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IVERMECTIN page 49-73

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Ivermectin (addendum)

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1. Explanation

Ivermectin (Chemical Abstracts Service no. 70288-86-7)[1] is a macrocyclic lactone that is a member of the avermectin series and is widely used as a broad-spectrum antiparasitic endectocide against nematode and arthropod parasites in food-producing animals. In human medicine, ivermectin is used to treat onchocerciasis, lymphatic filariasis, strongiloidiasis and scabies (Gonazález Canga et al., 2007). Ivermectin consists of two homologous compounds, 22,23-dihydroavermectin B_{1a} (H_2B_{1a} or ivermectin B_{1a}) and 22,23-dihydroavermectin B_{1b} (H_2B_{1b} or ivermectin B_{1b}), in the H_2B_{1a}:H_2B_{1b} ratio of 80:20. Ivermectin is used in cattle, sheep, goats, pigs, horses, reindeer and American bison at doses of 0.1–0.5 mg/kg body weight (bw) given subcutaneously, topically or orally as a single-dose treatment only. Withdrawal periods range from 14 to 122 days where ivermectin is approved for use.

Ivermectin was previously considered by the Committee at its thirty-sixth, fortieth, fifty-eighth, seventy-fifth and seventy-eighth meetings (Annex 1, references *91*, *104*, *157*, *208* and *217*). At its fortieth meeting, the Committee established an acceptable daily intake (ADI) of 0–1 µg/kg bw based on developmental toxicity of ivermectin in CF-1 mice and recommended maximum residue limits (MRLs) of 40 µg/kg for fat, 100 µg/kg for liver and 10 µg/kg for milk as ivermectin in cattle (using the marker ivermectin B_{1a}). At its seventy-eighth meeting, the Committee recommended an MRL of 4 µg/kg for cattle muscle based on 2 times the limit of quantification of the analytical method.

At its seventy-fifth meeting, the Committee concluded that there was a need to evaluate the toxicological information on ivermectin with a view to identifying a critical effect other than in the CF-1 mouse for the establishment of an ADI. The Codex Committee on Residues of Veterinary Drugs in Foods (CCRVDF) at its Twenty-second Session requested that JECFA re-evaluate the ADI and the MRLs in all cattle tissues (FAO/WHO, 2015). CCRVDF noted that the draft MRL for ivermectin in bovine muscle recommended at the seventy-eighth meeting was in some cases ≥2.5 times lower than the MRL established in other countries where ivermectin was used. This did not reflect good veterinary practice. Furthermore, JECFA had not recommended an MRL for bovine kidney.

The Committee considered data from a safety, tolerability and pharmacokinetics study in humans and information on various repeated-dose ivermectin treatment regimens in patients, which were provided by a sponsor. The Committee also considered previous evaluations by JECFA on ivermectin

[1] International Union of Pure and Applied Chemistry name: (1′*R*,2*R*,4′*S*,10′*E*,14′*E*,16′*E*,21′*R*)-6-(butan-2-yl)-21′,24′-dihydroxy-12′-{[(2*R*,4*S*,6*S*)-5-{[(2*S*,4*S*,6*S*)-5-hydroxy-4-methoxy-6-methyloxan-2-yl]-oxy}-4-methoxy-6-methyloxan-2-yl]oxy}-5,11′,13′,22′-tetramethyl-3′,7′,19′-trioxaspiro[oxane-2,6′-tetracyclo[15.6.1.1;{4,8}.0;{20,24}]pentacosane]-10′,14′,16′,22′-tetraen-2′-one.

in various animal species and the pharmacokinetics of ivermectin in dogs in particular, so that a more appropriate animal model could be used to establish an ADI. In light of the possibility for acute exposure to high concentrations of ivermectin from the injection site, the Committee also considered the acute toxicity of ivermectin with a view to establishing an acute reference dose (ARfD).

The critical animal studies were not performed to good laboratory practice (GLP) because the data were generated prior to the implementation of GLP. The human study was conducted according to the principles of the Declaration of Helsinki. The Committee considered that the database was adequate for the evaluation.

1.1 CF-1 mouse

The ADI established at the fortieth meeting of JECFA was based upon the developmental toxicity of ivermectin to the CF-1 mouse, as it was the most sensitive species studied. A no-observed-effect level (NOEL) (which would now be referred to as a no-observed-adverse-effect level [NOAEL]) of 0.1 mg/kg bw per day for maternal toxicity in the CF-1 mouse was combined with a safety (uncertainty) factor of 100 to derive an ADI for ivermectin of 0–1 μg/kg bw. However, subsequent consideration by the Joint FAO/WHO Meeting on Pesticide Residues (JMPR) and JECFA regarding the unique sensitivity of the CF-1 mouse to avermectins suggested that this mouse model of toxicity was inappropriate for establishing health-based guidance values for avermectins.

Data submitted to the 1994 meeting of JMPR as part of its consideration of abamectin-induced toxicity indicated that the high sensitivity of CF-1 mice to the neurotoxicity of avermectins was associated with P-glycoprotein deficiency in the small intestine and in the capillary endothelial cells of the blood–brain barrier (WHO, 1994). JMPR speculated that the heterogeneity of the response in CF-1 mice may explain the absence of a dose–response relationship for maternal toxicity in the studies of teratogenicity. Data submitted to JMPR in 1998 resolved the issue of the variability seen in earlier studies in CF-1 mice (WHO, 1998). In recent evaluations, JMPR and JECFA have moved to discount the effects observed in the CF-1 mouse in identifying critical effects for the establishment of ADIs for avermectins (FAO/WHO, 2016; Annex 1, reference *208*).

1.2 P-glycoprotein

P-glycoprotein is a 170 kDa transmembrane protein that belongs to the adenosine triphosphate binding cassette (ABC) protein superfamily and is coded for the multiple drug resistance (*MDR1*) gene, also known as the *ABCB1* gene (Hugnet, Lespine & Alvinerie, 2007). Although P-glycoprotein does not have any intrinsic metabolic functions, it is important for the active cellular efflux of a large number

of drugs, including macrocyclic lactones, and toxic compounds. Most of these P-glycoprotein substrates are also substrates of the major drug-metabolizing cytochrome P450 (CYP) 3A4 isotype enzyme. CYP3A4 and P-glycoproteins are expressed at high levels in the villus tip of enterocytes in the gastrointestinal system (Dowling, 2006). In the central nervous system, P-glycoprotein is found in the capillary endothelial cells that form the blood–brain barrier (Hugnet, Lespine & Alvinerie, 2007). P-glycoprotein is also found in the placenta (Ceckova-Novotna, Pavek & Staud, 2006).

In the intestinal tract, substrate drugs may be absorbed passively by the enterocytes; then they enter the systemic circulation, undergo metabolism by CYP3A4 or are extruded by P-glycoprotein back into the intestinal lumen. This extrusion effectively allows the substrate drug further access to CYP3A4 in enterocytes farther down the intestinal tract (Dowling, 2006). Although non-P-glycoprotein substrate drugs may need to pass through the enterocyte only once, P-glycoprotein substrate drugs may continuously cycle between the enterocyte and the intestinal lumen, resulting in repeated access to CYP3A4 or faecal excretion (Dowling, 2006).

Similarly, in the central nervous system, P-glycoprotein substrate drugs, such as avermectins, are transported by P-glycoprotein from the inside to the outside of the endothelial cells back into the lumen of the capillary, thus preventing further diffusion in the central nervous system (Hugnet, Lespine & Alvinerie, 2007).

In the absence of P-glycoprotein, avermectins may be absorbed more freely from the gastrointestinal tract and are capable of diffusing freely and accumulating in the central nervous system, which may lead to drug-induced neurotoxicity. P-glycoprotein-deficient animals such as the CF-1 mouse strain (Lankas, Cartwright & Umbenhauer, 1997), genetically engineered mice (e.g. *mdr1a*–/–) (Schinkel et al., 1996), Murray red cattle and certain dogs of the Collie breed are uniquely sensitive to the adverse effects of ivermectin (Hugnet, Lespine & Alvinerie, 2007). Genetic studies in dogs have documented the *mdr* gene deletion in a number of canine breeds (Australian Shepherds, Collies, English Shepherds, Longhaired Whippets, McNabs, Miniature Australian Shepherds, Old English Sheepdogs, Shetland Sheepdogs, Silken Windhounds and White German Shepherds), with the highest incidence in Collies (30% homozygous and 40% heterozygous). The gene deletion frequency in other herding breeds of Collie lineage is much lower (Dowling, 2006). There are no data to indicate that Beagles carry this deletion.

Importantly, studies in humans have established that P-glycoprotein is expressed at near adult levels in the newborn. Although polymorphisms of P-glycoprotein are known in humans, their impact on P-glycoprotein activity has been considered to be relatively modest (Annex 1, reference *208*).

More than 50 naturally occurring single-nucleotide polymorphisms have been identified in the human *ABCB1* gene (Macdonald & Gledhill, 2007). The vast majority are silent – that is, either they do not occur in the coding regions of the gene or, owing to the inherent redundancy of codon usage, they do not alter the amino acid sequence of the protein. Although there are conflicting reports of the effects of individual *ABCB1* single-nucleotide polymorphisms on P-glycoprotein expression and function in various tissues (Sakaeda, 2005; Kerb, 2006), there is currently no evidence for the existence of mutations in humans that might result in a loss of function analogous to that seen in the CF-1 mouse and Collie dog. Where human blood–brain barrier P-glycoprotein levels have been measured directly, the most common halotypes were found to have equal functionality. As heterozygous P-glycoprotein +/− mice and dogs do not exhibit ivermectin neurotoxicity at clinically relevant doses, it is likely that humans carrying at least one functional copy of the *ABCB1* gene will not be more susceptible to avermectin toxicity at clinically relevant doses or at the low exposure levels resulting from pesticide use. Calculations using allelic frequencies of known haplotypes indicated that homozygosity for any as yet uncharacterized haplotypes with severely reduced blood–brain barrier functionality is likely to be very rare in human populations (Macdonald & Gledhill, 2007). Taken together, this may indicate that individuals with significantly compromised P-glycoprotein functionality analogous to that seen in the CF-1 mouse and Collie dog do not exist or are very rare.

Overall, when the level or functionality of P-glycoprotein is reduced in animals, the animals absorb more avermectins following oral administration, develop higher avermectin levels in blood, accumulate greater amounts of avermectins in the central nervous system and appear to be more sensitive to the adverse health effects caused by these compounds compared with animals with a normal expression of P-glycoprotein (Shoop & Soll, 2002; Annex 1, reference *157*).

1.3 Response to JECFA call for data

In May 2015, JECFA issued a call for all data necessary to review the ADI for ivermectin and recommend MRLs for ivermectin in edible tissues of cattle.

In response to this call for data, the sponsor submitted a meeting abstract on a safety, tolerability and pharmacokinetics study in adults (Guzzo et al., 2002a) and a clinical report on the same study (Lasseter, 2001). The clinical study report was subsequently published as Guzzo et al. (2002b).

2. Biological data

2.1 Biochemical aspects

2.1.1 Human pharmacokinetics

Pharmacokinetics data were obtained from the safety, tolerability and pharmacokinetics study in humans (Lasseter, 2001). Twelve healthy human subjects per dose group were administered oral doses of ivermectin of 30 or 60 mg on days 1, 4 and 7 or single doses of 90 or 120 mg. An additional four healthy human subjects per dose group were administered a placebo. All subjects were fasted prior to dosing. A group of the subjects that received 30 mg were allowed a 1-week washout and then fed prior to administration of a single oral dose of 30 mg ivermectin.

Analysis of the pharmacokinetics data revealed that concentrations of ivermectin in plasma were generally proportional up to a single oral dose of 120 mg in fasted subjects. Dose linearity of the peak concentration in plasma (C_{max}) and the area under the plasma concentration–time curve (AUC) was confirmed after dose normalization. There were no differences in pharmacokinetic variables between men and women. Minimal accumulation was observed with repeated dosing, and the elimination half-life ranged from 18.8 to 20.1 hours for fasted subjects (Table 1). The ivermectin AUC was 2.57-fold greater in fed versus fasted subjects receiving a single dose of 30 mg, but the elimination half-life was shorter, at 15.0 hours.

Table 1
Arithmetic means (and standard deviations) for pharmacokinetic parameters on study day 1 by treatment regimen

	Ivermectin 30 mg (fed) ($n = 11$[a])		Ivermectin 30 mg (fasted) ($n = 12$[b])		Ivermectin 60 mg (fasted) ($n = 12$)		Ivermectin 90 mg (fasted) ($n = 12$)		Ivermectin 120 mg (fasted) ($n = 12$)	
	0.4 mg/kg bw[c]		0.4 mg/kg bw[c]		0.8 mg/kg bw[c]		1.2 mg/kg bw[c]		1.5 mg/kg bw[c]	
Parameter	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
$AUC_{0-\infty}$ (ng·h/mL)	4 564.6	1 892.5	1 724.3	830.5	2 984.0	1 530.1	2 910.2	1 801.0	4 547.7	2 402.9
C_{max} (ng/mL)	260.5	172.1	84.8	42.7	165.2	98.6	158.1	87.6	247.8	158.9
$t_{½}$ (h)[d]	15.0	NA	20.1	NA	19.6	NA	18.8	NA	19.1	NA
T_{max} (h)	4.6	0.9	4.3	1.0	3.6	0.9	4.9	1.8	4.2	0.9
Dose-normalized $AUC_{0-\infty}$ (ng·h/mL)	152	–	57	–	50	–	32	–	38	–
Dose-normalized C_{max} (ng/mL)	8.7	–	2.8	–	2.8	–	1.8	–	2.1	–

$AUC_{t-\infty}$: area under the plasma concentration–time curve from time 0 to infinity; bw: body weight; C_{max}: peak plasma concentration; *n*: number of subjects per treatment regimen; NA: not applicable; SD: standard deviation; $t_{½}$: elimination half-life; T_{max}: time to reach C_{max}

[a] One subject discontinued prior to receiving treatment.

[b] As prespecified in the study protocol amendment (Lasseter, 2001), plasma samples from three subjects were not analysed for ivermectin concentration and did not contribute to the pharmacokinetics analysis.

[c] Dose expressed as milligrams per kilogram median body weight.

[d] Harmonic mean.

Source: Lasseter (2001)

2.1.2 Canine pharmacokinetics

No data on the toxicokinetics of ivermectin were available from the pivotal 14-week oral toxicity study in dogs (see section 2.2.1 below). Therefore, a literature search was undertaken to identify any additional scientific articles that contained data on the pharmacokinetics of ivermectin in laboratory animals. The search strategy included the following terms: "ivermectin AND pharmacokinetics AND (mouse OR rat OR dog OR monkey)". The following database was searched on 19 October 2015: PubMed (United States National Library of Medicine, National Institutes of Health). Of the 153 articles retrieved, only six studies in dogs were identified that had relevant pharmacokinetics data (i.e. where ivermectin was given as an oral formulation). The pharmacokinetics data from these studies are tabulated in Table 2.

Table 2

Comparison of pharmacokinetics data following administration of a single oral dose of ivermectin to dogs

Breed (number)	Dose (µg/kg bw)	$t_{½}$ (days)	T_{max} (day)	C_{max} (ng/mL)	Dose-normalized C_{max} (ng/mL)	AUC (ng·d/mL)	Dose-normalized AUC (ng·d/mL)	Reference
Beagle (9)[a]	81.5	4.4	0.22	24.0	0.3	38.9	11.5	Dunn et al. (2011)
Beagle (16)[b]	100	ND	0.18	44.3	0.4	43	6.7	Daurio et al. (1992)
Cross-breed (5)[c]	200	3.3	0.23	116.8	0.6	237	28	Gokbulut et al. (2006)
Beagle (8)[d]	250	3.3	0.17	132.6	0.5	233	22.4	Al-Azzam et al. (2007)
Not defined (12)[e]	300	1.8	0.30	9.64	0.03	27.8	2.2	Gong et al. (2010)
Beagle (10)[f]	300	2.07	0.29	92.70	0.31	141.96	11.4	Walther, Allan & Roepke (2015)

AUC: area under the plasma concentration–time curve; bw: body weight; C_{max}: peak plasma concentration; ND: no data; $t_{½}$: elimination half-life; T_{max}: time to reach C_{max}

[a] Sex not defined. Body weight not defined. Fasting status not provided.

[b] Sixteen females. Body weight not defined. Fasting status not provided.

[c] Five females (15–30 kg). Not fasted.

[d] Four of each sex (7.9–16.3 kg) inoculated with *Brugia pahangi*. Fasting status not provided.

[e] Six of each sex (mean body weight ± SD: 9.80 ± 0.48 kg). Fasted.

[f] Five of each sex (mean body weight ± SD: 13.1 ± 1.2 kg). Fasting status not provided.

The data indicate that for a 3-fold increase in ivermectin dose (81.5–250 µg/kg bw), there was approximately a 5.5-fold increase in the ivermectin C_{max} (24.0–132.6 ng/mL) and a 6-fold increase in the plasma ivermectin AUC (38.9–237 ng·d/mL). The studies that used 300 µg/kg bw were not included in this comparison because (1) the study with the shortest elimination half-life for ivermectin in dogs (Gong et al., 2010) was associated with animals that were fasted prior to dosing, whereas in the other studies, the animals were assumed not to have been fasted; and (2) the C_{max} and AUC values obtained by Walther, Allan & Roepke (2015) were inconsistent with the higher values obtained for the 200 and 250 µg/kg bw doses by Gokbulut et al. (2006) and Al-Azzam et al. (2007). Dose normalization of the pharmacokinetics data from the oral dosing studies in dogs for the dose range 81.5–250 µg/kg bw confirmed the non-linear plasma pharmacokinetics of ivermectin in dogs. For this dose range, the elimination half-life ranged from 3.3 to 4.4 days.

2.2 Toxicological studies

The evaluation of the toxicity of ivermectin in laboratory animals has previously been undertaken by JECFA (Annex 1, reference *92*). As the toxicological effects noted in CF-1 mice are no longer considered relevant to humans, the derivation of an appropriate ADI should be based upon appropriate toxicity studies in either humans or other laboratory animals. However, no long-term, repeated-dose toxicity studies in humans or other laboratory animals were submitted to JECFA for consideration.

2.2.1 Short-term studies of toxicity

(a) Rats

A 14-week repeated-dose toxicity study in rats was previously evaluated by JECFA (Annex 1, reference *92*). The findings from this study are reproduced below:

> A fourteen-week toxicity study following in utero exposure was reported. Twenty rat pups of each sex between 3 and 4 weeks of age weighing 49 to 86 grams (males) or 43 to 77 grams (females) were treated at dosage levels of 0.4, 0.8, and 1.6 mg/kg b.w./day. No changes due to treatment occurred at 0.4 mg/kg b.w./day. The following effects could not be excluded as being treatment-related in the two other dosage level groups: spleen-enlargement and reactive bone-marrow hyperplasia, which occurred in 1 animal at 0.8 mg/kg b.w./day and in 3 animals at 1.6 mg/kg b.w./day (Merck & Co., Inc., 1979b).

Based on the findings of spleen enlargement and reactive bone marrow hyperplasia at 0.8 mg/kg bw per day, a NOAEL of 0.4 mg/kg bw per day was identified in this study.

The significance of the toxicological findings from this 14-week study in rats is questionable. Splenic enlargement and bone marrow hyperplasia have not been reported in other species. In particular, there was insufficient information in the description of the study to clearly identify the study design and to interpret the study's findings.

(b) Dogs

A 14-week repeated-dose toxicity study with ivermectin in Beagle dogs has previously been evaluated by JECFA (Annex 1, reference *92*). The findings from this study are reproduced below:

> Twenty male and 20 female beagle dogs, 39-43 weeks of age, weighing initially 8.2 - 12.1 kg (males) and 6.2 - 9.2 kg (females) were selected for oral treatment (gastric intubation) in five groups of four males and four females at doses of 0.5, 1.0, 2.0 mg/kg b.w./day. Controls received water or vehicle (sesame oil). At 2.0 mg/kg b.w./day, three males and one female developed tremors, ataxia, anorexia, and dehydration. All of these animals exhibited ptyalism and mydriasis followed by slight tremors, characterized by intermittent or constant shaking of all limbs, which generally increased in severity over 3 to 6 days. These animals were frequently found laterally recumbent and were ataxic when standing. They were sacrificed between weeks 4 and 12. Mydriasis was observed in all dogs at this level (beginning in week 1 and continuing until week 12 when it decreased in incidence). The four dogs sacrificed showed weight losses between 1.0 and 1.6 kg. At 1.0 mg/kg b.w./day, mydriasis was occasionally seen, particularly in week 3. Weight gain was retarded. At 0.5 mg/kg b.w./day, only slight retardation of weight gain was observed. No significant drug-related changes were observed for the following parameters: ocular abnormalities, electrocardiograms, haematologic parameters, urine-analysis, and pathological changes (Merck & Co., Inc., 1978).

Based on occasional mydriases and retarded weight gain, a NOAEL of 0.5 mg/kg bw per day was identified in this study.

It is noted that the NOAEL from this study was considered the most relevant for establishing an ADI for ivermectin by the European Medicines Agency (EMEA, 2005, 2014) and the United States Food and Drug Administration (USFDA, 2014).

(c) Rhesus monkeys

A 16-day repeated-dose toxicity study with ivermectin in immature rhesus monkeys has previously been evaluated by JECFA (Annex 1, reference *92*). The findings from this study are reproduced below:

> A 16-day oral toxicity study with ivermectin was conducted to determine its toxicity in immature rhesus monkeys (13 - 21 months old, weighing 2.1 to 3.2 kg (males) and 1.9 to 2.7 kg (females) at initiation). Each of the treatment groups (4 females, 4 males per group) were dosed daily by nasogastric intubation with ivermectin in sesame oil at dose levels of 0.3, 0.6, and 1.2 mg/kg body weight.
>
> These dose levels were chosen to provide an appropriate 6-fold safety margin relative to the human clinical dose, and based on the acute toxicity in rhesus monkeys. All animals were treated for at least 14 days and then sacrificed on days 15, 16 or (one animal) 17. No drug-related effects (physical signs, body weight, ocular lesions, haematology, serum biochemical parameters, or necropsy findings) were noted in any of the treated animals (Merck & Co., Inc., 1986).

A NOAEL of 1.2 mg/kg bw per day, the highest dose tested, was identified in this study.

JMPR (WHO, 1998) noted that:

> P-glycoprotein was present on the endothelial surface of capillaries in the cerebellum, cerebellar peduncle, and pons of rhesus monkey foetuses. The staining intensity was comparable in all areas of the brain. P-glycoprotein was also present in the placenta, but none was detected in fetal jejunum. The brain levels of P-glycoprotein in monkey foetuses were comparable to those in the brain of one to two year old rhesus monkeys examined in another study.

This comment from JMPR would suggest that fetal, neonatal and juvenile rhesus monkeys have a functional blood–brain barrier insofar as having adequate levels of P-glycoprotein in their central nervous system. This is supported by the lack of adverse findings in the 16-day toxicity study in rhesus monkeys.

2.2.2 Long-term studies of toxicity and carcinogenicity

JECFA has not evaluated any chronic toxicity or carcinogenicity studies in laboratory animals administered ivermectin. The Committee at its thirty-sixth meeting (Annex 1, reference *91*) concluded that given the structural similarities and comparative toxicological profiles of ivermectin and abamectin, such studies were not required. In a 94-week dietary carcinogenicity study in mice using abamectin doses of 0, 2, 4 and 8 mg/kg bw per day, a NOEL (NOAEL) of 4.0 mg/kg bw per day was identified (Merck & Co., Inc., 1983). Furthermore, in a 105-week dietary carcinogenicity study in rats with abamectin doses of 0, 0.75, 1.5 and 2.0 mg/kg bw per day, a NOEL (NOAEL) of 1.5 mg/kg bw per day was identified (Merck & Co., Inc., 1982).

2.2.3 Genotoxicity

JECFA has previously evaluated the genotoxicity of ivermectin and concluded that it was negative in three in vitro assays for genotoxicity, but no test of clastogenicity had been performed (Annex 1, reference *91*).

2.2.4 Reproductive and developmental toxicity

A reproductive toxicity study and a series of multigeneration toxicity studies have been carried out in rats. All of these studies have previously been evaluated by JECFA (Annex 1, reference *91*). The findings from these studies are reproduced below:

> Ivermectin was administered orally once daily to three groups of 15 female rats at dose levels of 0.4, 0.8, and 1.6 mg/kg body weight from 15 days prior to mating until 20 days post-partum. Two vehicle control groups received sesame oil in the same dosing regimen as the treated animals.
>
> There was no mortality or clinical evidence of toxicity in the females. Average body weight was significantly increased among females at 0.8 and 1.6 mg/kg b.w./day during the prebreeding period and at all dose levels during gestation.
>
> Ivermectin had no effect on mating, reproductive status, average length of gestation or post implantation survival rate. Statistically significant treatment-related increases in mortality among pups in the 1.6 mg/kg b.w./day group were observed on day 1 and from days 7-14 post-partum. Prior to death, several pups were observed to be hypothermic and to have no externally observable milk in the epigastric region. Throughout the lactation period, average pup weights were slightly higher than controls in the 0.4 mg/kg b.w./day group and significantly higher in the two other dose-level groups.
>
> Development (eye opening, ear opening, incisor eruption, and hair growth) was also slightly accelerated (Merck & Co., Inc., 1979a,b).

The NOAEL for maternal toxicity was 1.6 mg/kg bw per day, the highest dose tested. Based on pup mortality at 1.6 mg/kg bw per day, the NOAEL for offspring toxicity was 0.8 mg/kg bw per day.

* * *

> A series of three multigeneration studies was initiated in rats, the first two of which were halted prior to scheduled termination because neonatal toxicity was apparent at all dose levels tested.
>
> Dose rates of 0.4, 1.2, and 3.6 mg/kg b.w./day were used in the first study. It was necessary, however, to terminate this study before mating of the F_{1b}-generation because

it became apparent from toxic symptoms observed in the F_{1a}-, F_{1b}-, and F_{2a}-generations that a NOEL could not be derived from this study.… (Merck & Co., Inc., 1980).

A second multigeneration study was initiated at a dose of 2.0 mg/kg b.w./day in order to provide clear evidence of toxicity while allowing sufficient surviving offspring to permit continuous dosing throughout the production of two litters in each of three generations. This study was terminated prior to the production of the F_{1b}-litter when it became apparent that there was treatment-related neonatal toxicity present in the above concurrent multigeneration study at dose levels 1.2 and 0.4 mg/kg b.w./day (Merck & Co., Inc., 1981).

In a final multi-generation study the following dose groups were included: 0.05, 0.1, 0.2, and 0.4 mg/kg b.w./day. A vehicle control group received sesame oil daily in the same volume as drug-treated rats. The animals were 28 days old at the onset of the daily treatment and were mated 71 days later. Exposure was continued for the entire life-span.

The F_{1a}-litter was sacrificed on day 21 post-partum. Approximately three weeks later the F_0-rats were mated again to produce the F_{1b}-litter. On day 21 post partum of the F_{1b}-offspring, the F_0-generation was sacrificed. After 71 days of treatment, the F_{1b}-rats were mated to produce the F_{2a}-offspring which were also sacrificed on day 21 post-partum. Approximately three weeks later the F_{1b}-rats were again mated to produce the F_{2b}-offspring. Twenty-one days post partum of this offspring, the F_{1b}-generation was sacrificed. After 71 days of drug treatment, F_{2b}-rats were mated to produce the F_{3a}-offspring which were sacrificed on day 21 postpartum.

Approximately three weeks later the F_{2b}-rats were again mated to produce the F_{3b}-litter. The parents were sacrificed after weaning of the F_{3b}-litter. Twenty males and 20 females from each F_{3b}-offspring group were randomly selected for necropsy at 28 to 43 days of age. There was no treatment-related mortality or physical signs of toxicity among parents or offspring in any dosage group throughout the production of two litters in each of the F_0-, F_1-, and F_2-generations. Ivermectin had no treatment-related effects on the reproductive performance of male or female rats in any dosage group.

Treatment-related effects on body weight gain were limited to a slight but statistically significant decrease during the postweaning period in mean body weight gain among F_{1b}-females in the 0.4 mg/kg b.w./day group and among F_{2b}-males from the 0.2 and 0.4 mg/kg b.w./day groups. External, visceral, and skeletal examination of both the F_{3a}- and F_{3b}-offspring revealed no evidence of teratogenicity. Doses of less than or equal to 0.2 mg/kg b.w./day had no adverse effects on parents or progeny (Merck & Co., Inc., 1980, 1981).

The NOAEL for parental toxicity, reproductive toxicity and offspring toxicity was 0.4 mg/kg bw per day, the highest dose tested.

The significance of the toxicological findings from these reproductive toxicity studies in rats for human toxicology is questionable. The adverse effects observed in these studies appear to be related to in utero and postnatal exposure (via maternal milk) to ivermectin. Ivermectin has been shown to be more toxic to juvenile rats than to young adults, as a result of enhanced sensitivity to ivermectin due to an underdeveloped blood–brain barrier. Significantly higher brain–plasma drug concentration ratios in neonatal rats compared with adult rats have been reported (Lankas & Gordon, 1989), as well as higher drug levels in maternal milk compared with maternal plasma (WHO, 1998).

JMPR (WHO, 1998), in its consideration of the contribution of P-glycoprotein development in rodents to the observed toxicity of abamectin, noted:

> In the immature rat (about six weeks old), P-glycoprotein is present in the brain and in the brush border epithelial cells of the jejunum. In fetal animals (day 20 of gestation), however, minimal P-glycoprotein was detected in the brain, the levels being less than 1% of that in adult animals up to day 14 and then increasing rapidly. No P-glycoprotein was detected in the jejunum of fetal rats or in rats on days 2 or 5 post-partum; P-glycoprotein was detectable by day 8 post-partum, and the levels increased with time thereafter. These data indicate late expression of P-glycoprotein, occurring some 10-15 days post-partum. In non-pregnant adult rats, P-glycoprotein was not observed in the uterus; it was present, however, on the luminal surface of the uterine epithelium in pregnant rats.

In the same evaluation, JMPR (WHO, 1998) also commented on the ivermectin multigeneration study:

> Post-natal toxicity was assessed further in a series of cross-fosterings of newborn pups, with the toxicity being shown to be due to postnatal and not in-utero exposure….These data were interpreted by the JMPR to indicate that the development of the blood-brain barrier in rat offspring is delayed, occurring sometime after parturition. The postnatal toxicity observed in rats may be a function of the accessibility of the target organ to the toxin, owing to the late formation of the blood-brain barrier and to possible mobilization of ivermectin from adult fatty tissues.

Although dogs are not routinely used in developmental and reproductive toxicity studies, an ivermectin dose of 600 µg/kg bw was not found to have negative effects on reproductive status, as measured by the numbers of implantations, resorptions, and live or dead puppies. Furthermore, continuation of treatment after whelping had no effects on the puppies (Pulliam & Preston, 1989). In addition, no adverse effect on reproductive status was observed in dogs treated with 600 µg/kg bw monthly for 8 months and bred to untreated bitches (Daurio et al., 1987).

The hypersensitivity of fetal and neonatal rats to ivermectin (and other avermectins) indicates the limited utility of using a toxicological end-point from the abovementioned subchronic toxicity studies in rats.

Interestingly, P-glycoprotein has been detected in the brain capillaries of human fetuses aborted at 24 weeks, but not at earlier gestational ages. Nonetheless, the levels found were comparable to those in the adult brain. JMPR noted that in human placenta, P-glycoprotein was found in the syncytiotrophoblast microvillus border and in some placental macrophages in the first trimester, but mainly in the placental macrophages at term (WHO, 1998).

2.2.5 Special studies

(a) Microbiological effects

Considering the chemical structure and mode of action, the Committee did not anticipate any adverse effects of ivermectin residues on human gastrointestinal microbiota.

2.3 Observations in humans

2.3.1 Clinical study

The sponsor submitted a human clinical safety, tolerability and pharmacokinetics study and associated abstract. This study has been evaluated, and the key findings are summarized below.

Sixty-eight healthy, non-smoking human subjects (21–45 years of age, weighing 50–90 kg) were assigned to one of four treatment panels to receive either placebo ($n = 4$) or ivermectin ($n = 12$) in the fasted state as follows:

1. 30 mg (three doses over 1 week), followed by a 1-week wash-out after the last dose and then a single 30 mg dose after being fed a "standard high-fat diet", equivalent to 0.4 mg/kg bw based on the median body weight in this group;
2. 60 mg (three doses over 1 week), equivalent to 0.8 mg/kg bw based on the median body weight in this group;
3. 90 mg (single dose), equivalent to 1.2 mg/kg bw based on the median body weight in this group; or
4. 120 mg (single dose), equivalent to 1.5 mg/kg bw based on the median body weight in this group.

Clinical observation for adverse experiences (e.g. any neurological signs of toxicity, such as vomiting, mydriasis or gait disturbance) as well as neurological examinations (mental status, optic, coordination and gait, reflex, sensory and motor examinations), physical examinations, vital signs (blood

pressure, heart rate, respiratory rate and temperature), electrocardiograms and clinical laboratory tests (haematology, blood chemistry and urine analysis) were performed.

Sixty-six subjects completed the study. There were no deaths during the study. There were no reports of ataxia or mydriasis. All clinical adverse observations were considered to be transient and mild. There were no ivermectin-related effects on pupillometry, neurological examinations, vital signs, electrocardiography, physical examination, urine analysis or haematology.

Oral doses of ivermectin of up to 120 mg were well tolerated by human subjects. No adverse effects on human health, in particular upon the neurological system, were identified. The NOAEL for acute oral toxicity of ivermectin was identified as 120 mg (equivalent to 1.5 mg/kg bw based on the median body weight of 77.9 kg), the highest dose tested. These findings were considered to have utility in establishing an ARfD.

The findings from this study (Lasseter, 2001) have been published as Guzzo et al. (2002b).

2.3.2 Clinical experience

Ivermectin has been in use as a human therapeutic for more than 20 years. As noted by JECFA at its fifty-eighth meeting (Annex 1, reference *157*):

> Ivermectin has been administered to several million human patients in Africa and Latin America since its introduction in 1987 as the main treatment for onchocerciasis at a recommended dose level of 150 µg/kg bw administered once every 12 months. The adverse reactions that have been observed in treated patients have been described as allergic or inflammatory responses resulting from killing of microfilariae, referred to as the "Mazotti reaction". No signs of acute central nervous system toxicity have been reported. Ivermectin is now considered safe for use in pregnant women, on the basis of finding of P-glycoprotein in human placentae and in human foetuses by week 28 of gestation and the absence of adverse effects to the fetus when pregnant women were inadvertently treated with ivermectin.

Ivermectin is also used in the treatment of lymphatic filariasis, strongiloidiasis and scabies in several countries. The treatment of scabies may generally require a single oral dose of 200 µg/kg bw, but two or three repeated doses may be required, separated by an interval of 1 or 2 weeks, to be fully effective (Dourmishev, Dourmishev & Schwartz, 2005).

The sponsor identified a number of reported studies in which parasitized patients received up to 13 oral doses of ivermectin (800 µg/kg bw) during the course of treatment. These studies reported that ivermectin was well tolerated and

noted no serious adverse health effects. A recent review of the acute toxicity of macrocyclic lactones reported that adverse health effects of ivermectin treatment in patients with onchocerciasis were related not to the dosage of ivermectin, but to the skin microfilarial load (Yang, 2012).

The sponsor has provided information on a safety and tolerability study (Lasseter, 2001) and published studies in humans in which subjects/patients were given multiple doses of ivermectin (Table 3). Although a number of studies outlined in Table 3 indicate that patients may have received up to 13 doses of ivermectin during the course of treatment, there is little to suggest that these patients maintained significant systemic levels of ivermectin, thus limiting their utility in establishing an ADI for chronic toxicity. This is further supported by the pharmacokinetics profile of ivermectin in humans. Data from the safety and tolerability study (Lasseter, 2001) revealed that the half-life of ivermectin in plasma was approximately 18 hours in healthy subjects given a single oral dose of 30–120 mg (equivalent to 333–2000 µg/kg bw) (Table 1), which is similar to other published pharmacokinetics data for ivermectin in humans, with half-lives of 28 hours (Edwards & Breckenridge, 1988) and 37 hours (Baraka et al., 1996).

Similarly, the EMEA (2005), in its review of the Lasseter (2001) study, noted that:

> However, it was considered that the human study could not be used to establish the ADI because [of] the dosing regimen used. As indicated…, the time to reach steady state would be much longer than the maximum treatment period used (7 days). The plasma steady state concentration would be at least 1.5-fold higher than the levels achieved after administration on days 1, 3 and 7 only. The relation of these kinetics to central nervous system concentrations is unknown.

3. Comments

3.1 Biochemical data

Pharmacokinetics data were obtained from the submitted safety, tolerability and pharmacokinetics study in humans (Lasseter, 2001). Twelve fasted subjects per dosing group were given a single oral dose of 30, 60, 90 or 120 mg ivermectin or multiple doses of either 30 or 60 mg ivermectin over 7 days. Pharmacokinetic analysis revealed that ivermectin concentrations in plasma were generally proportional up to a single oral dose of 120 mg in fasted subjects. Dose linearity of C_{max} and AUC was confirmed after dose normalization. There were no differences in pharmacokinetic variables between men and women. Minimal accumulation was observed with repeated dosing, and the elimination half-life ranged from

Table 3
Summary of ivermectin repeated-dose treatment regimens in selected human clinical efficacy studies in parasitized patients

First dose (µg/kg bw)	Subsequent dose(s) (µg/kg bw)	Frequency of treatment	Total no. of doses	Total no. of subjects	Reference
100	100	Every 2 weeks	6	30	Duke et al. (1991)
150	150	Monthly	4, 8 or 12	32	Duke et al. (1990)
150	150	Every 3 months	4, 8 or 11	28	Duke et al. (1992)
20	200 or 400	Days 1 and 5	2	18	Addiss et al. (1993)
20	200 or 400	Days 1 and 5	2	20	Kazura et al. (1993)
20	200 or 400	Days 1 and 5	2	21	Shenoy et al. (1993)
20	200 or 400	Days 1 and 5	2	22	Dreyer et al. (1995)
20	400	Days 1 and 4, then every 2 weeks	13	14	Ismail et al. (1996)
100	100, then 400	Every 6 months	6 (3 + 3)	92	Nguyen, Moulia-Pelat & Cartel (1996)
150	400, 600 or 800	Days 1 and 4	2	25	Awadzi et al. (1995, 1999)
150	400, then 800	Days 1 and ~60–90, then every 12 months	4	172	Gardon et al. (2002)
150	150 or 400, then 800	Every 3 months	13	319	Gardon et al. (2002)
800	800	Days 1 and 13	2	12	Awadzi et al. (1999)

18.8 to 20.1 hours in fasted subjects. The ivermectin AUC was 2.57-fold greater in fed versus fasted subjects receiving a single dose of 30 mg, but the elimination half-life was shorter, at 15.0 hours.

A literature search identified a number of oral dosing studies in dogs that had relevant pharmacokinetics data from a test group treated with ivermectin. The data indicate that for a 3-fold increase in ivermectin dose (81.5–250 µg/kg bw per day), there was approximately a 5.5-fold increase in the ivermectin C_{max} (24.0–132.6 ng/mL) and a 6-fold increase in the plasma ivermectin AUC (38.9–237 ng·d/mL). Dose normalization of the pharmacokinetics data from the oral dosing studies in dogs confirmed non-linear plasma pharmacokinetics of ivermectin in dogs. Furthermore, for this dose range, the elimination half-life ranged from 3.3 to 4.4 days (Daurio et al., 1992; Gokbulut et al., 2006; Al-Azzam et al., 2007; Dunn et al., 2011).

3.2 Toxicological data

Repeated-dose studies with ivermectin in laboratory animals have previously been evaluated by JECFA (Annex 1, reference *91*). The findings from the most relevant of these non-GLP-compliant studies are summarized in Table 4 and below.

Table 4
Studies relevant to risk assessment

Species / study type (route of administration)	Doses (mg/kg bw per day)	Critical end-point	NOAEL (mg/kg bw per day)	LOAEL (mg/kg bw per day)
Rat				
Reproductive toxicity study (oral)	0, 0.4, 0.8, 1.6	Increase in pup mortality	0.8	1.6
Multigeneration reproductive toxicity study (oral)	0, 0.05, 0.1, 0.2, 0.4	No adverse findings	0.4[a]	–
Dog				
Fourteen-week toxicity study (gastric intubation)	0, 0.5, 1.0, 2.0	**Mydriasis, retarded body weight gain**	**0.5***	1.0
Rhesus monkey				
Sixteen-day toxicity study (nasogastric intubation)	0, 0.3, 0.6, 1.2	No adverse findings	1.2[a]	–
Human				
Safety, tolerability and pharmacokinetics study in healthy subjects (oral)	0, 0.4, 0.8, 1.2, 1.5	**No adverse findings**	**1.5[a,]****	–

*** Pivotal study value for the derivation of the ADI (Merck & Co., Inc., 1978)**
**** Pivotal study value for the derivation of the ARfD (Lasseter, 2001)**
[a] Highest dose tested.

In a 14-week study, ivermectin was given orally to rat pups 3–4 weeks of age, obtained from dams treated with ivermectin, at a dose of 0, 0.4, 0.8 or 1.6 mg/kg bw per day. Spleen enlargement and reactive bone marrow hyperplasia were observed in one animal at 0.8 mg/kg bw per day and in three animals at 1.6 mg/kg bw per day. Based on these observations, a lowest-observed-adverse-effect level (LOAEL) of 0.8 mg/kg bw per day was identified, and the NOAEL was 0.4 mg/kg bw per day (Merck & Co., Inc., 1979b). The Committee noted that the study design was not clearly explained and the findings were difficult to interpret.

In a 14-week study, ivermectin was given to dogs (four of each sex per group) by oral gastric intubation at a dose of 0, 0.5, 1.0 or 2.0 mg/kg bw per day. Controls received water or vehicle (sesame oil). At 2.0 mg/kg bw per day, mydriasis was observed in all animals; three males and one female developed tremors, ataxia, anorexia and dehydration, lost body weight (1.0–1.6 kg), were frequently found laterally recumbent and were ataxic when standing. Based on occasional mydriases and a retardation of weight gain in animals, the LOAEL was 1.0 mg/kg bw per day, and the NOAEL was 0.5 mg/kg bw per day (Merck & Co., Inc., 1978).

In a 16-day oral toxicity study, ivermectin was given to immature rhesus monkeys (13–21 months old) at a dose of 0, 0.3, 0.6 or 1.2 mg/kg bw by nasogastric intubation. Controls received vehicle (sesame oil). There were no

treatment-related effects noted in any of the treated animals. A NOAEL of 1.2 mg/kg bw per day, the highest dose tested, was identified (Merck & Co., Inc., 1986).

Long-term oral toxicity or carcinogenicity studies with ivermectin were not available, but the Committee at its thirty-sixth meeting concluded (Annex 1, reference *91*) that given the structural similarities and comparative toxicological profiles of ivermectin and abamectin, such studies were not required. In a 94-week dietary carcinogenicity study in mice using abamectin doses of 0, 2, 4 and 8 mg/kg bw per day, a NOEL (NOAEL) of 4.0 mg/kg bw per day was identified (Merck & Co., Inc., 1982). Furthermore, in a 105-week dietary carcinogenicity study in rats with abamectin doses of 0, 0.75, 1.5 and 2.0 mg/kg bw per day, a NOEL (NOAEL) of 1.5 mg/kg bw per day was identified (Merck & Co., Inc., 1983). The present Committee agrees with these conclusions.

In a reproductive toxicity study, ivermectin was given orally to female rats at a dose of 0, 0.4, 0.8 or 1.6 mg/kg bw per day from 15 days prior to mating until 20 days postpartum. Two control groups received the vehicle (sesame oil). Based on no adverse findings in the dams, a maternal toxicity NOAEL of 1.6 mg/kg bw per day, the highest dose tested, was identified. A statistically significant, treatment-related increase in pup mortality in the 1.6 mg/kg bw per day group was observed on day 1 and days 7–14 postpartum. An offspring toxicity LOAEL of 1.6 mg/kg bw per day was identified, and the offspring toxicity NOAEL was 0.8 mg/kg bw per day (Merck & Co., Inc., 1979a,b).

Three multigeneration reproductive toxicity studies were undertaken in rats. The first two studies failed to establish a NOAEL for ivermectin when given orally to rats at 0.4, 1.2 and 3.6 mg/kg bw per day or 2.0 mg/kg bw per day, respectively (Merck & Co., Inc., 1980, 1981). In a third multigeneration study, rats were given ivermectin orally at 0.05, 0.1, 0.2 or 0.4 mg/kg bw per day. A vehicle control group received sesame oil. Treatment-related effects were limited to a slight, but statistically significant, decrease in body weight gain during the post-weaning period in the F_{1b} females in the 0.4 mg/kg bw per day group and the F_{2b} males in the 0.2 and 0.4 mg/kg bw per day groups. There were no treatment-related effects on the reproductive performance of male or female rats in any dose group. There was no evidence of teratogenicity in the F_3 offspring. The NOAEL for parental, reproductive and offspring toxicity was 0.4 mg/kg bw per day, the highest dose tested (Merck & Co., Inc., 1980, 1981).

3.3 Observations in humans

In a double-blind, randomized, placebo-controlled, multiple-rising-dose study (0, 30, 60, 90 and 120 mg, equivalent to 0, 0.4, 0.8, 1.2 and 1.5 mg/kg bw, respectively, based on median body weight) to investigate the safety, tolerability

and pharmacokinetics of multiple doses of ivermectin, 12 healthy human subjects per dose group were administered oral doses of ivermectin of 30 or 60 mg on days 1, 4 and 7 or single doses of 90 or 120 mg. An additional four healthy human subjects per dose group were administered a placebo. All subjects were fasted prior to dosing. A group of the subjects who received 30 mg were allowed a 1-week washout and then fed prior to administration of a single oral dose of 30 mg ivermectin. All doses of ivermectin were well tolerated. No adverse effects on human health, in particular upon the neurological system, were identified. The NOAEL for acute oral toxicity of ivermectin was determined to be 120 mg, equivalent to 1.5 mg/kg bw, the highest dose tested, based on a median body weight of 77.9 kg (Lasseter, 2001).

Ivermectin has been administered to several million human patients for the treatment of onchocerciasis at a recommended oral dose level of 150 μg/kg bw administered once every 12 months. No signs of acute central nervous system toxicity have been reported. The adverse reactions that have been observed in treated patients have been described as allergic or inflammatory responses resulting from the killing of microfilariae, referred to as the "Mazotti reaction". No significant adverse effects on fetuses have been reported when pregnant women were inadvertently treated with ivermectin.

Ivermectin may also be used in the treatment of lymphatic filariasis, strongiloidiasis and scabies. The treatment of scabies generally requires a single oral dose of 200 μg/kg bw, but two or three repeated doses may be needed, separated by an interval of 1 or 2 weeks, to be fully effective (Dourmishev, Dourmishev & Schwartz, 2005). The sponsor identified a number of reported studies where parasitized patients received up to 13 oral doses of ivermectin (800 μg/kg bw) during the course of treatment. These studies reported that ivermectin was well tolerated and noted no serious adverse health effects. A recent review of the acute toxicity of macrocyclic lactones reported that adverse health effects of ivermectin treatment in patients with onchocerciasis were related not to the dosage of ivermectin, but to the skin microfilarial load (Yang, 2012).

3.4 Microbiological data

Considering the chemical structure and mode of action, the Committee did not anticipate any adverse effects of ivermectin residues on human gastrointestinal microbiota.

4. Evaluation

4.1 Acceptable daily intake

The Committee established an ADI of 0–10 μg/kg bw on the basis of a NOAEL of 0.5 mg/kg bw per day for neurological effects (mydriasis) and retardation of weight gain in a 14-week dog study, with application of an uncertainty factor of 50. The previous ADI of 0–1 μg/kg bw is withdrawn.

The Committee did not consider the human clinical data sufficient to assess the possible long-term effects of repeated exposure to ivermectin, such as would occur from its use as a veterinary drug. Therefore, the Committee identified the 14-week dog study as the most appropriate for use in establishing an ADI, given the non-relevance of effects in the CF-1 mouse and the neonatal rat due to their low expression of P-glycoprotein.

As the interspecies differences in pharmacokinetics between dogs and humans are such that humans would be exposed to less ivermectin at a given dose compared with dogs, a reduction in the interspecies uncertainty factor for pharmacokinetics would be appropriate. The quality of the information on pharmacokinetics in dogs was not sufficient to enable the Committee to calculate accurately a chemical-specific adjustment factor for interspecies differences in pharmacokinetics. A reduction by 50% was used as a conservative estimate. An uncertainty factor of 50, comprising a factor of 5 for interspecies differences and a factor of 10 for intraspecies differences, was therefore adopted.

4.2 Acute reference dose

As ivermectin may be administered to cattle in an injectable form, there is the possibility that humans may be exposed to animal tissue containing high concentrations of ivermectin from the injection site. For this scenario, the Committee evaluated the acute toxicity of the compound to determine the need for establishing an ARfD.

The Committee established an ARfD of 200 μg/kg bw, based on a NOAEL of 1.5 mg/kg bw, the highest dose tested in a safety, tolerability and pharmacokinetics study in healthy human subjects, with application of an uncertainty factor of 10 for intraspecies variability. The Committee identified the human study as the most appropriate study for use in establishing an ARfD, given the non-relevance of the embryo/fetal toxicity findings in juvenile rats due to their low expression of P-glycoprotein. The Committee noted that the ARfD was conservative, as an acute oral LOAEL for ivermectin has not been identified in humans.

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