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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OPP OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

Date: October 27, 2008

MEMORANDUM

SUBJECT: **Picaridin**: Evaluation of *in vitro* dermal penetration study using human and rat skin for KBR 3023.

PC Code: 070705
Decision No.: 361412
Petition No.: NA
Risk Assessment Type: NA
TXR No.: 0054457, 0054846
MRID No.: 47340901, 47342201

DP Barcode: D357835, D357898
Registration No.: 121-OT – Cutter Insect Repellent SS; Picaridin Technical (EPA Reg. #39967-48)
Regulatory Action: NA
Case No.: NA
CAS No.: 119515-38-7
40 CFR: NA

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And
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THRU: Christina Swartz, Branch Chief
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TO: Kevin Sweeney, Risk Manager Reviewer
Registration Division (RD) (7505P)

Action: At the request of the registrant, Lanxess Corporation, the Health Effects Division (HED) has reviewed two *in vitro* dermal penetration studies: (1) *in vitro* dermal absorption of KBR 3023 (Picaridin) technical and KBR 3023 in 15% ethanol using human and rat skin and (2) *in vitro* dermal absorption of the Cutter Insect Repellent Formula A vs. Cutter Insect Repellent SS (with sunscreen) using human skin.

issued in RIC 10/30/2008 EL

1. Background

In 2006, the registrant, Lanxess Corporation, requested a re-evaluation of the toxicity, pharmacokinetic, and exposure assumptions, and uncertainty factors for the end-use product: KBR 3023 All-Family Insect Repellent Cream (20% a.i.) containing the insecticide picaridin [1-methylpropyl 2-(2-hydroxyethyl)-1-piperidine carboxylate] as the sole active ingredient. The formulation was to be applied directly to the skin of adults and children. Similar products containing 5%, 10% and 15% active ingredient had been previously registered.

The re-evaluation addressed the hazard and exposure assumptions proposed by the registrant in the following submission: "KBR 3023-Based Insect Repellents: Probabilistic Exposure and Risk Analysis—20% Formulation" dated September 23, 2005 (*MRID 46658501*). The submission proposed modification of the absorbed doses used for risk assessment, and changes to the toxicological endpoints and uncertainty factors used to derive the level of concern. Furthermore, the submission included a probabilistic exposure analysis for adults and children using the forecasting and risk analysis program Crystal Ball® along with registrant-proposed input variables (i.e., exposure assumptions, such as frequency of use).

2.0 Introduction

The re-evaluation of the toxicity, and pharmacokinetic assumptions proposed by the registrant in 2005 were addressed by D. Smegal in the memo: "Re-Evaluation of Toxicity and Pharmacokinetic Assumptions for KBR 3023 based on Registrant Submission" (D323024, June 21, 2006). The Health Effects Division (HED) gave detailed consideration of each parameter proposed by the registrant (MRID 46658501), and concluded that the previous toxicity endpoints and pharmacokinetic assumptions identified by HED and used in the 2001 human health risk assessment were reasonable and sufficiently conservative.

In 2006, HED supported a rat:human dermal penetration factor (19.1%/1.66%) based on a comparison of male rat to male human absorption data, but recommended a slight modification to include the skin stripping results in the human study as potentially available for dermal absorption (i.e., 1.66% in urine + 0.02% on skin = 1.68%). HED believed the resulting ratio of 11.37 for rat:human dermal penetration was reasonable but may slightly overestimate rat:human absorption (thus underestimating human exposure and risk).

In addition, HED agreed with the registrant's proposal to account for the presence of ethanol in the KBR 3023 insect repellent formulation. The data available at the time showed that ethanol (15%) enhances the absorption of KBR 3023 on average approximately by 2.26 fold (ranging from 1 to 10 fold enhancement) relative to neat KBR 3023 in humans following dermal application.

In November 2006, HED concluded that the previous endpoints and pharmacokinetic assumptions should not be modified as proposed by the registrant in their submission (D. Smegal; D323024; June 21, 2006). In addition, HED added a human dermal absorption fraction of 2.26 to account for ethanol enhancement for adults and children.

In response to HED's conclusions, the Registrant submitted study protocols for an *in vitro* study using human skin to compare the dermal absorption of two formulations: Cutter Insect Repellent SS and Cutter Insect Repellent Formula A. The Registrant agreed to conduct an *in vitro* dermal absorption study with KBR 3023 (neat) and KBR 3023 15% in ethanol through human and rat skin. The proposed protocol was stated to follow OECD Guideline No. 428 and to be in compliance with several GLP regulations including U.S. EPA. These protocols were approved by the Agency with some additional recommendations (TXR 0054457).

3.0 Results/Conclusion

In 2008, 2 *in vitro* dermal penetration studies were submitted to the Agency as entitled (1) Cutter insect repellent SS and Cutter insect repellent formula A formulations: Comparative *in vitro* dermal absorption study using human skin (MRID 47340901) and (2) KBR 3023 technical and KBR 3023 15% in ethanol: Comparative *in vitro* dermal absorption study using human and rat skin (MRID 47342201).

At the request of the registrant, Lanxess Corporation, HED has reviewed the *in vitro* dermal penetration studies and classified these studies as acceptable/non-guideline. HED concluded that under the conditions of these studies, the *in vitro* dermal penetration studies using human and rat skin demonstrated that (1) the level of direct absorption of KBR 3023 (Picaridin) technical and in 15% ethanol through human skin was lower than that for rat skin; and (2) the addition of sunscreen to the Cutter Insect Repellent Formula A did not increase dermal penetration through human skin; rather, dermal penetration of the Cutter Formula A (without sunscreen) was approximately twice as high as dermal penetration for the same formulation with sunscreen added (Y.Yang; TXR 0054846; June 26, 2008). The studies were considered appropriate for use in risk assessment. Further, the results of these studies support the assumptions in the 2006 risk assessment as conservative and health protective. Therefore, both *in vitro* dermal penetration studies support the registration of the product containing picaridin at 20% ai and the proposed 15% ai product with sunscreen added (Cutter All Family Insect Repellent, or 121-OT).

4.0 References

MRID 47340901. Rascle J.B., Sangha G.K., and Metzger W.H. 2008. Cutter insect repellent SS and Cutter insect repellent formula A formulations: Comparative in vitro dermal absorption study using human skin. Bayer CropScience. January 31, 2008. Unpublished.

MRID 47342201. Rascle J.B., Sangha G.K., and Metzger W.H. 2008. KBR 3023 technical and KBR 3023 15% in ethanol: Comparative in vitro dermal absorption study using human and rat skin. Bayer CropScience. January 11, 2008. Unpublished.

EPA 2006. Re-Evaluation of Toxicity and Pharmacokinetic Assumptions for KBR 3023 based on Registrant Submission. Memo from D. Smegal (HED) to Z. Figueroa and C. Swartz (HED). June 21, 2006. D323024.

EPA 2006. Re-Evaluation of Exposure Assumptions for KBR 3023 (Picaridin). November 30, 2006. D323024.

EPA 2008. Picaridin: *In vitro* dermal penetration study using human and rat skin. Memo from Y. Yang (HED) to Z. Figueroa and C. Swartz (HED). June 26, 2008. D350983.

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R163266

Chemical Name: Picaridin

PC Code: 070705
HED File Code: 13000 Tox Reviews
Memo Date: *10/27/2008*
File ID: TX0054457
TX0054846
Accession #: 000-00-0126

HED Records Reference Center
10/30/2008