UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

Date: November 30, 2006

MEMORANDUM

SUBJECT: **Re-Evaluation of Exposure Assumptions for KBR 3023 (Picaridin).**
PC Code: 870705. DP Barcode: 323024 and 323062

Chemical Name: 1-methylpropyl 2-(2-hydroxyethyl)-1-piperidine carboxylate; Picaridin

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At the request of the registrant, Lanxess Corporation, the Health Effects Division (HED) has reviewed the exposure assumptions, and uncertainty factors proposed in the following submission: "KBR 3023-Based Insect Repellents: Probabilistic Exposure and Risk Analysis—20% Formulation" dated September 23, 2005 (MRID 46658501). This memorandum addresses residential exposures for KBR 3023 Cream (20% a.i.) for the purpose of making a registration eligibility decision for the proposed use as a dermally applied insect repellent for adults and children.

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1.0 Background

In an earlier petition (2001), the registrant, Bayer Corporation (now Lanxess Corporation), requested the registration of KBR 3023 All Family Insect Repellent Spray and KBR 3023 All Family Insect Cream for use as dermally applied insect repellents. Both products contain 20% KBR 3023 (picaridin) as the active ingredient. In 2001, the Health Effects Division (HED) revised the MOEs for the 20% products to include a rat:human dermal penetration factor of 11.5 (J. Whalan, & S.Weiss; *D279005; November 16, 2001*). Despite these adjustments, the only exposure scenarios that exceeded the target MOE of 100 were single applications to adults and children (MOEs of 180 and 110, respectively), while two and three applications per day were a concern to HED because the MOEs were below the target MOE of 100.

In the 2001 assessment, all exposure scenarios exceeded the target MOE of 100 for the 10% products except for three daily exposures on children (MOE = 70). With the 5% products, all exposure scenarios exceeded the target MOE.

In December 2001, the Agency granted full registration of KBR 3023 All Family Insect Repellent Spray and KBR 3023 All Family Insect Cream for formulations containing up to 10% KBR 3023. Since that time, a 15% KBR 3023 (picaridin) cream has been registered with a limitation of one application per day.

2.0 Introduction

The registrant, Lanxess Corporation, has 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. This active ingredient is referred to as "KBR 3023" throughout this document. This formulation is to be applied directly to the skin of adults and children.

This document addresses 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 proposes 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).

3.0 Hazard Characterization

The re-evaluation of the toxicity, and pharmacokinetic assumptions proposed by the registrant 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*). HED has given detailed consideration of each parameter proposed by the registrant (*MRID 46658501*), and concludes that the previous toxicity endpoints and pharmacokinetic assumptions identified by EPA and used in the 2001 Agency Human Health Risk Assessment are reasonable and sufficiently conservative (*D279005;*

November 16, 2001). The previous endpoints and pharmacokinetic assumptions should not be modified as proposed by the registrant in the current submission *(D. Smegal; D323024;* June 21, 2006) for the following reasons:

• HED supports the continued use of point estimate values for the human:rat dermal absorption ratio and dermal and oral no-observable-adverse effect levels (NOAELs).

• HED believes it is scientifically defensible to use a human:rat dermal absorption ratio based on similar dose levels and exposure durations (i.e. (0.6/0.612) mg/cm^2, and 8 hour exposure for both human and rats).

• HED believes it is highly doubtful that dermal exposure as high as 27,000 or 54,000 mg/kg/day could be considered a NOAEL for subchronic or acute dermal exposure, respectively given the observed irritation and skin effects noted in animal studies following exposure to concentrated KBR 3023 (97-99 % a.i.).

• HED believes there are insufficient data to reduce the intraspecies and interspecies uncertainty factors (UF) from 100 to 16 as proposed by the registrant.

Therefore, HED continues to recommend using a point estimate NOAEL value of 200 mg/kg/day for the dermal toxicity dose for risk assessment (a LOAEL was not identified in the developmental toxicity study, for the 90-day rat study, the endpoint was based on liver and kidney effects at the LOAEL of 500 mg/kg/day), and a NOAEL value of 308 mg/kg/day for the children's incidental oral dose for risk assessment (the endpoint was based on kidney and body weight effects observed at the LOAEL of 1034 mg/kg/day).

For the purpose of the current risk assessment, HED continues to support a rat:human dermal penetration factor (19.1%/1.66%) based on a comparison of male rat to male human absorption data, but recommends 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 believes the resulting value of 11.37 is reasonable but may slightly overestimate rat:human absorption (thus underestimating human exposure and risk).

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

Since the 2001 HED's Hazard Identification Assessment Review Committee (HIARC) report notes kidney effects following both oral and dermal exposure, HED believes that the route specific exposures should be combined to calculate a total Margin of Exposure (MOE). Although it is suggested that the oral effects may be possibly due to the alpha-2u-globulin accumulation, HED does not have the data to confirm this mechanism. The dermal studies, which note adverse kidney effects (hyaline degeneration, foci of tubular regeneration and chronic inflammation) do not mention it is possibly due to this mechanism. The mechanism may be relevant for both oral and dermal exposure routes. In addition, the effects on the liver (organ weight and hypertrophy) in the 5-week oral study

were considered to be an adaptive response since there were no adverse histopathological effects. The 14-day and 14-week oral studies observed liver hypertrophy, which were also considered adaptive. Liver effects (hypertrophy and necrotic liver cells) were noted in the 90-day dermal study, and are part of the basis for the dermal endpoint. It is possible to revisit this decision, if additional data to support the mechanism of kidney toxicity are submitted.

4.0 Exposure/Risk Considerations for KBR 3023

The registrant, Lanxess Corporation, is pursuing registration of formulations containing 20% a.i. KBR 3023. The registrant has conducted a refined Risk Assessment/Stochastic Analysis using existing exposure data that they considered more appropriate and realistic for characterization of the potential human health risks associated with the estimated exposures (*MRID 46658501*).

After reviewing the refined Risk Assessment/Stochastic Analysis proposed by the registrant, HED believes some of the proposed inputs variables may be appropriate in future assessments. The probabilistic assessment was reviewed; however, it could not be used to support the current registration action pending development of internal Agency guidelines and policies for routine probabilistic residential exposure analysis. In order to support the currently proposed 20% cream formulation of KBR 3023, HED relied on the updated hazard assumptions, along with additional characterization of risks calculated in 2001.

4.1 Dermal Exposure

4.1.1 Assumptions and Exposure Considerations

Based on the number of applications, and information provided by the registrant, adult and children exposures are expected for short-term (up to 30 days) and potentially intermediate-term (1 to 6 months) duration. Based on the available human use data derived from the most-used repellent DEET (Boomsma, J.C. et al. 1990), HED considered that the proposed products are for seasonal use and application. Since HED believes that KBR 3023 will be used as a seasonal repellent, this assessment only considered exposures for short-term and intermediate-term durations. Long-term (>6 months up to 1 year) and chronic exposures are not expected. Therefore, quantitative long-term and chronic risk assessments were not performed.

The following assumptions, parameters and factors have been used for the dermal exposure estimations:

Table 1: KBR 3023 – Assumptions for Dermal Exposure Assessment

Assumptions	Adult	Child (3 years)
Body Weight (mean)	70 kg	15 kg
Body Surface Area (mean)	18,150 cm^2	6,565 cm^2
Application Area (25%)	4,538 cm^2	1,641 cm^2
Rate of Application	1 mg formulation/cm^2 skin	1 mg formulation/cm^2 skin

Table 1: KBR 3023 – Assumptions for Dermal Exposure Assessment		
Assumptions	**Adult**	**Child (3 years)**
Mg ai/mg formulation	0.20	0.20
Human Dermal Absorption Fraction (Ethanol Enhances Absorption of KBR)	2.26 (2006 EPA Recommended Value)	2.26 (2006 EPA Recommended Value)
Rat:Human Dermal Absorption Ratio	11.37 (2006 EPA Recommended Value)	11.37 (2006 EPA Recommended Value)

Equations/Calculations

Using the assumptions listed above and the following equations, the 2001 exposures were re-calculated as shown in **Table 2**.

$$\text{Dermal Exposure (mg/kg)} = \frac{\text{application area (cm}^2\text{) x 1 mg formulation/cm}^2\text{ skin x 0.2 mg ai/mg formulation x 2.26 ethanol enhancement}}{\text{BW (70 kg for adults; 15 kg for child)}}$$

Daily Exposure (mg /kg/day) = [Dermal Exposure (mg/kg/day)] x # Applications/Day

Table 2: Picaridin Short- and Intermediate-term Exposures for Adults and Children		
Number of Applications	**Adult (70 kg)**	**Children (15 kg)**
	Daily Exposure (mg/kg/day)	**Daily Exposure (mg/kg/day)**
1	29.3	49.4
2	58.6	98.8
3	87.9	148.2

The exposure estimates provided in Table 2 represent a single day of exposure at the highest application rate (i.e., the product is applied 3 times per day, and no wash-off of the material is assumed).

4.1.2 Time-weighted Average of Dermal Exposures

An acute (i.e., single-dose, or single-day) endpoint for risk assessment was not identified for KBR 3023 in any of the submitted toxicology studies. Rather, a NOAEL of 200 mg/kg/day was identified in a rat dermal developmental toxicity study (28 days duration, 200 mg/kg/day was the highest dose tested) and in a 90-day dermal toxicity study in the rat. In the 90-day study, the endpoint at the LOAEL of 500 mg/kg/day was based on liver and kidney effects. These data indicate that a significant duration of exposure is required to result in toxic effects of concern, and that the NOAEL of 200 mg/kg/day is considered protective of those effects, for durations of up to 90 days. In addition, the dose of 200 mg/kg/day, the highest dose tested, was also considered a NOAEL in the dermal chronic study in the rat. Therefore, using the exposure estimates provided in Table 2, HED has calculated time-weighted average exposures for adults and children assuming a single day of exposure occurs in

28 or 90 days. Subsequently, HED calculated the number of consecutive days of exposure that could occur before risks would be of concern, i.e., before estimated MOEs would be <100.

Equations/Calculations

The following equations were used to calculate time-weighted average exposures and risks:

Dermal Exposure (mg/kg) =
application area (cm^2) x 1 mg formulation/cm^2 skin x 0.2 mg ai/mg formulation x 2.26 ethanol enhancement
BW (70 kg for adults; 15 kg for child)

Daily Exposure $_{28\text{-Day Period}}$ (mg /kg/day) = [Dermal Exposure (mg/kg/day)/28 days] x # Applications/Day

Daily Exposure $_{90\text{-Day Period}}$ (mg /kg/day) = [Dermal Exposure (mg/kg/day)/90 days] x # Applications/Day

MOE_{Dermal} = [$NOAEL_{Dermal}$ (200 mg/kg/day) x Rat: Human Dermal Abs. Ratio (11.37)]/ Daily Exposure (mg/kg/day)

4.1.3 Exposure and Risk Summary

The exposure and absorbed dose outputs for adults and children, based on a 28-day time-weighted exposure, are summarized in **Table 3a and 3b**. The risk estimates provided in Table 3a represent the time-weighted risks for a single day of exposure. Table 3b indicates the number of consecutive days of exposure that would result in MOEs of 100 or higher if no more exposures occurred during a 28 day period. HED notes that for children up to 3 years old (toddlers), it may be conservative to assume consecutive days of 3 applications per day, given that the product is expected to be efficacious for 6-10 hours. An assumption of 3 days of consecutive exposure for toddlers could be considered to be equivalent to the type of exposure expected for a weekend camping trip.

Table 3a: 28-day Time-Weighted Short-/Intermediate-Term Estimates of Dermal Daily Exposures for Picaridin.

Number of Applications	Adult (70 kg)		Child (15 kg)	
	Daily exposure[a] (mg/kg/day)	MOE[b]	Daily exposure[a] (mg/kg/day)	MOE[b]
1	1.05	2,200	1.76	1,300
2	2.09	1,100	3.53	640
3	3.14	720	5.29	430

Note:
a. Daily Exposure (mg /kg/day) = [Dermal Exposure (mg/kg/day)/28 days] x # Applications/Day
b. MOE_{Dermal} = [$NOAEL_{Dermal}$ (200 mg/kg/day) x Rat: Human Dermal Abs. Ratio (11.37)]/ Daily Exposure (mg/kg/day)

Table 3b: 28-day Time-Weighted Short-/Intermediate-Term Estimates of Dermal Daily Exposures for Picaridin.			
Adult (70 kg)			
Maximum Number of Consecutive Applications	**Maximum Number of Consecutive Days Exposed [a]**	**Daily Exposure [b] (mg/kg/day)**	**MOE [c]**
21	7	22.05	100
Child (15 kg)			
Maximum Number of Consecutive Applications	**Maximum Number of Consecutive Days Exposed [a]**	**Daily Exposure [b] (mg/kg/day)**	**MOE [c]**
13	4	22.88	100

Note:
a. Maximum Number of Consecutive Days Exposed = Maximum Number of Consecutive Applications/ 3 Applications per day
b. Daily Exposure (mg /kg/day) = [*Dermal Exposure (mg/kg/day)/28 days*] x # *Applications/Day*
c. MOE_{Dermal} = [$NOAEL_{Dermal}$ (200 mg/kg/day) x Rat: Human Dermal Abs. Ratio (11.37)]/ Daily Exposure (mg/kg/day)

The exposure and absorbed dose outputs for adults and children, based on a 90-day time-weighted average exposure, are summarized in **Table 4a and 4b**. The risk estimates provided in Table 4a represent the time-weighted risks for a single day of exposure. Table 4b indicates the number of consecutive days of exposure that would result in MOEs of 100 or higher if no more exposures occurred in a 90 day period.

Table 4a: 90-day Time-Weighted Short-/Intermediate-Term Estimates of Dermal Daily Exposures for Picaridin.				
Number of Applications	**Adult (70 kg)**		**Child (15 kg)**	
	***Daily Exposure*[a] (mg/kg/day)**	***MOE*[b]**	***Daily Exposure*[a] (mg/kg/day)**	***MOE*[b]**
1	0.33	6900	0.55	4100
2	0.65	3500	1.1	2100
3	0.98	2300	1.65	1400

Note:
a. Daily Exposure (mg /kg/day) = [Dermal Exposure (mg/kg/day)/90 days] x # Applications/Day
b. MOE_{Dermal} = [$NOAEL_{Dermal}$ (200 mg/kg/day) x Rat: Human Dermal Abs. Ratio (11.37)]/ Daily Exposure (mg/kg/day)

Table 4b: 90-day Time-Weighted Short-/Intermediate-Term Estimates of Dermal Daily Exposures for Picaridin.			
Adult (70 kg)			
Maximum Number of Consecutive Applications	**Maximum Number of Consecutive Days Exposed [a]**	**Daily exposure [b] (mg/kg/day)**	**MOE [c]**
69	23	22.77	100
Child (15 kg)			
Maximum Number of Consecutive Applications	**Maximum Number of Consecutive Days Exposed [a]**	**Daily exposure [b] (mg/kg/day)**	**MOE [c]**
41	13	22.55	100

Note:
a. Maximum Number of Consecutive Days Exposed = Maximum Number of Consecutive Applications/ 3 Applications per day
b. Daily Exposure (mg /kg/day) = [Dermal Exposure (mg/kg/day)/90 days] x # Applications/Day
c. MOE_{Dermal} = [$NOAEL_{Dermal}$ (200 mg/kg/day) x Rat: Human Dermal Abs. Ratio (11.37)]/ Daily Exposure (mg/kg/day)

HED notes that for adults, up to 23 consecutive days of exposure, with 3 applications per day, results in an MOE >100. Based on 2 applications per day, adults could receive up to 34 days of exposure with MOEs >100. For toddlers, the assumption of up to 13 consecutive days of exposure at 3 applications per day or 20 days of exposure at 2 applications per day results in risks that are not of concern. Again, these calculations assume that no additional exposures would occur during a 90 day period. If less than one application per day is used, then more consecutive days of exposure would result in risks that are below HED's level of concern. For example, if only 1 application per day is used on children, then up to 41 consecutive days of exposure could occur with MOEs greater than the target of 100.

These additional risk estimates have been provided for risk characterization purposes, since the exposure estimates were calculated based on a single dose, while doses and endpoints for risk assessment reflect 28 days to 90 days of dosing in toxicity studies.

4.2 Oral Exposure

This assessment addressed exposures via the dermal and oral routes. Although potential exposures from incidental oral ingestion are expected for adults and children, the dermal route is considered to be the main route of exposure and contributor of risk. Although HED has previously recommended aggregation of oral and dermal exposure, the current assessment does not include combined dermal and oral exposures; toddlers' oral exposure screening estimates for picaridin are considered to be conservative because the product is not intentionally applied to the hands of children. As the dermal route is the primary source of exposure and the calculated dermal values are expected to be more reflective of typical repeated use of the repellent, HED does not consider it appropriate to add the oral and dermal exposures.

4.2.1 Assumptions and Exposure Considerations

The following assumptions, parameters and factors have been used for the oral exposure estimations:

- Both hands of toddler are covered with product at the rate of 1 mg formulation/cm^2.
- The child ingests all of product applied from the palmar surface of 3 fingers.
- The palmar surface area (SA) of a child's 3 fingers on each hand is 20 cm^2.
- The body weight of child is 15 kg.
- The saliva extraction factor is 50% (Camman 1995).
- The removal of product from wiping hands on clothes or surfaces is not considered in this assessment.
- The removal of product from washing hands is not considered.

Assumptions	Child (3 years)
Body Weight (mean)	15 kg
Palmar Surface Area of a child's 3 fingers on each hand (mean)	20 cm^2
Rate of Application	1 mg formulation/cm^2 skin
Mg ai/mg formulation	0.20
Saliva Extraction Factor	50%

Equations/Calculations

Single Oral Exposure Event (mg/kg/event) =
[Surface area of child's hands in mouth (cm^2) x 1 mg formulation/cm^2 skin x 0.2 mg ai/mg formulation x saliva extraction factor]/BW (15 kg for child)

Daily Exposure mg ai /kg/day = Single Oral Exposure Event (mg/kg/event) x # Events/Day

MOE_{Oral} = $NOAEL_{Oral}$ (308 mg/kg/day)/Daily Exposure (mg/kg/day)

4.2.2 Exposure and Risk Summary

Using the assumptions and equations listed above, the 2001 exposures were re-calculated as shown in **Table 5** and the MOEs are still not of concern for HED (MOE<100).

Table 5: Oral MOEs for Hand-to-Mouth Contact with KBR 3023

% ai formulation	mg ai/mg formulation	Exposure for Single Event [a] (mg/kg bw/event)	MOE [a]									
			1 event/ day	2 events/ day	3 events/ day	4 events/ day	5 events/ day	6 events/ day	7 events/ day	8 events/ day	9 events/ day	10 events/ day
20%	0.2	0.1333	2300	1200	770	580	460	390	330	290	260	230

Note:
a. MOE_{Oral} = $NOAEL_{Oral}$ (308 mg/kg/day)/Daily Exposure (mg/kg/day)

5.0 References

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