FINAL

DATA EVALUATION REPORT

IMIDACLOPRID

Study Type: Metabolism

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GUIDELINE SERIES 85-1: Metabolism

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DATA EVALUATION REPORT

STUDY TYPE: Metabolism in rats; Guideline Series 85-1

EPA IDENTIFICATION NUMBERS

Tox. Chem. Number: 497E

EPA P.C. Code: 129099

MRID Numbers:
Part a) 422563-54
Part b) 422563-56
Part c) 422563-57
Part d) 422563-73
Part e) 422563-59
Part f) 422563-58
Part g) 422563-55

TEST MATERIAL: Imidacloprid

Part a) [Methylene-^{14}C] Imidacloprid
Part b) [Methylene-^{14}C] Imidacloprid
Part c) [Imidazolidine-4,5-^{14}C] Imidacloprid
Part d) [Methylene-^{14}C] Imidacloprid and
[Methylene-^{14}C] WAK 3839
Part e) Imidacloprid
Part f) Imidacloprid
Part g) [Methylene-^{14}C] Imidacloprid

SYNONYM: 1-[(6-chloro-3-pyridinyl)methyl]-4,5-dihydro-N-nitro-1H-imidazol-2-amine]; NTN 33893™

SPONSOR: Parts a, b, c, and g) Miles Inc., Stilwell, KS
Parts d, e, f) Mobay Corporation, Stilwell, KS

TESTING FACILITY: Parts a, b, c, d, and g) Bayer AG, Leverkusen-Bayerwerk, Germany
Parts e and f) Mobay Corporation, Stilwell, KS

AUTHORS:
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TITLE OF REPORTS:

Part a) [Methylene-[^{14}C] Imidacloprid: Metabolism Part of the General Metabolism Study in the Rat

Part b) [^{14}C]-NTN 33893: Biokinetic Part of the "General Metabolism Study" in the Rat

Part c) [Imidazolidine-4,5-^{14}C] Imidacloprid: Investigation of the Biokinetic Behavior and Metabolism in the Rat

Part d) Imidacloprid - WAK 3839: Comparison of Biokinetic Behavior and Metabolism in the Rat Following Single Oral Dosage and Investigation of the Metabolism after Chronic Feeding of Imidacloprid to Rats and Mice

Part e) A Liquid Chromatographic Method for the Determination of NTN 33893 in Aqueous Dose Mixtures

Part f) A Liquid Chromatographic Method for the Determination of NTN 33893 in Inhalation Chamber Atmospheres

Part g) [^{14}C]-NTN 33893: Investigations on the Distribution of the Total Radioactivity in the Rat by Whole-Body Autoradiography

REPORT NUMBERS:
Part a) M 182 0176-5
Part b) M 181 0175-3
Part c) M 31819004
Part d) M 71810016
Part e) 99875
Part f) 99874
Part g) M 181 0177-5

REPORTS ISSUED:
Part a) January 30, 1990
Part b) September 30, 1987
Part c) January 11, 1991
Part d) July 17, 1990
Part e) February 22, 1990
Part f) February 22, 1990
Part g) November 20, 1987

CONCLUSIONS: Imidacloprid was rapidly absorbed and eliminated in the excreta (90% of the dose within 24 hours) demonstrating no biologically significant differences between sexes, dose levels, or route of administration. Elimination was mainly renal (70%-80% of the dose) and fecal (17%-25%). The major part of the fecal radioactivity originated in the bile. Total body accumulation after 48 hours constituted 0.5% of the radioactivity with the liver, kidney, lung, skin, and plasma being the major sites of accumulation. Therefore, bioaccumulation of Imidacloprid is low in rats. Maximum plasma concentration was reached between 1.1 and 2.5 hours. Two major routes of biotransformation were proposed for Imidacloprid. The first route included an oxidative cleavage of the parent compound rendering 6-chloronicotinic acid and its glycine conjugate. Dechlorination of this metabolite formed the 6-hydroxy

nicotinic acid and its mercapturic acid derivative. The second route included the hydroxylation followed by elimination of water of the parent compound rendering NTN 35884.

A comparison between [methylene-^{14}C]-Imidacloprid and [imidazolidine-4,5-^{14}C]-Imidacloprid showed that, while the rate of excretion was similar, the renal portion was higher with the imidazolidine-labeled compound. In addition, accumulation in tissues was generally higher with the imidazolidine-labeled compound.

A comparison between Imidacloprid and one of its metabolites, WAK 3839, showed that the total elimination was the same for both compounds. The proposed metabolic pathways for these two compounds were different. WAK 3839 was formed following pretreatment (repeated dosing) of Imidacloprid.

CORE CLASSIFICATION: Acceptable. These studies meet the requirements set forth under Guideline Series 85-1 for a metabolism study in rats.

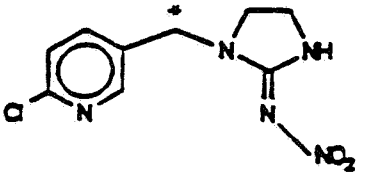
MATERIALS

Parts a and b

Imidacloprid

Purity:	99.9%
Contaminants:	None reported
Description:	Colorless crystals
Radiochemical purity:	>99% by HPLC and TLC
Specific activity:	150.7 μCi/mg
Batch numbers: (non-labeled compounds)	APF 08128650 and 880208ELB01

Chemical structure:



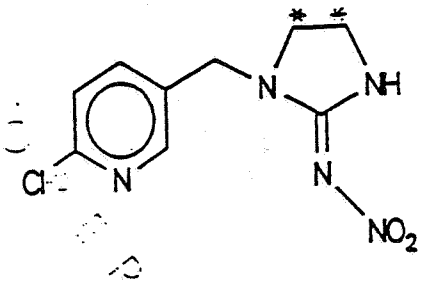
* denotes [^{14}C] labeling

Part c

Imidacloprid

Purity:	>99%
Contaminants:	None reported
Description:	Colorless crystals
Radiochemical purity:	>99%
Specific activity:	124 μCi/mg (low dose) 0.827 μCi/mg (high dose)
Batch numbers: (labeled compounds)	KML 16094 (low dose) 890315ELB01 (high dose)

Chemical structure:



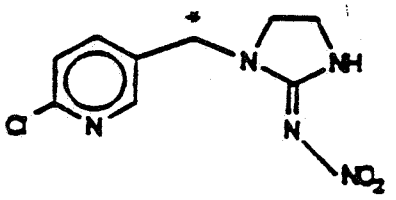
* denotes [^{14}C] labeling

Part d

Imidacloprid

Purity:	>99%
Contaminants:	None reported
Description:	Solids
Radiochemical purity:	>99%; 98.4%
Specific activity:	86.4 μCi/mg (low dose) 91.8 μCi/mg (high dose) 123 μCi/mg (pretreatment)
Batch numbers: (labeled compounds)	KML 1417, KML 1705

Chemical structure:

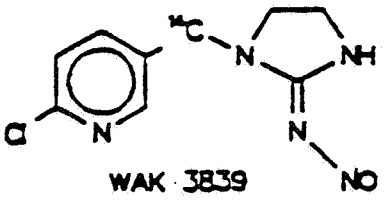


* denotes [^{14}C] labeling

WAK 3839

Purity:	>99%
Contaminants:	None reported
Description:	Solids
Radiochemical purity:	WAK 3839, 97.8-98.5%
Specific activity:	40.2 μCi/mg (low dose) 50.43 μCi/mg (isotope dilution rat) 128.8 μCi/mg (isotope dilution mouse)
Batch numbers: (labeled compounds)	TSH 3520, TSH 3550, TSH 3552

Chemical structure:



WAK 3839

* denotes [^{14}C] labeling

Vehicle (all studies): Physiological saline or 0.5% Tragacanth

Test Animals (all studies)

Species:	Rat
Strain:	Wistar BOR: WISW (SPF Cpb)
Source:	Winkelmann Versuchstierzucht GmbH & Co., Borchen, Germany
Age:	Not reported
Weight:	Approximately 200 g (individual data not submitted)

Animal husbandry (all studies)

Acclimation time was not reported. During the excretion studies, animals were housed in metabolism cages to allow for collection of the excreta; during other studies, animals were housed in plastic cages on wood shavings. Each animal was given 15 g of food per day (Altromin 1324 Standard Food, 4937 Lage, Germany). Water was available ad libitum throughout the study. During the nonradioactive pretreatment period and bile-fistulation portion of the studies, temperature and humidity were controlled at 20°C and 40%-80%, respectively. It was stated that during the test period, the animals were kept at room temperature; however, temperature and humidity were not specified.

Study Design

These studies were designed to assess the absorption, distribution, metabolism, and excretion of Imidacloprid when administered intravenously or via oral gavage to rats; when labelled at different molecular sites; and when compared to its metabolite, WAK 3839 (Parts a-d). Also, acute versus chronic exposure was compared as well as species differences following chronic exposure in the diet (Part d).

Group arrangement

Animals were randomized by lot for all experiments. The following experiments/groups were designed for the various investigative parts.

Parts a and b: Studies were designed to evaluate distribution, metabolism, and excretion of Imidacloprid, when administered intravenously or orally (single and repeated dosing studies).

Studies	Dose	Males	Females
Expired CO_2 experiment	20.0 mg/kg (oral)	5	--
Low-dose experiment	1.0 mg/kg (i.v.)	5	5
Low-dose experiment	1.0 mg/kg (oral)	5	5
High-dose experiment	20.0 mg/kg (oral)	5	5
Chronic low-dose experiment[a]	1.0 mg/kg (oral)	5	5
Bile-fistulation experiment[b]	1.0 mg/kg (intraduodenal)	5	--
High-dose experiment[c]	20.0 mg/kg (oral)	5[d]	--

[a]Nonradiolabeled 1.0 mg/kg/day for 14 days followed by radiolabeled 1.0 mg/kg/day on day 15
[b]Experiment conducted to quantify the absorbed amount of the total radioactivity and to determine the rate and extent of biliary excretion.
[c]Experiment conducted to fulfill Japanese MAFF requirements.
[d]Four groups of 5 animals per group were killed after 40 minutes, 1.5, 3, and 6 hours and tissue accumulations were evaluated.

Part c: Studies were designed to identify and compare metabolites of [methylene-^{14}C]-labelled Imidacloprid versus [imidazolidine-4,5-^{14}C]- labelled Imidacloprid when administered orally to rats.

Studies	Dose	Males	Females
Expired CO_2 experiment	1.0 mg/kg	5	--
Low-dose experiment	1.0 mg/kg	5	5
High-dose experiment	150.0 mg/kg	5	--

Part d: Studies were designed to identify and compare metabolites of [methylene-^{14}C]-labelled Imidacloprid versus [methylene-^{14}C]-labelled WAK 3839 (a metabolite of Imidacloprid) when administered orally (including non-radioactive pretreatment) to rats.

Studies	Volume	Dose	Males
Imidacloprid low-dose	10 mL	1.0 mg/kg	5
WAK 3839	10 mL	1.0 mg/kg	5
Imidacloprid high-dose	10 mL	150.0 mg/kg	7
Imidacloprid chronic[a]	2 mL	80.0 mg/kg	10

[a]Animals were pretreated with a diet containing 1800 ppm unlabelled Imidacloprid for one year then received an oral dose of ^{14}C-Imidacloprid.

Dosing Solutions (all studies)

For oral administration, the test material was administered in a volume of 10 mL/kg. For intraduodenal administration, the volume was 1 mL/kg. For i.v. administration, the volume was not specified. Test solutions, both labeled and unlabeled, were prepared by dissolving the test substance in physiological saline using an ultrasonic water bath at 70°C or by suspending the test substance homogeneously in 0.5% Tragacanth. Solutions were prepared immediately prior to administration with the exception of the nonradioactive portion of the chronic low-dose experiment, in which doses to be administered over the weekend were prepared the preceding Friday. The solutions were stable for 48 hours as demonstrated by thin layer chromatography. Methods for quantifying Imidacloprid concentrations in aqueous dose mixtures and in liquid aerosol atmosphere of inhalation chambers were described separately (MRID Nos. 422563-59 and 422563-58; Parts e and f, respectively).

Sample Collection (all studies)

Urine samples were collected for intervals 0-4, 4-8, 8-24, and 24-48 hours following dosing (deviations from these intervals are indicated in the tables). The cage rinsing solutions were collected in the urine containers. Radioactivity in urine, extracts, and solutions was determined by liquid scintillation counting (LSC).

Feces were collected for intervals 0-24 and 24-48 hours following dosing. Samples were lyophilized and homogenized prior to extraction, and then prepared for LSC.

Tissues were collected after 48 hours and included: plasma, erythrocytes, spleen, gastrointestinal tract, liver, bile, kidney, testis, muscle, bone, heart, lung, brain, skin, uterus, ovary, and renal fat. They were lyophilized and combusted in an oxygen atmosphere before radioactive determination. Radioactivity in both solids and liquid samples were determined by LSC.

Metabolite Analysis

Parts a and b: Major metabolites were isolated from the 6-hour urines and feces by HPLC. Minor metabolites were isolated from the 24-hour urines and feces. Five major and four minor fractions were obtained and further purified and analyzed by spectroscopic methods (e.g., gas chromatography, mass spectrometry, and/or nuclear magnetic resonance spectroscopy). Metabolites were identified with reference compounds.

Part c: Metabolites were isolated from the high-dose 0-24-hour urine sampling. Following several purification procedures, two peak groups appeared, which were further analyzed by NMR and mass spectroscopy. Metabolite analyses were not conducted on fecal samples since the fecal elimination route consisted of only 6%-8% of the administered dose.

Part d: Metabolites in urine were identified using renal samples from the 0-4 and 4-24-hour intervals combined and the alkaline solvent system for quantification. Metabolites in feces were identified using fecal samples from the 0-24-hour intervals which were lyophilized, extracted with water, and then further purified before being chromatographed.

Compliance

- Statements of No Data Confidentiality Claims, signed and dated, were provided.
- Statement of Compliance with EPA, OECD, and/or MAFF GLPs, signed and dated, were provided.
- Statements of Quality Assurance, signed and dated, were provided.

RESULTS

ELIMINATION AND RECOVERY

Parts a and b: More than 90% of the administered radioactivity was recovered in the tissues and excreta within 48 hours postexposure after oral and i.v. dosing (Tables 1 and 2). No biologically significant differences were observed between the sexes or with regard to route of administration and dose level. A slight difference in excretion of Imidacloprid was observed between males and females at the high-dose. The females excreted more of the radioactivity via urine than did males (Table 2). After 24 hours, renal elimination accounted for approximately 67%-78% of excreted radioactivity in all groups, while fecal elimination accounted for approximately 16%-24% in males and females (Table 1). After 48 hours, these values had increased to 69%-80% and 17%-25%, respectively. The tissues accounted for approximately 0.5% of the radioactivity (Table 2). For both sexes, irrespective of route of administration and dose level, the major sites for radioactive accumulation were liver, kidney, lung, skin, and plasma; the minor sites were brain and testis (Appendices I and II). Time was not a significant factor when considering tissue distribution of radioactivity.

The 'expired air'-experiment demonstrated that no significant amount of radioactivity was expired in male rats over 48 hours (Table 2), thus indicating that the labeling position within the molecule was stable under *in vivo* conditions.

The 'bile-fistulated'-experiment demonstrated that the major part of the fecal radioactivity originated in the bile (Table 2). Bile-fistulated animals excreted 5% in the feces versus 37% in the bile.

Part c: In the metabolism and biokinetic parts of the imidazolidine-4,5-^{14}C-labeled Imidacloprid studies, >99% of the administered radioactivity was also recovered within 48 hours in all groups (Table 3). Again, no biologically significant differences were observed between the sexes or with regard to dose level. After 24 hours, renal elimination accounted for approximately 76%-93% of excreted radioactivity, while fecal elimination accounted for 4%-8% (Table 3). After 48 hours, these values had increased to 90%-94% for renal elimination and 6%-8% for fecal elimination. The tissues accounted for approximately 1% of the radioactivity (Table 3). For both sexes, irrespective of dose level, the major sites of radioactive accumulation were liver, kidney, lung, and skin (Appendix III); the minor sites were brain and muscle. In addition, the female values were slightly lower than the male values.

The 'expired air'-experiment (data not shown) demonstrated that no significant amount of radioactivity (0.111% of recovered radioactivity) was expired in male rats over 48 hours. This indicated that the labeling position within the molecule was stable under *in vivo* conditions.

Part d: In the comparison of methylene-labelled Imidacloprid and WAK 3839 (see page 6 for the chemical structure), no significant differences were noted in the absorption, distribution, and excretion of the total radioactivity. The renal/fecal elimination rate was ≈3:1. Forty-eight hours after oral administration of 1 mg/kg Imidacloprid and 1 mg/kg WAK 3839, 77% and 73% of the given dose, respectively, were eliminated via urine, while 21% and 14%, respectively, were eliminated via feces (Table 4). The final amount was similar for both compounds. Fecal elimination was almost complete within 24 hours for both compounds. In general, the pretreatment group showed similar renal and fecal excretion patterns as single dose groups.

Although more radioactivity was found in the tissues of the Imidacloprid animals, total body accumulation was <1% for both compounds at the low-dose level (Table 4). In the Imidacloprid high-dose group, 3% of administered radioactivity was recovered. Main sites of accumulation included skin, lung, liver, and kidney for Imidacloprid animals, while it included lung, renal fat, liver and kidney for WAK 3839 animals (Appendix IV). For both compounds, testis and brain were the minor sites of accumulation.

Part g: In a separate whole-body radiography study, it was further demonstrated that tissue distribution of Imidacloprid was not time-dependent. In this qualitative experiment, male rats were investigated 1, 4, 8, and 48 hours after oral administration or 5 minutes after i.v. administration of 20 mg/kg methylene-labeled Imidacloprid (data not shown). The relative tissue distribution did not change significantly over time, although the amount of radioactivity rapidly diminished. As estimated from the radiograph, within

the first hour, major accumulation of radioactivity was detectable in the liver, kidney, adrenal, muscle, skin, walls of the aorta, stomach, and small intestine, connective tissue attached to the spinal cord, and salivary, cowperian, and thyroid glands. Minor accumulation was noted in the lungs, fat, brain, testis, and the mineral part of the bones. After 24 hours, no radioactivity was observed in the stomach, but radioactivity was accumulating in the intestine. After 48 hours, the only tissues above the detection limit were skin, nasal mucosa, liver, kidney, thyroid, walls of the aorta, and the connective tissue attached to the spinal cord. Overall, these results were in agreement with the quantitative tissue distribution studies.

PHARMACOKINETICS

Part b: For methylene-labeled Imidacloprid, plasma curve analysis demonstrated that the compound was absorbed immediately with <2.5 minutes of calculated lagtime for all dose groups. The maximum relative concentration in plasma was between 1.1 and 2.5 hours. The compound and its metabolites were easily distributed into peripheral compartments as demonstrated by the distribution volume under steady state conditions (roughly equal). The average distribution half-life was 35 minutes. Elimination half-lives (calculated from two exponential terms) were 3 and 26-118 hours.

Part c: For imidazolidine 4,5-^{14}C-labeled Imidacloprid, one hour after low-dose administration and 4 hours after high-dose administration, maximum plasma concentrations were reached in males; 1.5 hours after low-dose administration it was reached in females. Terminal elimination half-lives were dose dependent. They were 21.34 hours (females) and 24.89 hours (males) for low-dose animals and 9.04 hours for high-dose males (females not evaluated). The mean residence time was longer for the high-dose animals (low-dose: 9.0 hours [males] and 8.56 hours [females]; high-dose: 14.25 hours). Consequently, the renal excretion rate was slightly slower, although the same amount of radioactivity was eliminated in the urine at the end of the test period.

Part d: In the studies comparing methylene-labeled Imidacloprid and WAK 3839, the time-course of the plasma levels were similar for both Imidacloprid and WAK 3839. Absorption started immediately and estimated distribution half-lives were ≈22 minutes. The two compounds differed with regard to maximum plasma concentration of the radioactivity (0.77 hours for WAK 3839; 1.16 hours for Imidacloprid). Significant differences were observed in the pharmacokinetic basic parameters, in total and renal clearance, and in distribution volume at steady state. No significant differences were noted in terminal half-lives, areas under the curves, and mean residence times.

METABOLISM

Part a: In the metabolism part of the methylene-labeled Imidacloprid studies, identified metabolites were found in both sexes and all dose groups. No biologically significant differences were observed in the pattern of excretion with regard to sex, dose level, and route of administration. Two major routes of biotransformation were evident. The first route included an

oxidative cleavage of the parent compound rendering 6-chloronicotinic acid and its glycine conjugate. Dechlorination of this metabolite formed the 6-hydroxy nicotinic acid and its mercapturic acid derivative. The second route included the hydroxylation of imidazolidine followed by elimination of water of the parent compound rendering NTN 35884. A summary of results is presented in Tables 5 and 6. The proposed degradation pathway is presented in Figure 1.

Urinary metabolites (Table 5) consisted of WAK 3583 (males: 17%-28%; females: 19%-24%), 5-OH-Imidacloprid (WAK 4103) (males: 16%-18%; females: 15%-16%), NTN 35884 (males: 9%-13%; females: 8%-9%), chloronicotinic acid (males: 4%-8%; females: 3%-8%), and the parent compound, Imidacloprid (males: 9%-14%; females: 11%-15%). A glycine conjugate of 6-S-CH_3-nicotinic acid appeared as a minor metabolite, accounting for 2%-6% (males and females) of the recovered radioactivity. NTN 33823 was not detected in the urine.

Fecal metabolites (Table 6) consisted of NTN 33823 (males and females: 2%-3%), glycine conjugate of 6-S-CH_3-nicotinic acid (males and females: 1%-2%), NTN 35884 (males and females: 1%-2%), and the parent compound, Imidacloprid (males and females: 1%-2%). WAK 3583, WAK 4103, and chloronicotinic acid were not detected in the feces.

There were minor differences between dose and sex groups. The amount of unchanged parent compound in excreta was slightly higher after i.v. low-dosing than after oral low-dosing. Males formed slightly more 6-chloro-nicotinic acid and WAK 3583 in the urine than did females after iv or oral low-dosing. Nonradioactive pretreatment in animals produced less WAK 3583 and more 6-chloronicotinic acid formation in both sexes as compared to single oral low-dosing. The amount of unchanged parent compound was higher and the amount of NTN 35884 was lower in excreta of females than of males after oral high-dosing.

Part c: No significant differences were observed in the pattern of excretion of various metabolites with regard to sex. However, there was a dose-related difference and a metabolic saturation may have occurred after high oral dosing. In the high-dose males, the amount of KNO 0523 was reduced to 19% and the amount of NTN 33968 and the parent compound was increased to 15% and 14%, respectively, as compared to the low-dose males. Urinary metabolites at 24 hours after oral administration of [imidazolidine-4,5-^{14}C]-Imidacloprid is presented in Table 7.

Renal metabolites included KNO 0523, NTN 33968, WAK 4103, NTN 35884, and the parent compound. Together, they constituted 73%-83% of the recovered urinary radioactivity. An unidentified metabolite accounted for 10%-18% of the radioactivity. Due to its linkage to very polar matrix components, this metabolite could not be identified but this metabolite should comprise the imidazolidine moiety only. In addition, the urinary metabolites of Imidacloprid were already completely identified by the previous analysis of fecal metabolites of [methylene-^{14}C] Imidacloprid.

Fecal metabolites were not identified since they constituted only 6.2%-11.2% of recovered radioactivity. In addition, the previous analysis of fecal metabolites of [methylene-^{14}C] Imidacloprid identified more than 50% of the fecal metabolites.

A comparison between the two differently labeled Imidacloprid compounds (Table 8) showed that, while the rate of excretion was similar, the renal portion was higher with the imidazolidine-labeled compound (90% versus 75% with the methylene-labeled compound; see Tables 2 and 3). In addition, accumulation of radioactivity in tissues was low (<1% of administered dose) and, in general, higher with the imidazolidine-labeled compound. A qualitative comparison with regard to metabolites demonstrated that, as long as the metabolites contained both heterocycles, they rendered the same kind of metabolites (i.e., parent compound, WAK 4103, and NTN 35884). A quantitative comparison between these same metabolites (Table 8) demonstrated that they were of the same order regardless of labeling moiety. The proposed degradation pathway is presented in Figure 2.

Part d: In the studies comparing methylene-labeled Imidacloprid and WAK 3839, the identification of renal and fecal metabolites in the low-dose groups demonstrated different metabolic pathways (Tables 9 and 10). The following metabolites in urine and feces were found in Imidacloprid animals after 24 hours postexposure: 6-chloronicotinic acid (7% of total recovered radioactivity); WAK 3583 (25%); NTN 35884 (10%); WAK 3839 (0.5%); WAK 4103 (14%); and unchanged parent compound (11%). In the WAK 3839 animals, only unchanged parent compound (63%) and NTN 33823 (6%) were found in the excreta after 24 hours postexposure.

WAK 3839 formed at a higher rate during chronic feeding of Imidacloprid. The amount of WAK 3839 excreted in the urine of single-dosed rats was comparative to the trace impurity contained in the radioactive batch of Imidacloprid indicating no *in vivo* formation of this metabolite (Table 9). However, the amount of WAK 3839 excreted in the pretreated rats showed an increasing amount from 1% at 0-7 hours to 17% at 24-48 hours (Table 9), which is further supported by the findings of the isotope analysis in urine from chronically fed rats and mice. Rats and mice were fed 1800 and 2000 ppm of Imidacloprid, respectively, for one year, then received a single oral dose of [methylene-^{14}C]-WAK 3839 (Study Nos. T303005 and T4029986). The concentrations of WAK 3839 were estimated to be 9 and 1.5 mg/100 mL urine in rats and mice, respectively. The proposed metabolic pathways are presented in Figure 3.

REVIEWERS' DISCUSSION/CONCLUSIONS

The methylene-labelled Imidacloprid was rapidly absorbed following a calculated lagtime of <2.5 minutes and eliminated in the excreta (90% of the dose within 24 hours; 96% within 48 hours) demonstrating no biologically significant differences between sexes, dose levels, or route of administration. Elimination was mainly renal (70%-80%) with less contribution from feces (17%-25%). The major part of the fecal radioactivity originated in the bile. Total body accumulation after 48 hours constituted only 0.5% of the radioactivity with the liver, kidney, lung, skin, and plasma being the major sites of accumulation. Maximum plasma concentration was reached between 1.1 and 2.5 hours. Elimination half-lives were 3 and 26-118 hours. Two major routes of biotransformation were evident. The first route included an oxidative cleavage of the parent compound rendering 6-chloronicotinic acid and its glycine conjugate. Dechlorination of this metabolite formed the 6-hydroxy nicotinic acid and its mercapturic acid derivative. The second route included

the hydroxylation followed by elimination of water of the parent compound rendering NTN 35884.

A comparison between [methylene-^{14}C] Imidacloprid and [imidazolidine-4,5-^{14}C] Imidacloprid demonstrated that, while the rate of excretion was similar, the renal portion was higher with the imidazolidine-labeled compound (90% versus 75% with the methylene-labeled compound). In addition, accumulation in tissues was generally higher with the imidazolidine-labelled compound. As long as the metabolites contained both heterocycles, they rendered the same kind of metabolites (parent compound, WAK 4103, and NTN 35884).

A comparison between Imidacloprid and one of its metabolites, WAK 3839, showed that the renal elimination of WAK 3839 was faster although the total elimination was the same for both compounds (Part d). The proposed metabolic pathways for these two compounds were different. WAK 3839 was formed following pretreatment (repeated dosing) of Imidacloprid.

These studies have been classified as Acceptable based on well executed designs and more than adequate data reporting. Every study (reported and referred to) has been described in adequate detail and fulfilled the Guideline requirements. However, the overall data reporting would have greatly benefited from an overall summary of study designs, strategies, results, and conclusions.

TABLE 1. Percent Recovery of Administered Radioactivity After I.V. or Oral Administration of Imidacloprid (Parts a and b)[a]

Fraction	Dose Group (% of Administered Dose) i.v. 1 mg/kg	p.o. 1 mg/kg	p.o. 1 mg/kg pretreatment	p.o. 20 mg/kg
		Males		
URINE				
0 to 4 hours	26.18	22.52	13.20	28.86
0 to 8	61.26	56.77	44.70	56.06
0 to 24	72.72	71.23	67.32	72.15
0 to 48	73.43	72.57	69.04	73.26
FECES				
0 to 24 hours	18.83	19.63	21.90	20.70
0 to 48	19.34	20.26	23.83	21.25
TOTAL RECOVERY	92.78	92.83	92.87	94.51
		Females		
URINE				
0 to 4 hours	27.27	29.78	19.30	27.39
0 to 8	52.51	55.86	38.86	50.41
0 to 24	70.79	70.76	69.64	77.81
0 to 48	72.53	72.42	71.83	79.50
FECES				
0 to 24 hours	16.06	24.45	20.58	16.79
0 to 48	17.45	25.45	22.74	17.14
TOTAL RECOVERY	89.99	97.87	94.57	96.64

[a]Data were extracted from Study No. M 182 0176-5, Table I.

TABLE 2. Percent Recovery of Radioactivity 48 Hours After I.V. or Oral Administration of Imidacloprid (Parts a and b)[a]

Fraction	Dose Group (% of Recovered Radioactivity)					
	i.v. 1 mg/kg	p.o. 1 mg/kg	p.o. 1 mg/kg pretreatment	p.o. 20 mg/kg	p.o. 20 mg/kg CO_2 test	i.d. 1 mg/kg bile test
			Males			
CO_2					0.033	
BILE						36.57
URINE	78.71	77.77	73.80	76.99	75.77	57.52
FECES	20.73	21.71	25.47	22.33	23.61	4.78
BODY	0.56	0.52	0.72	0.68	0.58	1.13
TOTAL	100	100	100	100	100	100
			Females			
URINE	80.21	73.68	75.43	81.89		
FECES	19.30	25.89	23.88	17.66		
BODY	0.50	0.42	0.69	0.45		
TOTAL	100	100	100	100		

[a]Data were extracted from Study Nos. M 182 0176-5, Table II-b and M 181 0175-3, Table 3.

TABLE 3. Percent Recovery of Radioactivity After Oral Administration of [Imidazolidine-4,5-^{14}C] Imidacloprid (Part c)[a]

Fraction	Dose Group (% of Administered Dose)			
	1 mg/kg male	1 mg/kg female	150 mg/kg male	female
URINE				
0 to 4 hours	41.31	39.41	9.97	NR[b]
0 to 8	76.32	70.10	31.29	NR
0 to 24	88.80	92.59	75.76	NR
0 to 48	89.88	93.79	90.69	NR
FECES				
0 to 24 hours	8.09	6.08	4.40	NR
0 to 48	8.44	6.30	7.50	NR
URINE + FECES RECOVERY	98.32	100.09	98.19	NR
BODY	1.00	0.63	1.14	NR
TOTAL RECOVERY	99.32	100.72	99.33	NR

[a]Data were extracted from Study No. M 31819004, Tables I and III.

[b]Not reported

TABLE 4. Percent Recovery of Radioactivity After Oral Administration of Imidacloprid and WAK 3839 (Part d)[a]

Fraction	Dose Group (% of Administered Dose)			
	Imidacloprid 1 mg/kg	WAK 3839 1 mg/kg	Imidacloprid 150 mg/kg	Imidacloprid 80 mg/kg (chronic)
URINE				
0 to 4 hours	39.09	51.51	5.25	8.32
0 to 8	68.47	69.62	16.26	16.91[b]
0 to 24	76.71	72.38	46.75	71.96
0 to 48	77.29	72.71	74.16	79.76
FECES				
0 to 24 hours	20.83	14.04	6.75	5.96
0 to 48	21.37	14.26	19.73	16.62
URINE + FECES RECOVERY	98.66	86.97	93.92	97.86
BODY	0.886	0.224	3.42	--
TOTAL RECOVERY	99.55	87.19	97.31	97.86

[a]Data were extracted from Study No. M 71810016, Tables I and IV.

[b]Urine was measured after 7 hours instead of 8 hours.

TABLE 5. Percent Recovery of Radioactive Metabolites in Urine 24 Hours After I.V. or Oral Administration of Imidacloprid (Parts a and b)[a]

Fraction	Dose Group (% of Recovered Radioactivity)			
	i.v. 1 mg/kg	p.o. 1 mg/kg	p.o. 1 mg/kg pretreatment	p.o. 20 mg/kg
		Males		
6-Chloronicotinic acid	7.61	4.29	7.03	7.22
Glycine conjugate of 6-S-CH_3-nicotinic acid	2.32	2.73	4.01	2.49
WAK 3583	25.90	28.11	16.58	23.61
NTN 35884	9.05	9.89	12.63	13.22
WAK 4103[b]	15.97	16.86	18.23	17.34
Imidacloprid	13.68	11.32	10.52	8.92
TOTAL IDENTIFIED	74.53	73.20	69.00	72.80
UNASSIGNED[c]	4.17	4.57	4.80	4.20
TOTAL RECOVERY	78.70	77.77	73.80	77.00
		Females		
6-Chloronicotinic acid	5.57	3.22	5.92	8.15
Glycine conjugate of 6-S-CH_3-nicotinic acid	5.08	5.13	5.70	3.16
WAK 3583	21.66	24.11	18.89	24.23
NTN 35884	8.75	8.61	9.23	8.07
WAK 4103[b]	16.27	14.84	14.99	15.96
Imidacloprid	14.80	11.30	12.52	15.37
TOTAL IDENTIFIED	72.13	67.21	67.25	74.94
UNASSIGNED[c]	8.08	6.48	8.18	6.95
TOTAL RECOVERY	80.21	73.69	75.43	81.89

[a]Data were extracted from Study No. M 182 0176-5, Tables VIII - XV.

[b]Includes 4-OH-Imidacloprid

[c]Includes metabolites 6-hydroxynicotinic acid, 6-methylmercaptonicotinic acid, and the S-Mercapturic acid derivative of nicotinic acid; not quantitated separately due to small amount

TABLE 6. Percent Recovery of Radioactive Metabolites in Feces 24 Hours After I.V. or Oral Administration of Imidacloprid (Parts a and b)[a]

Fraction	Dose Group (% of Recovered Radioactivity) i.v. 1 mg/kg	p.o. 1 mg/kg	p.o. 1 mg/kg pretreatment	p.o. 20 mg/kg
		Males		
Glycine conjugate of 6-S-CH_3-nicotinic acid	1.76	1.98	2.00	2.37
NTN 35884	1.32	1.13	1.20	1.71
NTN 33823	2.64	2.34	3.36	2.18
Imidacloprid	1.63	2.10	1.49	0.91
TOTAL IDENTIFIED	7.35	7.55	8.05	7.17
UNASSIGNED[b]	6.08	6.96	6.04	6.50
TOTAL RECOVERY	13.43	14.51	14.09	13.67
		Females		
Glycine conjugate of 6-S-CH_3-nicotinic acid	1.44	1.91	1.63	1.09
NTN 35884	0.81	1.34	1.07	0.58
NTN 33823	2.40	2.43	2.96	2.21
Imidacloprid	2.22	1.88	1.50	0.53
TOTAL IDENTIFIED	6.87	7.56	7.16	4.41
UNASSIGNED[b]	4.33	5.36	6.24	5.22
TOTAL RECOVERY	11.20	12.92	13.40	9.63

[a]Data were extracted from Study No. M 182 0176-5, Tables VIII - XV.

[b]Includes metabolites 6-hydroxynicotinic acid, 6-methylmercaptonicotinic acid, and the S-Mercapturic acid derivative of nicotinic acid; not quantitated separately due to small amount

TABLE 7. Percent Recovery of Radioactive Metabolites in Urine 24 Hours After Oral Administration of [Imidazolidine-4,5-^{14}C] Imidacloprid (Part c)[a]

Metabolite	Dose Group (% of Recovered Urinary Radioactivity)		
	1 mg/kg male	1 mg/kg female	150 mg/kg male
KNO 0523	34.7	29.6	19.1
NTN 33968	8.0	15.7	18.4
WAK 4103	14.7	13.7	14.6
NTN 35884	8.4	7.7	9.1
Imidacloprid	6.9	16.5	14.2
TOTALLY IDENTIFIED	72.7	83.2	75.4
UNKNOWN[b]	17.8	10.0	16.0
TOTAL	90.6	93.2	91.4

[a]Data were extracted from Study No. M 31819004, Table VI.

[b]The unknown radioactivity represents one single metabolite. This metabolite was "linked to very polar matrix components which prevented further structural elucidation procedures." This metabolite should comprise the imidazolidine moiety only.

TABLE 8. Percent Recovery of Radioactive Metabolites in Urine 24 Hours After Oral Administration of [Imidazolidine-4,5-^{14}C] Imidacloprid and [Methylene-^{14}C] Imidacloprid (Part c)[a]

	Dose Group (% of Recovered Urinary Radioactivity)			
	[Imidazolidine-4,5-^{14}C] 1 mg/kg		[Methylene-^{14}C] 1 mg/kg	
Metabolite	Male	Female	Male	Female
KNO 0523	34.7	29.6		
WAK 3583			28.1	24.1
NTN 33968	8.0	15.7		
6-Cl-Nicot. acid			4.3	3.2
6-S-CH_3-Nicot. acid			2.7	5.1
WAK 4103	14.7	13.7	16.9	14.8
NTN 35884	8.4	7.7	9.9	8.6
Imidacloprid	6.9	16.5	11.3	11.3
TOTALLY IDENTIFIED	72.7	83.2	73.2	67.1

[a]Data were extracted from Study No. M 31819004, Table VII.

TABLE 9. Percent Recovery of Radioactive Metabolites in Urine 24 Hours After Oral Administration of Imidacloprid or WAK 3839 (Part d)[a]

Metabolite	Dose Group (% of Total Recovered Radioactivity)						
	Imidacloprid 1 mg/kg		WAK 3839 1 mg/kg		Imidacloprid 80 mg/kg (chronic)		
Sampling period (hours)	0-4	4-24	0-4	4-24	0-7	7-24	24-48
6-Chloronicotinic acid	8.68	7.10			12.43	7.27	2.97
WAK 3583	33.84	29.38			31.50	21.89	0.62
NTN 35884	10.08	12.38			18.18	17.71	15.27
WAK 3839	0.33	0.76	82.16	59.40	1.36	11.41	17.24
WAK 4103[b]	16.43	20.74			6.07	14.14	11.36
NTN 33823			6.12	9.86			
Imidacloprid	14.03	11.08			20.70	10.49	5.32
TOTALLY IDENTIFIED	83.39	81.44	88.28	69.26	90.24	82.91	52.78
UNASSIGNED	16.61	18.57	11.71	30.74	9.85	17.09	47.23
TOTAL	100.00	100.01	99.99	99.98	100.09	100.00	100.01

[a]Data were extracted from Study No. M 71810016, Table VI.

[b]Includes 4-OH-Imidacloprid

TABLE 10. Percent Recovery of Radioactive Metabolites in Urine and Feces 24 Hours After Oral Administration of Imidacloprid or WAK 3839 (Part d)[a]

Metabolite	Dose Group (% of Total Recovered Radioactivity) Imidacloprid 1 mg/kg	WAK 3839 1 mg/kg
6-Chloronicotinic acid	6.51	
WAK 3583	24.61	
NTN 35884	9.51	
WAK 3839	0.42	62.76
WAK 4103[b]	14.29	
NTN 33823		5.98
Imidacloprid	10.60	
TOTALLY IDENTIFIED	65.58	68.74
UNASSIGNED	32.41	14.28
TOTAL	97.99	83.02

[a]Data were extracted from Study No. M 71810016, Table X.

[b]Includes 4-OH-Imidacloprid

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