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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

TXR No.: 0051568

Date: June 21, 2006

MEMORANDUM

SUBJECT: **Re-Evaluation of Toxicity and Pharmacokinetic Assumptions for KBR 3023 based on Registrant Submission.** PC Code: 070705. DP Barcode: D323024

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

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JUL 07 2006

Summary and Conclusions:

- 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).

- The Agency 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).

- The Agency 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 relative to neat KBR 3023 in humans following dermal application.

- The Agency believes 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% ai).

- The Agency disagrees with the registrant proposal that 1,730 mg/kg/day is an acute oral NOAEL. In two acute oral LD_{50} studies rats exposed to a single dose of 500 mg/kg exhibited signs of toxicity.

- There are a number of limitations in the available data for KBR 3023 that contribute to scientific uncertainty, including:

  - In the rat metabolism study (Ecker and Weber 1997) between 18.9% and 33% of the administered radioactivity was not recovered in this study.

  - The human dermal absorption study did not recover all of the radioactivity. An average of 3% radioactivity was unaccounted, compared to value of 1.68% used in this comparison. It is difficult to determine if all the urine and feces were collected because the individual daily volumes are not reported in the study submission.

  - The rat and human data represent an 8 hour exposure duration. Washing occurred after 8 hours. It is possible that absorption would be higher in humans with longer exposure because rat data suggests increased dermal absorption with increasing exposure duration.

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

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- Interspecies UF. The Agency believes the difference in rats and humans with regard to principal metabolites, and the uncertainties in the available data support the default interspecies UF of 10. For example, the human metabolism study only evaluated 3 male subjects at one dose level (0.2 mg/kg). Further, the human data are not directly comparable to the rat data because of differences in dose levels tested, and because KBR 3023 was in ethanol in the human study, but applied neat in the rat study.

- Intraspecies UF. The registrant proposes to reduce the intraspecies toxicokinetic factor from 3.2 to 2. However, the dermal absorption of KBR 3023 ranged more than 3-fold for six male individuals. In addition, rat data indicate some sex differences with regard to KBR excretion. Female human toxicokinetic data are lacking to determine if similar sex differences occur in humans.

1.0 Introduction

The Re-registration Branch 1 (RRB1) was requested to review the toxicity and pharmacokinetic assumptions, and uncertainty factors 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 Agency appreciates the registrant's time and effort in developing this very complicated probabilistic risk assessment, and has given detailed consideration of each parameter proposed by the registrant. In general, HED disagrees with many of the registrant proposed assumptions and believes the previously identified EPA toxicity endpoints and pharmacokinetic assumptions used in the 2001 Agency Human Health Risk Assessment (D279005, November 16, 2001) are reasonable and sufficiently conservative and thus should not be modified as proposed by the registrant. In addition, for most toxicity and pharmacokinetic parameters, the registrant has proposed values to 4 and 5 significant figures, which suggests a level of precision that the Agency believes are not supported given the scientific uncertainties.

However, the Agency 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. This is consistent with data derived from another insect repellent. Inclusion of an additional human dermal absorption fraction factor in the risk assessment appears to be reasonable.

Table 1 below summarizes a comparison of the EPA and registrant-proposed assumptions for KBR 3023. Tables 2 and 3 provide details of the rat and human dermal absorption data used to develop a human:rat dermal absorption ratio. In the following sections, the Agency provides additional characterization and discussion of important factors that may

affect the KBR 3023 risk assessment. Finally, the Agency provides a discussion of the uncertainty factors proposed by the registrant.

Table 1
Comparison of EPA and Registrant Toxicity and Pharmacokinetic Assumptions

Parameter	Original EPA value (2001 Risk Assessment)	Registrant Proposal			2006 EPA recommended value	Comments
	Mean	min	max	mean		
Human:Rat dermal absorption ratio (neat KBR) (acute)	0.087 (1.66/19.1) (11.5 for rat:human)	0.037 (0.7/19.1) (Value appears to be a typographical error—see comments) assumes rat dermal absorption is 19.1% and human absorption is 0.7% (both values based on 8 hr exposure) (0.7%/ 19.1%)	0.138 (2.29/ 16.6) assumes rat dermal absorption is 16.6% and human absorption is 2.29% (both values based on 8 hr exposure) (2.29%/ 16.6%)	0.087 (1.66/19.1) (11.5 for rat:human) assumes rat dermal absorption is 19.1% and human absorption is 1.66% (both values based on 8 hr exposure) (1.66%/ 19.1%)	Mean: 0.088 (1.68/19.1) (11.37 for rat:human) assumes rat dermal absorption is 19.1% and human absorption is1.68% (both values based on 8 hr exposure)	The Agency recommends using a point estimate mean value for the human:rat dermal absorption ratio consistent with the previous Agency risk assessment. The Agency recommends this value be used for all dermal exposure durations. The Agency recognizes there is a distribution for dermal absorption and believes the mean value of 0.088 is reasonable, but likely to overestimate the rat:human absorption. The Agency has not established a policy for using distributions for modifying toxicity parameters. However, the Agency intends to present distributions of risk estimates as part of risk characterization. The 2006 EPA recommended value is revised slightly to include the skin stripping data (mean of 0.02%) which is potentially available for absorption. These data were added to the mean of 1.66% in the urine. The minimum value proposed by the registrant of 0.037 appears to be a mathematical or typographical error. Based on the data presented on page 17 (Table 3), the Agency estimates this value should be 0.0328 (0.7/21.3).

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Parameter	**Original EPA value (2001 Risk Assessment)**	**Registrant Proposal**			**2006 EPA recommended value**	**Comments**
	Mean	**min**	**max**	**mean**		
Human:Rat dermal absorption ratio (neat KBR) (subchronic)	0.087 (1.66/19.1) (11.5 for rat:human)	0.010 assumes rat dermal absorption is 67.6% (single 7 day exposure) and human absorption is 0.7% for 8 hours (with wash off) (0.7%/ 67.6%)	0.075 assumes rat dermal absorption is 30.6% (single 7 day exposure) and human absorption is 2.29% for 8 hours (with wash off) (2.29%/ 30.6%)	0.030 assumes rat dermal absorption is 54.9% (single 7 day exposure) and human absorption is 1.66% for 8 hours (with wash off) (1.66%/ 54.9%) (11.5 for rat:human)	Mean: 0.088 (1.68/19.1) (11.37 for rat:human)	The Agency recommends using a point estimate mean value of 0.088 for the human:rat dermal absorption ratio consistent with the previous Agency risk assessment. The Agency has not established a policy for using distributions for modifying toxicity parameters. The Agency recommends this value be used for all dermal exposure durations. The Agency believes the human:rat dermal absorption ratio should be based on studies that evaluated similar exposure durations (8 hours) for both humans and rats. The values proposed by the registrant are based on a 7 day exposure regimen for rats and an 8 hour exposure regimen for humans. The 2006 EPA recommended value is revised slightly to include the skin stripping data (mean of 0.02%) which is potentially available for absorption. These data were added to the mean of 1.66% in the urine. For subchronic exposure, the registrant proposes to use rat dermal absorption data from the metabolism study (Ecker and Weber 1997) which applied a single dose of 20 or 200 mg/kg KBR (neat), and followed animals for 7 days (with no wash off). In this study, higher dermal absorption was noted when KBR 3023 was not washed off following dermal

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	Mean	**min**	**max**	**mean**		
						application. The registrant estimates dermal absorption in rats was between 30.6% and 67.6% with a mean of 54.9% based on the Ecker and Weber (1997) metabolism study. However, between 18.9% and 33% of the administered radioactivity was not recovered in this study. This is a significant limitation. In addition, the Ecker and Weber (1997) (MRID 44408735) study applied 20 mg/kg or approximately 0.5 mg/cm2 KBR (10 cm2 treated area) for 7 days, whereas the human dermal absorption study applied 0.2 mg/kg or approximately 0.612 mg/cm2 (24 cm2 treated area) for 8 hours. The differences in KBR doses, surface area treated and exposure regimen (8 hours versus 7 days) are likely to contribute to the differences in dermal absorption and contribute to scientific uncertainty when estimating a human:rat dermal absorption ratio.
Human Dermal Absorption Fraction (based on ethanol)	Not included	0.022	0.07	0.0376	Mean: 2.26 (3.8/1.68) assumes 3.8% KBR is absorbed in ethanol and 1.68% KBR neat is absorbed.	Registrant values are fraction absorbed for KBR in 15% ethanol. Since ethanol enhances absorption of KBR, values should be relative to neat absorption value used to develop human:rat dermal absorption ratio. The Agency recommends using a point estimate mean value to account for the enhanced absorption of KBR 3023 due to ethanol.

Table 1 Comparison of EPA and Registrant Toxicity and Pharmacokinetic Assumptions						
Parameter	**Original EPA value (2001 Risk Assessment)**	**Registrant Proposal**			**2006 EPA recommended value**	**Comments**
	Mean	**min**	**max**	**mean**		
Subchronic Dermal NOAEL	200 mg/kg (dose tested in toxicity study)	3848 mg/kg (calculated value) (288/0.0748 =3850) (assumes rat dermal absorption is 30.6% and human absorption is 2.29%)	27813 mg/kg (calculated value) (288/ 0.0104= 27,692) (assumes rat dermal absorption is 67.6% and human absorption is 0.7%)	9525 mg/kg (calculated value) (288/0.0302 = 9563) (assumes rat dermal absorption is 54.9% and human absorption is 1.66%)	200 mg/kg (dose tested in toxicity study)	The Agency recommends using a point estimate NOAEL value for the dermal toxicity endpoint consistent with the previous Agency risk assessment. The Agency has not established a policy for using distributions for toxicity endpoints The Agency disagrees with the registrant proposed values. The proposed registrant values are based on a cumulative NOAEL of 288 mg/kg (NOAEL of 200 mg/kg in dermal study adjusted for carryover and lack of washing). The NOAEL was further adjusted for proposed rat and human dermal absorption differences for subchronic exposure. Higher dermal absorption was noted in rat studies that did not wash KBR 3023 following dermal application. The registrant estimates dermal absorption in rats was between 30.6% and 67.6% with a mean of 54.9% based on the Ecker and Weber (1997) metabolism study. However, between 18.9% and 33% of the administered radioactivity was not recovered in this study. This is a significant limitation. In addition, the Ecker and Weber (1997) (MRID 44408735) study applied 20 mg/kg or approximately 0.5 mg/cm2 KBR (10 cm2 treated area), whereas the rat dermal absorption study (44408737) applied 40 mg/kg or approximately 0.6 mg/cm2 (15 cm2 treated area). In comparison, the human dermal absorption study applied 0.2 mg/kg or approximately

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	Mean	**min**	**max**	**mean**		
						0.612 mg/cm2 (24 cm2 treated area). The differences in KBR doses are likely to contribute to the differences in dermal absorption and contribute to scientific uncertainty when estimating a human:rat dermal absorption ratio. The registrant has proposed values to 4 and 5 significant figures, which implies a level of precision and certainty that the Agency believes are not scientifically supported given the uncertainties. The Agency does not modify an established NOAEL to a higher value unless it has convincing data to support this change. The Agency has concerns for potential irritation effects of products applied directly to the skin of children in concentrated formulations. Dermal irritation and skin effects were noted in two studies following repeat dermal exposure to 97%-99% ai KBR 3023. In the dermal rabbit developmental study (MRID 44408721), dermal irritation was noted at 50 mg/kg/day (slight erythema, edema and cracked skin). In the rat subchronic study (MRID 44408716) irritation was noted at 80 mg/kg/day as scabs, red foci and exfoliation at the treatment site. The Agency is highly doubtful that dermal exposure as high as 27,000 mg/kg/day could be considered a NOAEL given the observed irritation and skin

Table 1 Comparison of EPA and Registrant Toxicity and Pharmacokinetic Assumptions						
Parameter	**Original EPA value (2001 Risk Assessment)**	**Registrant Proposal**			**2006 EPA recommended value**	**Comments**
	Mean	**min**	**max**	**mean**		
						effects noted in animal studies.
Acute/Short-term Dermal NOAEL	Not used	14,498 mg/kg (2000 / 0.138= 14,492)	54,571 mg/kg (2000/ 0.037= 54,054)	23,012 mg/kg (2000/0.087 = 22,988)	Not necessary, use the short-term dermal NOAEL of 200 mg/kg/day	The registrant proposes to use the acute dermal NOAEL of 2000 mg/kg from the dermal LD50 study with adjustment for the human:rat dermal absorption ratio. As noted previously, the Agency is highly doubtful that dermal exposure as high as 54,000 mg/kg/day could be considered a NOAEL given the observed irritation and skin effects noted in animal studies.
Acute Oral NOAEL	Not used			1731 mg/kg	Not necessary, use the short-term oral NOAEL of 308 mg/kg/day	In two acute oral LD50 studies (MRID 44408705, 44408706) the data showed that at 500 mg/kg both fasted and non-fasted male rats exhibited signs of languor, spasms, apathy, aggravated breathing, staggering gait, reduced motility, salivation, temporary grooming movements and soft stools. The acute NOAEL was 100 mg/kg in these studies. Thus, the Agency disagrees that 1730 mg/kg is an acute oral NOAEL.

2.0 Dermal Absorption Data

Rat Dermal Absorption Data (MRID 44408737)

Table 2
Dermal Absorption Results for Rats Following a Single 8 Hour Exposure to 40 mg/kg KBR 3023 (98.2% ai)

Time Interval Postapplication	Actual Dose mg/cm2	Minimum	Maximum	Mean % Dose Absorbed	Recovery
Males					
8 hour	0.590	14.7	21.1	17.5	111.7%
24 hour post appl	0.593	13.6	19.6	15.7	108.4%
7 days post appl	0.604	16.7	21.3	**19.1*** **	104.8%
Females					
8 hour	0.623	13.5	27.9	21.4	106.6%
24 hour	0.619	20.4	24.7	22.3	100.7%
7 days	0.610	14.1	21.1	17.5	96.5%

*** Value used in 2001 EPA Assessment (D279005) to develop rat:human dermal absorption factor of 11.5.
All values based on average of n=4 Sprague Dawley rats
Values based on skin, blood, urine, feces, total carcass and cage wash.
Target dose was 0.67 mg/cm2 (approx 40 mg/kg). KBR 3023 was applied to 15 cm2 treatment area. After 8 hour exposure, the non-occlusive cover was removed and the treatment site was washed by wiping twice with pads containing detergent solution and then wiped with pads containing water and then wiped with a dry pad.

Human Dermal Absorption Data (MRID 44408738)

Table 3
Dermal Absorption Results for Males following a single 8 hour exposure to 0.2 mg/kg KBR 3023 (98% ai)

Time Interval Postapplication	Mean Actual Dose mg/cm2	Mean Actual Dose mg/kg	Individual Values (% Absorbed)	Min and Max % Absorbed (a)	Mean % Dose Absorbed (a)	% Recovery
Neat KBR (98%)						
5 days (120-128 hours after washing)	0.612	0.207	2.19 1.76 0.74 1.67 2.31 1.41	0.74-2.31	1.68	97 (mean) 94.7-99.57
KBR in 15% ethanol						
5 days (120-128 hours after washing)	0.625	0.203	2.81 3.22 4.93 7.01 2.21 2.62	2.21-7	3.8	98.12
Ratio of absorption for KBR 3023 in Ethanol relative to Neat				**0.96-10**	**2.26**	

All values based on average of n=6 adult males
Target dose was 0.625 mg/cm2 (15 mg/person) KBR 3023 was applied to 24 cm2 of the forearm.
(a) Based on urine, feces and skin stripping results. Agency originally used the mean urine value of 1.66% to estimate human absorption. The last skin stripping was collected 3 days postapplication.
After 8 hour exposure, the ventilated aluminum dome cover was removed and the treatment site was washed by wiping 12-16 times with cotton swabs soaked in isopropyl alcohol. The treatment site was then rinsed with isopropyl alcohol and covered with a gauze pad.

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3.0 EPA Rat:Human Absorption Factor for Neat KBR 3023

In the EPA 2001 risk assessment (November 16, 2001, D279005) the Agency estimated a rat:human dermal penetration factor of 11.5 (19.1% / 1.66%) based on a comparison of male rat to male human absorption data. This value was based on the following analysis:

Exposure	Total skin residue and urine/feces
8 hours	17.5/1.66=10.5 **(should be 17.5/1.68= 10.41)**
24 hours	15.7/1.66=9.5 **(should be 15.7/1.68=9.34)**
7 days rats (5 days humans)	19.1/1.66=11.5 **(should be 19.1/1.68=11.37)**

The Agency continues to support this analysis, but recommends a slight modification as shown above 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%). This adjustment is recommended to be consistent with the rat data that included skin data.

The Agency believes the value of 11.37 (or 0.088 as shown on Table 1) is very reasonable but likely to overestimate rat:human absorption (thus underestimating exposure and risk):

(1) Human study did not recover all radioactivity. Average of 3% radioactivity was unaccounted, compared to value of 1.68% used in this comparison. This contributes to scientific uncertainty. It is difficult to determine if all the urine and feces were collected because the individual daily volumes are not reported.

(2) rat value represents skin, blood, urine, feces and total carcass at 7 days while human value only represents urine, and feces at 5 days and skin at 3 days

(3) rat value of 19.1% is probably overestimated since radioactive recovery was 104.8%.

(4) The rat and human data represent an 8 hour exposure duration. Washing occurred after 8 hours. It is possible that absorption would be higher in humans with longer exposure because rat data suggests increased dermal absorption with increasing exposure duration.

4.0 Impact of Ethanol in KBR 3023 Insect Repellent Formulation

The available human data shows that ethanol, which is a constituent of the formulation appears to enhance the dermal absorption of KBR 3023.

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(1) The Agency did not consider this in our original risk assessment. Estimated range of potential enhancement ranges from 0.96-10 with a mean of 2.26.

(2) The registrant submission acknowledges (p 17) that dermal absorption is approximately double the neat material. However, it appears their submission used values of 0.02 to 0.07 to reduce dermal exposure.

5.0 Consideration of Uncertainty Factors for Interspecies and Intraspecies Toxicokinetics

The registrant proposes a combined uncertainty factor of 16 for interspecies variability rather than the typical default value of 100. The factor of 16 is based on an interspecies variability factor of 2.5 and an intraspecies uncertainty factor of 6.4.

Interspecies Uncertainty Factor (UF). The registrant believes the database shows similar toxicokinetics, including metabolism in humans and the laboratory rat. Thus, they believe the uncertainty factor can be reduced to 1 (out of 4) for the toxicokinetics portion of the UF for interspecies variability. Due to limitations in the available human data on KBR 3023 toxicodynamics, the registrant believes the standard default value of 2.5 for the toxicodynamics portion of the UF for interspecies variability. Thus, the registrant proposes a total interspecies factor of 2.5 (1 x 2.5) instead of the standard default factor of 10.

Intraspecies Uncertainty Factor (UF). The registrant has proposed an intraspecies UF of 6.4 based on a toxicokinetic factor of 2 (out of possible 3.2), and a toxicodynamics standard default value of 3.2. The registrant believes the available study on absorption, distribution, metabolism and excretion of KBR 3023 in humans (Selim 1994, MRID 44408738) shows moderate differences between individuals, and justifies a reduced factor of 2.

Agency Response:

Interspecies UF. The Agency Data Evaluation Records (DERs) for metabolism indicate a difference in the metabolites between humans and rats. In addition, there are **significant uncertainties** in the available human data which only evaluated 3 male subjects at one dose level (0.2 mg/kg). Further, the human data are not directly comparable to the rat data because of differences in dose levels tested, and because KBR 3023 was in ethanol in the human study, but applied neat in the rat study. Table 4 presents a comparison of the metabolite data for humans and rats. The Agency believes the differences in rats and humans, and the uncertainties in the available data support the default interspecies UF.

Table 4 Comparison of Human and Rat Metabolism Data Following Dermal Application			
Metabolite	Percent of Administered Dose (% of Radioactivity in Urine)		
	Male Human (MRID 44408736) (n=3) 0.2 mg/kg 8 hr exposure in ethanol	Rat (MRID 44408735) neat single (1X) Application left on for 7 days (20 mg/kg)	
		Male (n=5)	Female (n=5)
M1	0.11 (3.1) (M1-M4)	0.95	1.19
M2		2.62	2.16
M3		1.36	1.37
M4		2.6	1.91
M5	0.63 (17.4)	0.62	0.67
M6	0.08 (2.3)	0.98	1.88
M7	0.03 (0.9)	1.23	1.38
M8	0.22 (6.2)	11.62	8.43
M9	0.09 (2.6)	11.53	13.46
M10	0.09 (2.4)	4.62	2.84
M11-M13	0.25 (6.9)	Not detected	0.76
M14	0.57 (15.8)	0.62	0.78
M15	1.0 (27.3)	0.89	1.46
M16	0.31 (8.5)	4.87	13.26
M18	Not detected	0.26	0.14
M19	Not detected	0.15	0.09
Parent	Not detected	1.3	1.02
Total identified	3.38 (93.5)	46.26	52.81
Total unidentified	0.23 (6.5)	6.41	6.35
Total accounted for	3.61	68.53	71.51

(a) Human data is for urine only, while rat data is for urine and feces. Less than 0.01 percent of the KBR 3023 dose was excreted in the feces of humans.

Rat Metabolism Data. In rat metabolism study, dermal absorption was dose dependent with lower levels of absorption occurring in the high dose animals. In rats, urinary elimination was the primary route. In low-dose rats (20 mg/kg), urinary elimination accounted for 55-56% of the dose for females and 43-46% of the dose for males, and fecal elimination accounted for 7% of the dose in females and 12-15% of the dose in males.

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The rat metabolism DER states "However, regardless of dose group or sex, the principal metabolites identified in excreta of rats included: M8 (4.9-18.5% dose), M9 (5.7-21.1% dose), M10 (2.0-8.7% dose) and M16 (2.5-40.2%dose). Collectively, these four metabolites accounted for 17-70.6% of the dose or 67-91% of the identified metabolites. The remaining metabolites, M1-M7, M11-M15, M18 and M19 were minor components that individually accounted for <5.0% of the dose." The above table only presents the data for the low dose (20 mg/kg) group to be more comparable with the available human data for 0.2 mg/kg.

A major limitation of this study is that 18.9-33.1% of the dosed radioactivity was not recovered in the dermally exposed rats.

Human Metabolism Data. Three men were dosed with 0.2 mg/kg KBR 3023 in ethanol for 8 hours (MRID 44408736). In male humans, 94% of the radioactivity in urine was excreted within 24 hours of dosing. Metabolites M14 and M15 accounted for 43.1% of the radioactivity in the urine. Other major metabolites in urine included: M5 (17.4%), M16 (8.5%), M8 (6.2%), and M11-M13 (6.9%). The remaining metabolites, M1-M4, M6, M7, M9 and M10 each accounted for <3.1% of the radioactivity in urine. Thus, the principal metabolites in human urine are different than those found in rat urine.

This study submission is incomplete because many of the raw data tables are absent from the study report. Data in the Appendices of the submission refer to Tables in the final report, which were not made available to the Agency for review. For example, it is difficult to determine if all the urine and feces were collected because the individual daily volumes are not reported. Aliquots of urine were combined for all 3 of the subjects for 4-8 and 8-12 hour intervals without adequate discussion. These data omissions contribute uncertainty to the available human metabolism data, and further support the full interspecies uncertainty factor of 10.

Intraspecies UF. As noted previously, the human metabolism study (Selim 1994, MRID 44408738) only evaluated three male subjects following a single dose level of KBR 3023 for 8 hours. These data are not sufficiently robust to reduce the intraspecies toxicokinetic factor from 3.2 to 2. In the rat metabolism study, there were some sex differences with regard to urinary excretion, fecal excretion, and elimination of radioactivity from plasma. Female human toxicokinetic data are lacking to determine if similar sex differences occur in humans.

In addition, as shown on Table 3, the dermal absorption of KBR 3023 ranged more than 3-fold for six male individuals (MRID 44408738). Dermal absorption ranged from 0.74 to 2.3% for neat KBR, and from 2.21-7% for KBR in ethanol. These data are for one dose level of 0.2 mg/kg and period of exposure (8 hours).

6.0 References

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Chemical: Picaridin

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HED File Code: 13000 Tox Reviews
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