and oral exposure. None of them have examined dermal exposure. Whereas the EPA used to do hazard identification similar to that done by the ROC, the 2003 Draft Final Guidelines for Cancer Risk Assessment (February 27, 2003) now provide for Risk Characterization. Differences related to exposure data and Mode of Action are brought out in the narrative to improve how scientists and the general public interpret the assessment. I urge you to move in this same direction with the ROC. In this case, *lead is reasonably anticipated to be a human carcinogen following inhalation and oral exposure*. I do not believe the data are strong enough to say that it is *a known human carcinogen following inhalation and oral exposure* due to the inseparable issues of confounding with arsenic and smoking. With respect to the use of lead acetate in hair dyes, regulatory agencies across the world have found it to be suitable and safe to use for that purpose.

The section on dermal absorption (6.1) does an inadequate job of describing what is known about dermal absorption of inorganic lead. It cites a single paper by Stauber et al., (1994) that used a 24 to 48 hour occluded patch for exposure, a method that far exceeds any human exposure model. What is even more important is that the ROC document fails to describe some of the critical observations and interpretations of the paper. For example, lead was detected in whole blood, serum, sweat and urine. Further analysis demonstrated that it was only present in extracellular fluid. The authors stated "Skin-absorbed lead obviously behaves very differently to intravenously

injected lead." They went on to say that "One may speculate that, on passage through the skin, lead forms a stable protein complex that is not absorbed by erythrocytes." From a Mode of Action standpoint, if dermally absorbed lead remains in extracellular fluid until it is excreted, there is no known mechanism by which it could cause cancer. It must enter a cell to cause direct or indirect damage to DNA, chronic cell proliferation, etc. Thus, the superficial reporting associated with dermal absorption in the draft ROC document totally missed critical information and gives an incorrect summation of our scientific understanding. The document also missed several other papers on dermal absorption, including a German paper on the application of lead acetate in a hair dye preparation for 6 months in a double blind study with 53 subjects. This study did not find any changes in lead levels in whole blood or urine, 5-aminolevulinic acid dehdratase, free erythrocyte porphyrin, 5-aminolevulinic acid in urine, total porphyrin or porphobilinogen in urine, changes in erythrocyte or leukocyte number, or changes in hemoglobin or cyanmethemoglobin (Ippen et al, 1981). A dermal absorption study using ^{203}lead acetate hair dyes in eight subjects was conducted by Moore et al., (1980). Dermal absorption ranged from 0 to 0.3% of the dose applied to the forehead for 12 hr. This was assessed by counting whole blood, urine and the calf region of the leg. Absorption was slightly higher if the skin was dry and scratched. Finally, a review of the toxicology of lead acetate use in hair dyes was published in 1991 by Cohen and Roe and concluded that this use of lead acetate was toxicologically insignificant. When a weight of the evidence assessment of the toxicology and risk for cancer is then done for dermal exposure, there is no evidence that this route of exposure is carcinogenic. It is important that this clarification become a part of the final ROC report on lead and lead products.

Please feel free to contact me if I can be of any further assistance. My telephone number is 919-966-6139 and my email is james_swenberg@unc.edu. Thank you for giving me this opportunity to comment on the ROC Draft Document.

Sincerely,

James A. Swenberg, D.V.M., Ph.D., D.A.C.V.P.
Director

Additional References

Cohen, A.J. and F.J.C. Roe. Review of lead toxicology relevant to the safety assessment of lead acetate as a hair colouring. *Food Chemical Toxicology* 7: 485-507, 1991.

Ippen, H., S. Seubert, A. Seubert, H.P. Bertram and F. H. Kemper. Investigations on the dermatotoxicologic assessment of lead acetate as a hair-dyeing agent (German). *Arzliche Kosmetologie*, 2: 93-98, 1981.

Moore, M.R., P.A. Meredith, W.S. Watson, D.J. Sumner, K.M. Taylor and A. Goldberg. The percutaneous absorption of lead-203 in humans from cosmetic preparations containing lead acetate, as assessed by whole-body counting and other techniques. *Food Cosmetic Toxicology* 18: 399-405, 1980.