Chapter 101

Toxicology and Safety Evaluation of the New Insect Repellent Picaridin (Saltidin)

G.K. (Ghona) Sangha
Lanxess Corporation, Pittsburgh, Pennsylvania

101.1 INTRODUCTION

Picaridin is a new generation of customized active ingredient specifically designed to repel a variety of arthropods and is marketed under the name Saltidin (registered trade name of Saltigo GmbH, LANXESS Group). It was developed by Bayer as an alternative to DEET and is now owned by LANXESS Corporation (previously a Division of Bayer Corporation). It was tailor-made, based on the hypothesis that the repellent effect is triggered by the action of a given substance on specific olfactory receptors of the arthropod. Molecular modeling techniques were utilized during the development process, which allows for the three-dimensional construction and mapping of molecules. Existing repellent products were altered at specific sites where an interaction with an arthropods' receptor was anticipated. More than 800 substances were synthesized and screened for efficacy, cosmetic properties and safety. Picaridin (laboratory name KBR 3023) represented the best compromise of all the required properties for an ideal repellent. Picaridin showed the best performance regarding efficacy against a variety of arthropods (Boeckh *et al.,* 1996) and had the most desired attributes regarding safety as well as compatibility with skin and plastic materials. The report of the fourth WHOPES (WHO Pesticide Evaluation Scheme) Working Group meeting in December, 2000 (WHO, 2000) concluded that Picaridin has a good safety profile and cosmetic properties, and recommended it as the repellent of choice for malaria prevention. Alone or in typical formulations, it does not significantly attack common household materials including plastics, coatings, foils, and varnishes.

101.2 GENERAL OVERVIEW

101.2.1 Chemistry

During product development, Picaridin (U.S. registered name) was identified by several names. The current common name is Picaridin, and the current trade name Saltidin. It was developed under the laboratory code name KBR 3023 with the registered trade name Bayrepel and was subsequently sold under the brand name Autan.

The chemical name (CAS) for Picaridin is 1-piperidine-carboxylic acid, 2-(2-hydroxy-ethyl), 1-methylpropylester. However, the INCI (International Nomenclature of Cosmetic Ingredients) name was given as hydroxy ethyl isobutyl piperidine carbamate. The common name, Picaridin, was rejected by ISO (International Organization for Standards) as it was not considered a pesticide. The common name Picaridin was also rejected by WHO/INN (World Health Organization/International Non-proprietary Name) but the common name, Icaridin, was accepted by WHO/INN. The structural formula is presented in Figure 101.1.

Picaridin has high stability toward light, oxidation, water, and sweat. It has good compatibility with skin and mucous membranes, is compatible with plastic materials and has low skin penetration. Key physical-chemical of Picaridin are shown in Table 101.1.

101.2.2 Mode of Action

In general, repellent activity is thought to be the result of any number of physiological and biochemical events. Mosquito repellency is thought to be due to blocking of the lactic acid receptors resulting in "losing" the host (Peterson and Coats,

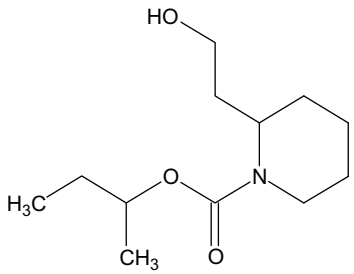

FIGURE 101.1 Structural formula.

TABLE 101.1 Key Physical-chemical Properties of KBR 3023

Parameter (units)	Value
CAS No.	119515-38-7
Chemical name	1-piperidine carboxylic acid, 2-(hydroxy-ethyl), 1-methylpropylester
Molecular formula	$C_{12}H_{23}NO_3$
Physical state	Liquid
Molecular weight (g/mol)	229.3
Color	Colorless
Density (g/cm^3 at 20°C)	1.04
Solubility in water (at 20°C)	8.6 g/l in unbuffered
	8.2 g/l in buffered
Dissociation constant	No acidic or basic properties in aqueous solutions
Solubility in organic solvents (at 20°C)	>250 g/l
Flashpoint (°C)	142
Freezing point (°C)	<−170
Boiling point (°C)	272
Vapor pressure (kPa at 20°C)	3.40E-04

2001). Electrophysiological studies on the insects' olfactory receptor organs reveal that certain cell types, which are not involved in perception of the attractive odorants, respond to Picaridin. As soon as Picaridin is presented together with an attractant, a new input is activated in the nervous system, which adds to the input from other receptors activated by the attractant. This new overall pattern clearly differs from that elicited by the attractant, so that the insect is no longer able to detect the attractant.

The specificity and mode of action of Picaridin was investigated by experiments exploring second-messenger responses of male cockroaches. Picaridin induced a rapid increase in the concentration of inositol triphosphate in a dose-dependent and tissue-specific manner; other second-messenger systems were not affected. These observations suggest that Picaridin may act via subsets of G-protein-coupled receptors in sensory neurons. The repellent effect of the active substance starts immediately after application on the skin and develops full performance within a few minutes (Boeckh *et al.,* 1996).

101.2.3 Effectiveness Against Disease Vectors

Biting and blood feeding by the arthropod pests can cause annoyance, blood loss, allergic reaction, and may be the means by which people get infected with pathogenic organisms. Arthropod-borne pathogens are known to occur in North America and throughout the world. The most important are malaria, West Nile Virus, several types of viral encephalitis (Western Equine, Eastern Equine, and St. Louis) transmitted by mosquito species, Lyme Disease transmitted by tick species and leishmaniasis by the sand fly.

Picaridin containing insect repellent formulations (cream, pump spray, aerosol, or wipes) containing 5–20% Picaridin have broad spectrum efficacy and are highly effective against a variety of blood sucking arthropod pests, especially the primary pest, mosquitoes (*Aedes aegypti*, *Aedes albopictus*, *Aedes increpitus*, *Aedes melanimon*, *Aedes nigromaculis*, *Aedes sierrensis*, *Aedes sticticus*, *Aedes vexans*, *Culex quinquefasciatus*, *Culex tarsalis*, *Ochlerotatus taeniorhynchus*, *Anopheles dirus*, *Anopheles freeborni*, *Anopheles franciscanus*). The other arthropod pests that are effectively repelled by Picaridin include ticks (*Ixodes ricinus*, *Ixodes scapularis*), flies (*Tabanus bovinus*, *Haematopota pluvialis*, *Stomoxys calcitrans*, *Chrysops relictus*), gnats, chiggers, biting midges (*Culicoides impunctatus*), fleas, and sand flies (*Phlebotomus*). Based on broad-spectrum effectiveness to biting arthropod species, Picaridin products are intended for use by nonprofessional users of the general public including adults and children.

101.2.3.1 Effectiveness

Numerous field and laboratory tests of various formulations of Picaridin using human volunteers and animals have been conducted in various parts of the world by different researchers, including studies sponsored by the producers of the product, World Health Organization, and the militaries of many countries including the U.S. and Australian armies. These tests have shown Picaridin to be a safe and effective repellent of numerous pests and effectiveness was dependent on species, population density, geographical region, and concentration of Picaridin in the formulation (Table 101.2). The 20% formulations provide 8-h protection against various arthropod species, including mosquitoes, ticks, biting flies, sand flies, and biting midge. In recent field studies conducted in the United States, formulations containing 20% Picaridin provided 12–14 h of protection against mosquitoes including those carrying West Nile Virus (Carroll, 2008a).

A similar field test conducted with 15% formulation in combination with sunscreen showed an enhancement in the effectiveness against mosquitoes (Carroll, 2008b). In a laboratory test with ticks using the sunscreen combination effectiveness against ticks was slightly decreased (Carroll, 2008c).

The report of the fourth WHOPES Working Group meeting in December, 2000 concluded that: "KBR 3023 was tested under temperate and tropical conditions against important disease vectors *Aedes albopictus*, *Anopheles*

TABLE 101.2 Effectiveness of Picaridin Against Various Disease Vectors in the Field Environment

Species	Formulation (% Picaridin)	Protection time (hours)	Reference
Mosquitoes	20%	8–14	Carroll (2008a,b); Yap *et al.* (1998, 2000); Frances *et al.* (2002, 2004); Barnard *et al.* (2002); Luepkes (2005)
	15%[a]	11.7–13.3	
	15%	10.3	
	10%	4–8	
	5%	4–7	
Ticks	20%	4–α	Sixl (1993); Carroll (2008c); Todd (1997)
	15%[a]	8.2–8.7	
	15%	9.7–11.8	
Flies	12%	7	Nentwig (1997); Muelhofer (1993)
	7.5%	4–6	
Sand fly	20%	7.7–10.3	Perrotey (2002)
	10%[b]	8.8–9.1	
Biting midge	20%	7–8	Mordue (1999); Carpenter (2005)
Fleas	20%	9	Nentwig (1998)

[a]*With sunscreen.*
[b]*With polyester acrylate.*

gambiae and *Culex quinquefasciatus* and several pest mosquitoes, demonstrating excellent repellent properties comparable to, and often superior to those of the standard DEET."

KBR 3023 conferred more than 95% protection up to 6–7 h after application. At comparable doses, KBR 3023 showed significantly longer protection times than DEET against *Anopheles gambiae* complex malaria vectors. "KBR 3023 can be recommended as the repellent of choice for malaria prevention."

101.3 METABOLISM AND TOXICOKINETICS

The absorption, distribution, metabolism and excretion of [^{14}C]-Picaridin were studied in rats and human volunteers following dermal application. The dermal route was chosen instead of the oral route because Picaridin is used in dermally applied insect repellents and dermal absorption is the foreseeable route of systemic exposure.

In the rat, the test compound was administered either intravenously as a single dose of 20 mg/kg body weight (bw) or dermally as single doses of 20 or 200 mg/kg bw. In addition, [^{14}C]-Picaridin was applied dermally to rats at a dose of 20 mg/kg bw following 14 daily dermal exposures to unlabeled Picaridin. Rats in the i.v. study were sacrificed 2 days after injection, whereas rats in the dermal study were sacrificed immediately after the 7-day-exposure period.

These data indicate that renal excretion is the principal pathway for elimination of KBR 3023 from rats following either intravenous or dermal dosing.

Nineteen metabolites were identified in urine and feces of both i.v. and dermally dosed rats (Figure 101.2). Analysis of excreta from i.v. dosed rats identified 61–78% of the dose in urine and 6% of the dose in feces. For the dermally dosed groups, analysis of urine and feces identified 24–53% of the dose, or 75–85% of the radioactivity recovered in excreta. With the exception of two metabolites M18 and M19 (each at <0.3% of dose) that were found only in feces, the metabolite profile and relative distribution of metabolites was the same in urine and feces. There was also no qualitative difference in the metabolite profile between dose groups and sexes.

The metabolism of KBR 3023 in rats primarily involves oxidation of the 2-hydroxyethyl group to an acid to form metabolite M16, coupled with hydroxylation of the 1-methylpropyl group to form metabolites M8, M9, and M10. The other minor phase I metabolites result from hydroxylation of the piperidine ring (Ml–M4 and M7). Minor phase II metabolites result from conjugation of glucuronic acid with parent (M14 and M15) or phase I metabolites (M5, M6, and M11–M13).

The metabolic profile in the human was investigated from the dermal absorption study in male volunteers dosed dermally on a forearm with either neat [^{14}C] KBR 3023 (>98% purity) or [^{14}C] KBR 3023 in ethanol (15% w/w) at

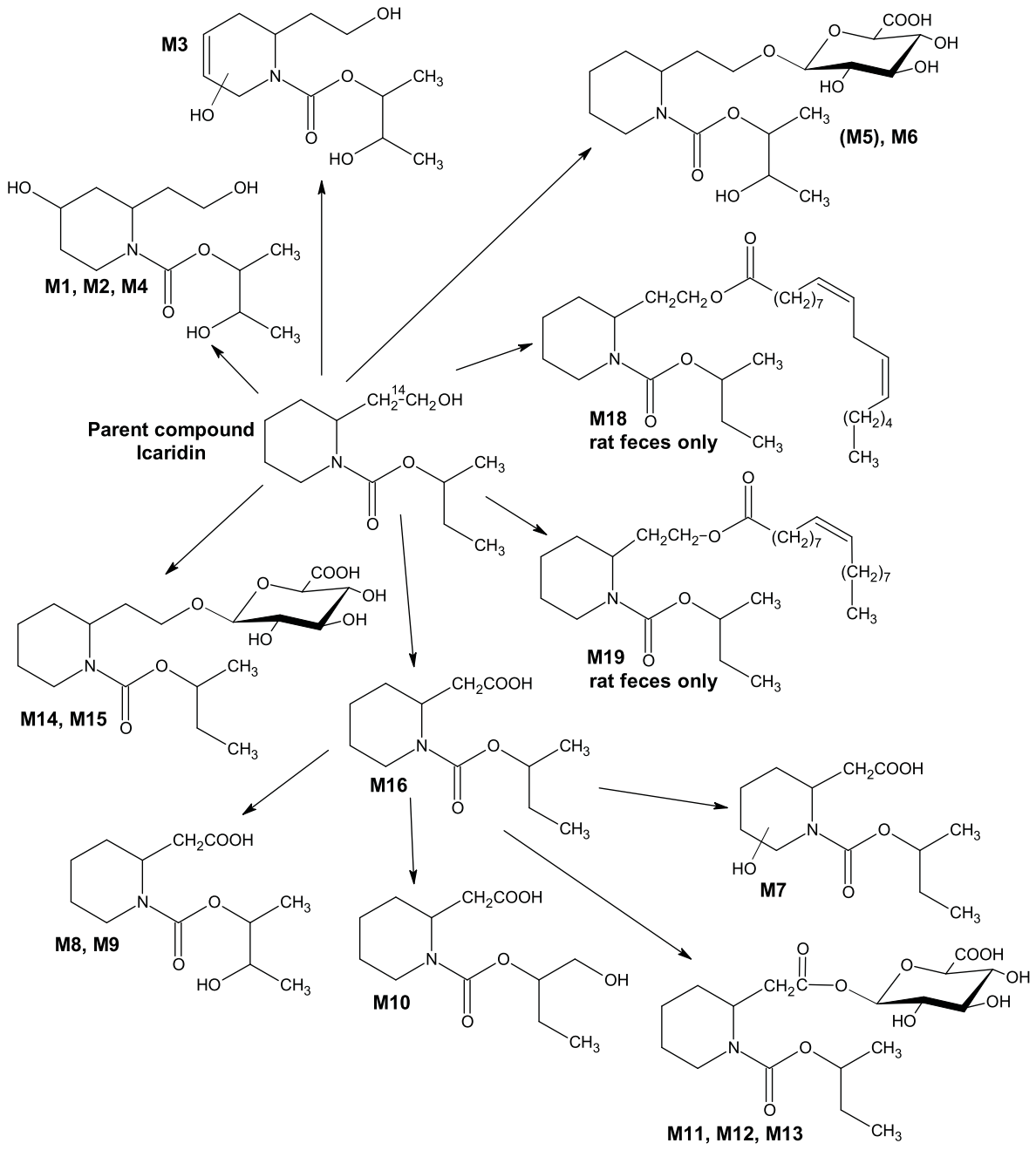

FIGURE 101.2 Proposed metabolic pathway for KBR 3023 in rats.

a nominal dose level of 15 mg/person (0.625 mg/cm^2) (Selim, 1994). Nearly all the absorbed radioactivity was excreted in the urine (1.66–3.76%) for both dose groups, with 94% of the radioactivity in urine being excreted within 24 h of initial dosing. Concentrations of radioactivity in plasma drawn from the contralateral arm were similar between the two dose groups over time. Radioactivity in plasma increased to a maximum at 8 h when the treatment site was washed and then declined rapidly, returning to background levels by 8 h after removal of the test substance.

Biotransformation of [^{14}C] KBR 3023 in humans primarily involved conjugation of KBR 3023 with glucuronic acid through the 2-hydroxyethyl moiety to form metabolites M14 and M15 (Figure 101.2), which together accounted for 43.1% of the radioactivity in urine. Other major metabolites in urine included M5 (17.4%), another glucuronic acid conjugate that is hydroxylated in the 1-methyl-propyl moiety; M16 (8.5%), in which the 2-hydroxyethyl group is oxidized to an acid; M8 (6.2%), in which the 2-hydroxyethyl group is oxidized and the 1-methyl-propyl group is hydroxylated; and M11–M13 (6.9%), which are isomers in which the 2-hydroxyethyl group has been oxidized to an acid and conjugated with glucuronic acid. The remaining metabolites, M1–M4, M6, M7, M9, and M10 each accounted for ≤3.1% of the radioactivity in urine.

Based on the available data on Picaridin, the patterns of metabolism, absorption, distribution, and excretion are similar in humans and rats (Ecker, 1997). The kinetic studies in humans and rats clearly show there is no qualitative difference between Picaridin metabolism in rats and humans. Excretion of KBR 3023 metabolites by humans was substantially faster than by rats, which may be due to the markedly higher percentage of secondary metabolites (glucuronides) found in humans compared to the rat. The excretion half-life in humans was 8.2 h compared to 23.3 h in rats at the low dose (Driver *et al.,* 2005).

101.4 MAMMALIAN TOXICOLOGY

The toxicological profile of KBR 3023 is well characterized. All toxicology data were developed using the dermal route of exposure, the most relevant route based on the use pattern of the product. Picaridin is used in products intended solely for dermal application and dermal penetration will certainly be the dominant route of uptake. The rationale of product development using the dermal route of exposure was considered at the suggestion of the U.S. EPA (U.S. Environmental Protection Agency) and in agreement with U.S. EPA, BGA (German authorities) and Health & Welfare Canada.

A complete toxicology study required for the registration of an insecticide including acute and subchronic neurotoxicity and metabolism studies was conducted by the dermal route. Additionally 14-day, 5-week, and 14-week dietary feeding studies were conducted to assess any hazard associated with hand-to-mouth transfer from dermal use of Picaridin. In all repeated-dose dermal studies, Picaridin was applied 5 days per week without wiping and covering 10% of the body surface area of the animals, and the administered dose volumes were based on the mean weekly body weight for each dose group and every 3 days for pups in the reproduction study. All application sites were carefully shaved prior to application and in repeated dose studies animals were shaved periodically. Dose application sites were not covered; thus, in order to avoid animal access and subsequent oral ingestion of the test material, all rodent species and rabbits were fitted with Elizabethan collars for the duration of exposures. The collar sizes were adjusted to accommodate the animal's growth. In the reproduction study, collars were not used during lactation period and pups were fitted with collars after weaning.

The highest dermal dose for long-term studies was selected to be 200 mg/kg/day based on the limit of application, to avoid changes in skin integrity (seen at higher doses) for the 18- to 24-month exposure for mouse and rat studies, respectively, and to maximize the systemic dose because the dermal absorption/kinetic data show that absorption is decreased with increasing dosage, thus lowering overall systemic dose. Given that the dose site was not wiped during the 5-day/week dermal application, the realistic mean dose was at least 50% greater than the target dose. Dermal absorption studies were conducted both in the rats and human volunteers to assess the human risk on the absorbed dose analysis associated with the consumer use of the product. Additionally, *in vitro* dermal penetration studies using human skin were also conducted to compare the dermal absorption of formulations of Picaridin.

The toxicology database for Picaridin provided in this chapter was developed by Bayer and LANXESS laboratories to support the registration of commercial products. All toxicology, metabolism, and dermal absorption studies were conducted in compliance with Good Laboratory Practice (GLP) requirements and in accordance with regulatory guidelines of the U.S. EPA (FIFRA), the OECD, and the Japanese MAFF. Human subject studies including dermal absorption, pharmacokinetics, phototoxicity, and efficacy were conducted with IRB-approved protocols. All toxicology studies were conducted with technical-grade Picaridin having a purity ranging from 96.7 to 98.7%. Published information on the toxicology of Picaridin is limited to publications of the Bayer and LANXESS data.

101.4.1 Acute Toxicity

The acute toxicity of Picaridin Technical (KBR 3023) is very low, regardless of the route of administration (Table 101.3). The tests for oral toxicity were conducted on males only, but the studies using other routes of exposure showed no indication for an appreciable gender difference in the toxicity of Picaridin. Picaridin is not irritating to the skin and only slightly irritating to the eye. Picaridin was also negative for skin sensitization in the Buehler patch test on guinea pigs.

An additional study with human volunteers demonstrated that Picaridin presented no potential for phototoxic hazard to the test subjects (Lehmann, 1996).

Toxicity data for the formulations containing 20% Picaridin (the highest percent formulation on the market) show that Picaridin had low toxicity via all routes of exposure (Table 101.4).

TABLE 101.3 Summary of the Acute Toxicity Testing with Picaridin (KBR 3023 Technical)

Study type	Results
Acute oral – rat	LD_{50} = 4743 mg/kg (male) LD_{50} = 2236 mg/kg (male)
Acute dermal – rat	LD_{50} > 2000 mg/kg LD_{50} > 5000 mg/kg (male)
Acute inhalation – rat	LC_{50} > 4.364 mg/l
Eye irritation – rabbit	Ocular irritant, slightly
Skin irritation – rabbit	Not a dermal irritant
Dermal sensitization – guinea pig	Not a dermal sensitizer

TABLE 101.4 Summary of the Acute Toxicity Testing with 20% Picaridin Formulation

Study type	Results
Acute oral – rat	LD_{50} = 5100 mg/kg (male) LD_{50} = 5050 mg/kg (male)
Acute dermal – rat	LD_{50} > 5040 mg/kg (male) LD_{50} > 5020 mg/kg (male)
Acute inhalation – rat	LC_{50} > 3.02 mg/l LC_{50} > 3.02 mg/l
Eye irritation – rabbit	Ocular irritant, moderate
Skin irritation – rabbit	Not a dermal irritant
Dermal sensitization – guinea pig	Not a dermal sensitizer

101.4.2 Subchronic Toxicity

101.4.2.1 Oral

In a 5-week toxicity study (Wahle, 2001a), Picaridin was administered in the diet to 10 Sprague-Dawley rats/sex/dose at nominal dose levels of 0, 100, 150, 300, or 1000 mg/kg/day (actual average daily dose levels of 0, 99, 152, 308, or 1034 mg/kg bw/day in males and 0, 121, 189, 360, or 1141 mg/kg bw/day in females, based on food consumption and body weight data).

In a 14-week toxicity study (Wahle 2001b), Picaridin was administered in the diet to 10 Sprague-Dawley rats/sex/dose at nominal dose levels of 0, 100, 150, 300, or 1000 mg/kg/day (actual average daily dose levels of 0, 100, 149, 301, or 1033 mg/kg bw/day in males and 0, 126, 194, 382, or 1192 mg/kg bw/day in females).

In both studies, a decreased body weight gain was noted in both sexes at the highest dose level tested. Effects on the male kidney included an increased relative kidney weight and an increased incidence of protein droplet degenerative nephropathy (possibly due to $\alpha 2\mu$-globulin accumulation). The systemic subchronic no observed adverse effect levels (NOAEL) for the 5- and 14-week oral rat studies were 301 and 308 mg/kg/day, respectively.

101.4.2.2 Dermal

In a dermal subchronic 90-day toxicity study (Sheets, 1995), Picaridin was applied to the shaved skin of young adult Sprague-Dawley rats (10–20/sex/dose) at dose levels of 0, 80, 200, 500, or 1000 mg/kg/day for 5 days/week, 5 h/day, for 90 days. Following 90 days of treatment, 10 rats/sex/dose were sacrificed. The remaining 10 rats/sex in the 0 and 1000 mg/kg/day groups were maintained without treatment for an additional 4 weeks to assess recovery potential.

Liver and kidney lesions were seen at dose levels 500 and 1000 mg/kg/day, including increased liver and kidney weight, diffuse liver hypertrophy, necrotic liver cells, slight hyaline degeneration in the kidneys, increased incidence of foci of tubular regeneration, and chronic kidney inflammation. However, there were no clinical pathology anomalies to corroborate these findings. The kidney lesions, seen only in male rats, were associated with $\alpha 2\mu$-globulin and are not relevant to humans. In addition, animals of all treatment groups showed irritative lesions at the application site. These lesions are a common reaction toward repeated application of a variety of materials, including water or medicinal petrolatum, and are not considered a substance-related adverse effect. After a 4-week recovery period, treated and control groups were similar for all parameters. The systemic subchronic NOAEL for the dermal rat study was 200 mg/kg/day. Based on the irritative lesions seen at dose levels above 200 mg/kg/day, the highest dose tested in all repeated dose studies was selected to be 200 mg/kg/day to ensure skin integrity was not compromised over the exposure period.

In a 13-week toxicity study (Wahle *et al.,* 1999b), technical grade Picaridin was administered dermally to the CD-1 mouse (15 animals/dose/sex) at constant nominal dosages of 0, 80, or 200 mg Picaridin/kg bw/day. All in-life parameters, which included body weight, food consumption, clinical observations, survival, and hematology, were unaffected by dermal exposure to Picaridin. Similarly, postmortem analyses, which included organ weights, gross pathology, and histopathology, were also unchanged following exposure to Picaridin. Thus, the NOAEL was 200 mg/kg/day.

Subchronic toxicity studies in the dog were not conducted.

101.4.3 Chronic Toxicity and Oncogenicity

101.4.3.1 Chronic Toxicity in the Dog

In a chronic dermal toxicity study (Jones and Hastings, 1995), Picaridin was applied to the clipped skin of beagle dogs (four/sex/dose) at dose levels of 0, 50, 100, or 200 mg/kg/day, 5 days/week, for one year. Toxicity was not observed in this 1-year dermal chronic toxicity study in the dog. A systemic chronic NOAEL was established in the dog at the highest dose tested (HDT) of 200 mg/kg/day.

101.4.3.2 Combined Chronic Toxicity and Oncogenicity in the Rat

The dermal chronic (1-year) toxicity study in rats (Wahle *et al.,* 1999b) was conducted in combination with a 2-year carcinogenicity study. In this study, undiluted Picaridin technical

was administered dermally on the dorsal aspect of the trunk to 50 Sprague-Dawley rats/sex/dose at dose levels of 0, 50, 100, or 200 mg/kg/day on 5 consecutive days/week for 24 months. In addition, 10–20 rats/sex/group were killed at 12 months.

Picaridin has a very low order of toxicity in the rat following repeated dermal administration. In the dermal chronic toxicity/carcinogenicity study in rats, there were no treatment-related effects produced at any dose level. Adaptive liver changes consisting of cystic degeneration were observed at the HDT of 200 mg/kg/day, but with no corroborating liver weight or clinical pathology anomalies. The rat NOAEL for 1 and 2 years was established at 200 mg/kg/day and no oncogenic potential was observed.

101.4.3.3 Oncogenicity in the Mouse

In an oncogenicity study (Wahle *et al.,* 1999a), Picaridin was administered dermally on the dorsal aspect of the trunk to 50 CD-1 mice/sex/dose at dose levels of 0, 50, 100, or 200 mg/kg/day on 5 consecutive days/week for 18 months. No toxicity or evidence of an oncogenic potential was observed at any dose level, up to and including the HDT of 200 mg/kg/day. The long-term mouse dermal NOAEL was 200 mg/kg bw/day.

101.4.3.4 Classification for Carcinogenicity

Evidence of carcinogenicity was not seen in the rat or mouse oncogenicity studies and Picaridin was negative for genotoxicity. On April 22, 1999, EPA Health Effects Division's Hazard Identification Assessment Review Committee (HIARC) determined that Picaridin was not likely to be a carcinogen by the dermal route, and found no evidence of endocrine disruption.

101.4.4 Genotoxicity

Picaridin was non-mutagenic in bacteria and in the mammalian V79 cell line, both with and without metabolic activation (Herbold, 1990, 1991). In an HPRT-forward-mutation study in CHO cells (Brendler, 1991), the Picaridin concentrations tested did not produce sufficient cytotoxicity. In subsequent studies, chromosome aberrations occurred only at cytotoxic concentrations in CHO cells. One study (Gahlmann, 1996) found chromosomal damage in the absence and presence of S9 mix, whereas Gudi and Schadly (1997) detected chromosomal aberrations only when S9 mix was absent. The overall assessment for this endpoint is therefore negative. No unscheduled DNA synthesis was found in rat primary hepatocytes that were treated with Picaridin (Brendler, 1992). Picaridin did not induce micronucleus formation in murine bone marrow erythroblasts at the maximum tolerated oral dose of 350 mg/kg (Herbold, 1994).

101.5 DEVELOPMENTAL TOXICITY

101.5.1 Rat

A developmental toxicity study in Sprague-Dawley rats was conducted at dose levels of 0, 50, 200, or 400 mg/kg/day. Dams were treated from days 0 through 20 of gestation (Astroff *et al.,* 2000).

At the dose site, local dermal reactions (scab and scaling of the skin) were seen on all treated animals. At 400 mg/kg/day, a slight increase in absolute and relative liver weights was seen and was considered an adaptive response. Treatment-related effects on external, visceral or skeletal malformations or external and visceral variations were not seen at any dose level. The maternal and developmental NOAELs were 400 mg/kg/day, the highest dose tested.

101.5.2 Rabbit

Developmental toxicity in the rabbit was conducted at dose levels of 0, 50, 100, or 200 mg/kg bw/day. Animals were treated dermally from days 0 to 28 of gestation (Astroff *et al.*, 2000). A dose-dependent increase was evident for the dermal reactions (slight edema and erythema, cracked skin, squamous skin) to treatment. No toxicity was seen in the rabbit does or fetuses at the maximum dose of 200 mg/kg/day. NOAEL for maternal and developmental toxicity is 200 mg/kg body weight/day.

101.6 REPRODUCTIVE TOXICITY

In a two-generation reproduction study (Astroff *et al.,* 1999), Picaridin was administered to the shaved skin of Sprague-Dawley rats (30/sex/dose) at dose levels of 0, 50, 100, or 200 mg/kg/day for 5 days/week. Starting at approximately 8–9 weeks of age, parental (P) animals were administered the test compound dermally for 10 weeks before mating. After the mating period, P males were sacrificed and necropsied. P female dosing continued throughout gestation and lactation. Litters were culled to eight pups/litter on day 4 of lactation and weaned at 21 days of age. P dams were sacrificed and necropsied after weaning. Upon weaning, first-generation (F1) animals were dosed dermally with the same dose of test compound as their dams for 10 weeks before they were mated to produce the second generation (F2). F1 adults and F2 litters were sacrificed and necropsied at weaning. Exposure of all animals to the test material was 5 days/week throughout the study. Dosing was based on the weekly body weight determination, except for F1 pups, where body weight measurements were taken every 3 days from weaning until the start of the premating phase. Elizabethan collars were worn by all P animals for the duration of the study, beginning at least 7 days prior to the initiation of dosing. F1 pups received their collars when

placed into individual cages, approximately 1 week after weaning.

No treatment-related parental systemic toxicity was observed. There were no clinical signs of toxicity or changes in pup weight, viability, or litter sizes noted in the pups at any dose level for the F1 or F2 generations. No treatment-related macroscopic findings in the F1 or F2 pups were observed at any dose level. The NOAEL for parental systemic and developmental toxicity was 200 mg/kg body weight/day.

101.7 NEUROTOXICITY

101.7.1 Acute

In an acute neurotoxicity study (Sheets, 1996a), Picaridin was applied to the shaved skin of young adult Fischer 344 rats (12/sex/dose) for 24 h at dose levels of 0, 200, 600, or 2000 mg/kg. The rats were evaluated for reactions in functional observations and motor activity measurements at 4 h and 7 and 14 days posttreatment.

101.7.2 Subchronic

In a subchronic neurotoxicity study (Sheets, 1996b), Picaridin was applied to the shaved skin of young adult Fischer 344 rats (12/sex/dose) at dose levels of 0, 50, 100, or 200 mg/kg/day, 5 days/week for 13 weeks. The rats were evaluated for reactions in functional observations and motor activity testing at 4 hours and during weeks 4, 8, and 13 of treatment.

There was no evidence of systemic toxicity or neurotoxicity at the highest doses tested in either the acute (NOAEL = 2000 mg/kg) or subchronic (NOAEL = 200 mg/kg/day) neurotoxicity studies.

101.8 DERMAL ABSORPTION

101.8.1 Rat

In a dermal absorption study in rats (Warren and Sturdivant, 1997), animals were treated with [^{14}C] Picaridin at dose levels of 8 mg/kg bw (0.133 mg/cm^2), 40 mg/kg bw (0.67 mg/cm^2), or 200 mg/kg bw (3.33 mg/cm^2) for 8 h. The absorption patterns were similar between males and females and between all dosage groups. In all treatment groups, the primary route of excretion was via the urine. The majority of radioactivity was excreted within 2 days after application. Total recovery of radiolabel from all groups was high, averaging 95.2% of the applied dose. The data also suggested that the radiotracer did not bind to the application site of the skin. Average absorption (percent of applied dose) was 20.5, 19.1, and 13.8% for males and 27.0, 17.5, and 22.2% for females at respective dose rates of 0.133, 0.67, and 3.33 mg/cm^2. The dermal absorption value of 19.1% from the rat study was used for risk assessment as this value corresponded with the dermal dose used in the human study.

101.8.2 Human Volunteers

In a dermal absorption and excretion study in human volunteers, six healthy male volunteers were treated on 4 × 6 cm^2 of the forearm with Picaridin [^{14}C] either as a 15% (w/w) solution in ethanol or as the undiluted technical grade product for 8 h (Selim, 1994). Blood, urine, feces, and tape strippings of the skin were collected.

Single dermal applications of 100 µl (0.625 mg Picaridin/cm^2) of the 15% ethanol solution or 15 µl (0.612 mg Picaridin/cm^2) neat Picaridin were well tolerated by the test subjects. Less than 4% of the dermal applied dose of Picaridin, either as a 15% formulation or the neat technical grade substance, was absorbed through the skin during an 8-h exposure period and 120 h thereafter. The absorbed part of Picaridin was rapidly excreted via the urine. More than 93% of the absorbed dose was excreted within the first 24 h after exposure had begun. For subjects treated with 15% ethanol solution, Picaridin absorbed was 3.67% of the applied dose, while for treatment with the neat material only 1.66% of the Picaridin was absorbed. There was no evidence that dermal applied Picaridin accumulated in the skin.

The dermal absorption studies in humans and rats showed a marked species difference in absorption of neat Picaridin over several days. At equivalent doses (0.625 mg/cm^2 in humans; 0.67 mg/cm^2 in rats), dermal absorption was considerably greater in rats (19.1% after 7 days) than in humans (1.66% after 5 days) due to greater skin permeability, retention in rat skin (7.6% 16 h after washing), and systemic accumulation. Systemic accumulation is less likely to occur in humans because skin permeability is low, retention in the epidermis of the skin was very low (0.02% 1 h after dosing site wash based on tape stripping, which under normal exposure conditions would be expected to flake off), and excretion was rapid (94% within 24 h). At a comparable dose, humans would be expected to have extremely low systemic Picaridin levels compared to rats, and experience no toxicity. Thus, humans are better protected than rats due to low skin permeability and retention, rapid excretion, and a minimum of systemic accumulation. To account for this species difference in risk assessments, a rat:human dermal penetration factor of 11.5 (19.1% ÷ 1.66%) was used in risk assessments.

101.8.3 Human Skin

An *in vitro* study using human skin was conducted with technical Picaridin and 15% ethanolic solution (Rascle, 2008a) at dose levels of 0.63 mg/cm^2 of [^{14}C] Picaridin for 8 h. The dermal absorption over 24-h period was 10.66% and 9.812% for Technical and 15% ethanolic solution, respectively. The results indicate that dermal absorption was higher in the *in vitro* study by a factor of 6.42 and 2.6 for [^{14}C] Picaridin technical and [^{14}C] Picaridin in 15% ethanolic solution respectively.

In a similar study conducted with 15% formulation with and without sunscreen (Rascle, 2008b), the results showed that the addition of sunscreen decreased dermal penetration through the human skin. It can be hypothesized that sunscreen acted as a barrier to dermal penetration of Picaridin. *In vitro* studies conducted by Gu and Chen (2009), using various combinations of Picaridin and an oxybenzone formulation also showed that dermal penetration of Picaridin was suppressed and the degree of suppression was dependent on the concentration and formulation.

101.9 EXPOSURE AND SAFETY EVALUATION

The risk assessment for formulations containing 20% Picaridin (highest concentration on the market) was conducted on the basis of relative bioavailability of Picaridin derived from the rat and human dermal absorption data (rat/human ratio).

The dermal toxicological end point selected by the EPA for risk assessment was 200 mg/kg/day for acute (1-day exposure); short-term exposure (up to 30 days), and intermediate-term exposure (1–6 months) with dermal penetration ratio (rat/human) of 11.5. Use of repellents is generally seasonal, while long-term and chronic exposures are not anticipated. For calculating margin of exposure (MOE) for children's hand-to-mouth exposure, a NOAEL of 308 mg/kg/day (from oral 5-week study in rats) was used.

The consumer use estimates were derived from a study conducted with the most-used repellent DEET (Boomsma *et al.,* 1990). The inputs used in single-dose exposure estimation are provided in Table 101.5. Short- to intermediate-term dose and MOE are provided in Table 101.6. The MOEs for use of the product were ≥100.

However, the inputs and the NOAELs used in risk calculations by EPA were extremely conservative based on the following:

- The number of total and consecutive days the repellents are used.
- Three applications/day are not warranted based on the long-lasting effectiveness of Picaridin-based repellents.
- The NOAEL used for all dermal exposure scenarios was 200 mg/kg/day (nominal concentration) from the repeated dose animal studies. However, the actual dose experienced by the animals was much higher as the dose was repeatedly applied and the dose site was not washed at the end of the exposure day and the dermal absorption in the rat following repeated exposure was higher (>50%) compared to the single 8-h exposure (19.1%).

Based on the above observations, the realistic dose experienced by animals was estimated to be 288 mg/kg/day (Driver *et al.,* 2005) and the actual MOEs would be much higher than those provided in Table 101.6.

The exposure-risk analyses for the 20% formulations show that sufficient MOEs exist and based on the low skin penetration, rapid excretion of the absorbed material along with high compatibility with skin, Picaridin-based repellents can be safely used by adults and children.

CONCLUSION

The toxicology and safety profile of Picaridin is well characterized. All toxicology data were developed by the dermal route of exposure, the most relevant route based on the use pattern of the product. Picaridin and Picaridin-based products have low acute toxicity by all routes and are not

TABLE 101.5 Assumptions for Dermal Exposure Assessment and Exposures for Single-Day Exposure

	Mean body weight (kg)	Mean body surface area (cm^2)	Application area (25%) (cm^2)	Rate of application
Adult	70	18,150	4538	1 mg formulation/cm^2 skin
Children (3 years)	15	6565	1641	1 mg formulation/cm^2 skin
Short-term (single-day) exposures				
	Daily exposure (mg/kg/day)			
	1 application	**2 applications**	**3 applications**	
Adult	29.3	58.6	87.9	
Children	49.4	98.8	148.2	

TABLE 101.6 Time-weighted Short-/Intermediate-Term Estimates of Dermal Daily Exposures for Picaridin

Number of Applications	Adult (70 kg)				Child (15 kg)			
	Daily exposure (mg/kg/day)		MOE		Daily exposure (mg/kg/day)		MOE	
	28-day	**90-day**	**28-day**	**90-day**	**28-day**	**90-day**	**28-day**	**90-day**
1	1.05	0.33	2200	6900	1.76	0.55	1300	4100
2	2.09	0.65	1100	3500	3.53	1.1	640	2100
3	3.14	0.98	720	2300	5.29	1.65	430	1400
	Adult				**Children**			
	28-day	**90-day**	**28-day**	**90-day**	**28-day**	**90-day**	**28-day**	**90-day**
Maximum number of consecutive applications	22	69	MOE 100	MOE 100	13	41	MOE 100	MOE 100
Maximum number of consecutive days exposed	7	23			4	13		
Daily exposure (mg/kg/day)	22.05	22.77			22.88	22.5		

skin sensitizers. Picaridin showed no neurological or developmental toxicity and there was no evidence of genotoxicity. Chronic dermal dosing in mice, rats, and dogs produced no evidence of adverse toxicity changes and it was not oncogenic in rats and mice. Additional subchronic toxicology studies were conducted by the oral route of exposure. The toxicology profile by the oral route was similar to that of the dermal route and no cumulative effects were evident by oral or dermal routes of exposure. Picaridin is poorly absorbed through the human skin compared to rats and the absorbed dose is rapidly excreted.

A conservative risk assessment conducted on the basis of relative bioavailability (rat/human ratio) shows that margins of safety are sufficient and acceptable. Based on favorable toxicology profile, low skin penetration, rapid excretion of the absorbed material along with high compatibility with skin, Picaridin-based repellents can be safely used by adults and children.

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