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March 29, 2005

Via Hand Delivery

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

Re: Docket No. 2004N-0050; Supplement to Submission of Safety and Effectiveness Data for Piroctone Olamine

On behalf of Clariant GmbH, on August 13, 2004, we submitted safety and effectiveness information to support the use of piroctone olamine (tradename Octopirox®) as a single active ingredient in topical OTC products to relieve or control dandruff, seborrheic dermatitis, and/or psoriasis, consistent with the final OTC monograph for these products found at 21 C.F.R. Part 358, Subpart H (21 C.F.R. §§ 358.701- .750). The proposed concentrations are 0.05% to 0.5 % in leave-on and 0.1% to 1.0 % in rinse-off dosage forms.

Clariant hereby provides the enclosed materials as a supplement to its August 13, 2004, submission. As discussed in the enclosure, the purpose of this report is to provide additional perspective on certain *in vitro* results in the data submitted by another party. Clariant does not view the enclosed materials as confidential and does not object to this information being placed in the docket.

Thank you for your consideration of this submission. Please feel free to contact me if you have any questions or need additional information.

Sincerely,



Frederick A. Stearns

Enclosures

- Letter from Clariant (March 29, 2005)
- Published reference

cc: Michael L. Koenig, Ph.D. (FDA) (via email)
Keith J. Olin (FDA) (via email)

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D-65840 Sulzbach am Taunus, 29.03.2005

Dr. R. Kreiling
Toxicology
Tel.: (0 6196) 757-8781
Fax: (0 6196) 757-8092

Re: Docket No. 2004N-0050

Dear Sir or Madam,

Following FDA's review of a Time and Extent Application (TEA) for Piroctone Olamine Clariant GmbH submitted safety and effectiveness information on August 13, 2004. Additional non-clinical safety studies were submitted by the Procter & Gamble Company on August 4, 2004. Before P&G provided these study reports to FDA's Docket, they were not available to be included into Clariant's submission. What we aim at with this writing is to communicate supplementary information concerning these non-clinical safety studies which may be helpful for the evaluation of the data.

Clariant GmbH has reviewed the data package submitted by P&G and special attention has been given to the interpretation of results of some mechanistic studies. These are especially in vitro test systems (e.g. Mouse Lymphoma Assay; CHO/HGPRT Mutation Assay) for which „positive“ findings were reported (see study no. 26 to 30 according to P&G submission index). Please find hereafter some additional remarks helpful as to the interpretation of these findings.

Most of the mechanistic in vitro test systems to identify potential mutagens are based on the ability to distinguish a mutant phenotype from a nonmutant phenotype by placing the cells in a medium that selects for one or the other. Selection is mainly based on enzyme activities for which cells – after treatment – are competent or incompetent. Especially in the two test systems described above, selection is due to lack of Thymidine Kinase or HGPRT capability caused by mutation. However, since these enzymes could be inactivated by several additional factors also (e.g. chelating properties of substances; cytotoxicity), it is possible to obtain a „positive“ response without any direct damage to the DNA. Technical grade Piroctone Olamine is a strong chelating substance and is also cytotoxic and thus may inactivate both enzymes. This inhibition of enzyme activities is not a mutagenic phenomenon, but will lead to an apparent „mutagenic“ effect and thus a false positive result will appear.

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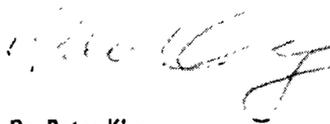
The unacceptable high incidence of false positives and consequent difficulties in the interpretation of the data, has to be seen as a clear disadvantage of this test system. Additionally, there is more and more evidence that the induction of „mutations“ in mouse lymphoma L5817Y cells, is much less reliable in indicating in vivo genotoxicity compared to other test systems (see attached publication „Perspective on the Usefulness of the Mouse Lymphoma Assay as an Indicator of a Genotoxic Carcinogen; Teratogenesis, Carcinogenesis, and Mutagenesis 13: 185-190 (1993). In this context we would like to point out, that none of the in vivo data with Piroctone Olamine have shown any indications of a genotoxic risk (see Clariant`s S&E Submission, § 1.5.2). From a DNA binding study it is evident that Piroctone Olamine does not interact with the genetic material to form adducts (see Clariant`s S&E Submission, § 1.5.2.4).

We hope that the presented informations in this letter will be of help with regard to the evaluation of the whole data package. If there is the need for any additional information, we would be happy to assist and are prepared to discuss this topic in a meeting if necessary.

With kind regards



Dr. Reinhard Kreiling
Deputy Head Toxicology
CLARIANT GmbH



Dr. Peter Klug
Global R&D Manager Personal Care
Division Functional Chemicals

Attachment: Perspective on the Usefulness of the Mouse Lymphoma Assay as an Indicator of a Genotoxic Carcinogen: Ten compounds which are positive in the Mouse Lymphoma Assay but are not genotoxic carcinogens; Teratogenesis, Carcinogenesis, and Mutagenesis 13: 185-190 (1993)