12-27-90

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

008241

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

Subject: Review of Petition for tolerance and registration for FOLICUR Technical fungicide, Folicur 1.2 EC and Elite 45 DF
I.D. Nos. 3125-GIG, 9F3724, 9H5575
Record No. 248,430; 248,431; 248,433
Tox Chem No. 463P
HED Project No. 9-1815

From: James N. Rowe, Ph.D., Head James N. Rowe 12/27/90
Review Section III
Toxicology Branch II
Health Effects Division (H7509C)

To: Ms. Susan Lewis/Mr. Benjamin Chambliss
Product Manager, Team 21
Fungicide-Herbicide Branch
Registration Division (H7505C)

Thru: Marcia van Gemert, Ph.D., Chief
Toxicology Branch II
Health Effects Division (H7509C)

ACTION: Mobay Corporation, Agricultural Chemicals Division, has submitted a petition for pesticide tolerance and registrations for FOLICUR Technical fungicide, Folicur 1.2 EC and Elite 45 DF.

A. Tolerances are proposed for residues of tebuconazole (α-[2-(4-Chlorophenyl)ethyl]-α-(1,1-dimethylethyl)-1H-1,2,4-triazole-1-ethanol) in or on the following commodities:

Commodity	Preharvest interval (days)	Proposed toler. (ppm)
Barley, grain	28	2.0
Barley, green forage	28	5.0
Barley, straw	28	5.0
Grapes	14	2.0
Grass, seed cleanings (incl. hulls)	5	25.0

Commodity (continued)	Preharvest interval (days)	Proposed toler. (ppm)
Grass, seed straw (incl. chaff)	5	30.0
Peanuts	14	0.05
Peanut hulls	14	3.5
Peanut hay	14	50.0
Wheat, grain	28	0.40
Wheat, green forage	28	4.5
Wheat, straw	28	50.0
FOOD ADDITIVE TOLERANCE PROPOSAL		
Barley, milled fractions (except flour)		1.0
Wheat, milled fractions (except flour)		1.0
Raisins	14	3.0
FEED ADDITIVE TOLERANCE PROPOSAL		
Grape pomace (wet)		4.0
Grape pomace (dry)		12.0
Raisin waste		6.0

B. Tolerances are proposed for combined residues of tebuconazole and its 1-(4-chlorophenyl)-4,4-dimethyl-3-(1H-1,2,4-triazole-1-yl-methyl)-pentan-3,5-diol metabolite in the following commodities:

Commodity	Proposed Tolerance (ppm)
Eggs	0.02
Meat, fat & meat byproducts of poultry	0.05
Meat, fat & meat byproducts of cattle, goats, hogs horses & sheep	0.15
Milk	0.01

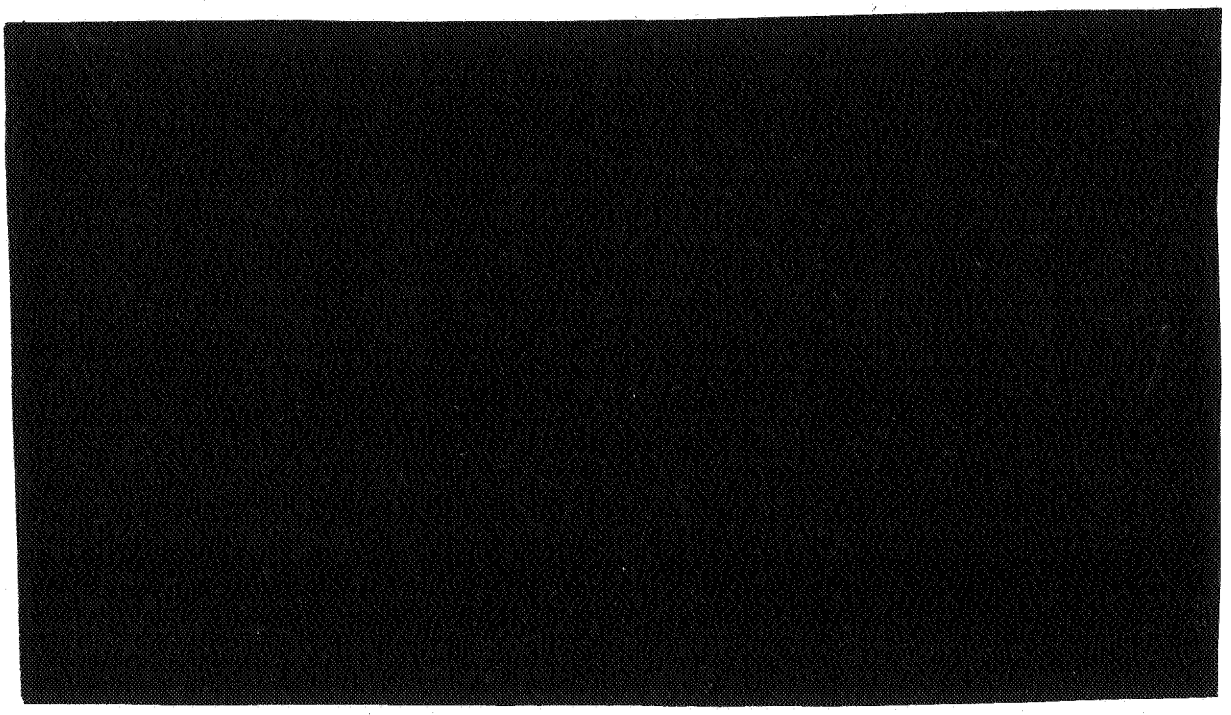
DISCUSSION

1. Technical material data requirements/toxicology issues

Evaluation of the toxicology data base for Tebuconazole Technical indicates that a mouse oncogenicity study and a metabolism study remain data gaps for registration of the technical material. The registrant has indicated that they are in the process of generating a new 18-month feeding study in the mouse to fill this data gap. In addition, the metabolism and dermal absorption studies submitted by the registrant have recently been reviewed by the Toxicology Branch. The dermal penetration study was found acceptable but the metabolism study was classified as supplementary data (see attached reviews). There is no indication that Tebuconazole has a carcinogenicity issue based on the two chronic studies in the rat and mouse submitted.

Developmental toxicity NOELs in oral studies in the rat, mouse and rabbit have been noted at 10 to 30 mg/kg/day while a dermal teratology study in the rat has reported a develcpmental toxicity NOEL of 1000 mg/kg or greater (technical material). It is anticipated that the HED Developmental Toxicity Peer Review Committee will examine the issue of the potential human developmental effects of Tebuconazole.

2. Acute data for formulations:



RECOMMENDATIONS:

Toxicology Branch II objects to the granting of permanent tolerances for food and feed crops and recommends that the registration of the 2 product formulations be delayed until the technical material is fully registered and potential toxicological endpoints, including carcinogenesis and developmental toxicity, have been fully evaluated. This includes receipt of an acceptable mouse oncogenicity study and additional information for the general metabolism study for Tebuconazole Technical. [redacted]

Based upon the developmental toxicity issue, it is further recommended that an analysis of the exposure potential of workers mixing and applying this material to crops as well as bystander exposures be performed. Results of this analysis should be forwarded to Toxicology Branch II for determination of tentative margins-of-exposure ("safety").

cc F. Griffith (H7509C)
A. Schlosser (H7509C)

Reviewed by: Alberto Protzel, Ph.D. 12/19/90
Section III, Tox. Branch II(H7509C)
Secondary reviewer: James N. Rowe, Ph.D. 12/19/90
Section III, Tox. Branch II(H7509C)

DATA EVALUATION REPORT

STUDY TYPE: Primary dermal irritation in rabbits; TOX. CHEM NO: 463P
EPA Guideline 81-5

ACCESSION NUMBER: MRID NO.: 409959-10

TEST MATERIAL: FOLICUR® Technical grade

SYNONYMS: Tebuconazole

STUDY NUMBER: 88-323-AV

SPONSOR: Mobay Corporation

TESTING FACILITY: Mobay Corporation, Corporate Toxicology Department, Stilwell, KS

TITLE OF REPORT: Primary Dermal Irritation of Technical Grade FOLICUR® in Rabbits.

AUTHOR(S): L.P. Sheets

REPORT ISSUED: October 4, 1988

CONCLUSION:

Toxicity Category: IV

Core Classification: CORE minimum.

Primary Skin Irritation Rating: Not a primary dermal irritant.

MATERIALS:

1. Test compound: Tebuconazole: Technical grade, 96.6% active, Description: Crystalline solid, Batch #: 86R0082I, Purity: 96.6% a.i.

2. Test animals: Species: rabbit, Strain: New Zealand White; Age: 17 weeks; Weight: unspecified, Source: Small Stock Industries, Pea Ridge, Arkansas.

METHODS:

Six young adult rabbits (3 males, 3 females) were shaved (6-cm^2 area) and were dermally treated with a single application of the test material. The test material (500 mg) was moistened with tap water, applied to the shaved area of skin and covered with gauze and a plastic square and secured with adhesive

bandage. An adjacent, untreated area was used as control. Four hours after treatment, dressings were removed and test areas were wiped with paper towels dampened with tap water for scoring for erythema and edema. Treated sites were scored for erythema and edema at 0.5-1, 24, 48, and 72 hours after r moval of the patch.

RESULTS:

Individual results and irritation grades were presented; these results (0.0 at all times for all animals) indicated that the test material did not induce a primary skin irritation response in the six test animals at any of the scoring intervals up to 72 hours after patch removal.

It is concluded that technical Folicur is not a primary dermal irritant.

A signed quality assurance statement and a signed GLP compliance statement were present.

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Page _____ is not included in this copy.

Pages 7 through 8 are not included in this copy.

The material not included contains the following type of information:

___ Identity of product inert ingredients

___ Identity of product impurities

___ Description of the product manufacturing process

___ Description of product quality control procedures

___ Identity of the source of product ingredients

___ Sales or other commercial/financial information

___ A draft product label

___ The product confidential statement of formula

X Information about a pending registration action

___ FIFRA registration data

___ The document is a duplicate of page(s) _____

___ The document is not responsive to the request

The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.

Reviewed by: Alberto Protzel, Ph.D. 12/19/90
Section III, Toxicology Branch II(H7509C)
Secondary Review by: James N. Rowe, Ph.D. 12/19/90
Review Section III, Toxicology Branch II(H7509C)

00824

DATA EVALUATION RECORD

Study Type: Metabolism - Pharmacokinetics (Oral dosing).
Species: Rat
Guideline: 85-1

EPA Identification Nos.: EPA MRID Nos. 409959-11 and 409959-12
EPA ID No.
EPA Record No.
EPA Pesticide Chemical Code
Caswell No. 463P
HED Project No. 9-1815
Document No. 97438 and 97439

Test Material: [Phenyl-UL-^{14}C] HWG 1608 and [Triazole-3,5-^{14}C] HWG 1608

Synonyms: Tebuconazole; α-[2-(4-Chlorophenyl)ethyl]-α-(1,1-dimethylethyl)-1H - 1,2,4-triazole-1-ethanol

Sponsor: Mobay Corporation

Study Number(s): M 181089-7 (Document 97439); M 181088-6, M 181090-9, M 1810131-5, M 182091-1, M 182092-2, & M 1820133-8 (Document 97438)

Testing Facility: BAYER AB
Institute of Metabolism Research
Monheim
Federal Republic of Germany

Title of Reports: The metabolism study was submitted in two volumes: Document No. 97438 (MRID 409959-11; metabolite characterization): "FOLICUR^{R}: Metabolism part of the general metabolism study in the rat."; Document No. 97439 (MRID 409959-12; pharmacokinetics): "[Phenyl-U-^{14}C] HWG 1608: Study of biokinetic behavior in the rat."

Author(s): W. Ecker, A. Brauner, O. Klein, and H. Weber (for Document 97438). H. Weber (for Document No. 97439).

Report Issued: December 21, 1987 (Document No. 97438). October 6, 1987 (Document No. 97439).

Conclusions: The metabolism of [phenyl-UL-^{14}C]- and [triazole-3,5-^{14}C]labeled HWG 1608 [tebuconazole] was studied im male and female Wistar rats. The phenyl-labeled compound was administered as a single oral dose of 2 or 20 mg/kg or as a single oral dose of 2 mg/kg following oral administration of unlabeled HWG 1608 at 2 mg/kg/day for 14 days. The triazole-labeled compound was administered

as a single oral dose of 20 mg/kg.

At least 98.1% of a single oral dose (2 mg/kg) of [phenyl-UL-^{14}C] HWG 1608 administered to bile fistulated male Wistar rats, appeared to have been absorbed, based on 48-hour data for bile and urine excretion. Total recovery of radioactivity 72 hours after dosing accounted for 94 to 100% of the low dose and 87 to 97% of the high dose. Approximately 14 to 33% of the dose was eliminated in the urine and 61 to 82% of the dose was eliminated in feces, with no apparent differences between the two dose groups. After dosing with the [^{14}C] phenyl-labeled compound, males excreted significantly less radioactivity in the urine (14 to 17% of the dose) than females (29 to 33% of the dose); in the case of the [^{14}C] triazole-labeled compound there were no sex-dependent differences in the urine to feces ratio of radioactivity excretion. At sacrifice total radioactive residue in the body, excluding the GI tract, amounted to 0.34 to 0.54% of the dose at the low dose level and to 0.24 to 0.63% of the dose at the high dose level in rats dosed with the phenyl-labeled compound. Experiments with male bile-fistulated rats indicated that, at least in low-dose males, the test material (and/or its metabolites) undergo enterohepatic circulation and that radioactivity in feces may be attributed largely to biliary excretion. Elimination of radioactivity in expired air as $^{14}CO_2$ amounted to 0.03% of the dose over a 72-hour collection period.

A total of ten compounds were identified in excreta, amounting to 50.9-58.3% of the dose in males and 67.9-71.3 % of the dose in females dosed with [phenyl-UL-^{14}C] HWG 1608. Only three of those compounds (HWG 2443, HWG 2061, and HWG 1608) were identified with reference to synthetic standards. Of the other seven (9.6-14.9% of the dose), six were identified tentatively based on GC/MS and NMR patterns but without comparison to synthetic standards, and thus remain as putative metabolites. The untransformed parent compound, was present in small amounts (0.5-2.2% of the dose). A large fraction of the identified metabolites corresponded to successive stages in the oxidation of one of the methyl groups in the t-butyl moiety of HWG 1608. Hydroxylated HWG 1608 ("diol") plus its sulfate (ECW 4390) and glucuronide (ECW 4393) amounted to 16.2-20.0% of the dose in males and to 25.7-34.2% of the dose in females; the product of further oxidation to the carboxylic acid ("acid", WWG 2443) amounted to 14.1-32.5% of the dose in males and to 29.7-36.1% of the dose in females.

Dose-dependant changes in metabolite ratios were reported. These changes are suggestive of changes in detoxication patterns at the high dose resulting from metabolic saturation.

Although no statement of compliance with EPA GLP was provided for the pharmacokinetics part of this study (MRID 409959-12), a statement indicating that a GLP requirements of 40 CFR Part 160 do not apply to this study was supplied.

Classification: Core Supplementary. This study may be upgraded if the following additional information is provided and is judged to be acceptable:

1) A rationale for dose selection is required. The change in metabolite ratios observed at the high-dose suggests a possible trend towards changes in detoxication patterns at the high-dose.

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2) Additional work of metabolite identification at a dose higher than 20 mg/kg would be required to elucidate the apparent trend in metabolite patterns observed at the current high dose.

3) A discussion of the origin of the isopropyl derivative (HWG 2251) is required. HWG 2251 is not depicted in the author's scheme for the biotransformation pathways of HWG 1608 and its origin is not discussed in the text.

4) A rationale as to why GLP requirements of 40 CFR Part 160 do not apply to this study should be submitted.

5) A statement indicating whether the rats were acclimated prior to dosing should be included.

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A. Materials

A copy of the "Materials and methods" section from each one of the study reports is appended.

Test Compound:

Pharmacokinetic studies (Document No. 97439):

[Phenyl-U-^{14}C] HWG 1608,
Radiochemical purity >99%
Specific activity: 84.4 µCi/mg (at 2 mg/kg, low dose) or 8.4 µCi/mg (at 20 mg/kg, high dose).

Non radioactive HWG 1608,
Purity: 99.5%
Batch No.: APF 13028500
Contaminants: not listed.

Metabolite characterization (Document No. 97438):

[Phenyl-U-^{14}C] HWG 1608,
Radiochemical purity >99%
Although the specific activity was indicated to be "84.4 µCi/mg", it was not indicated to which dose it corresponded. Thus, in effect, the specific activity of the administered material was not given.

[Triazole-3,5-^{14}C] HWG 1608,
Radiochemical purity 98.4%
The specific activity was indicated as "56.5 µCi/mg", however the specific activity at the time of compound administration was not indicated.

Non radioactive HWG 1608,
Purity: 99.5%
Batch No.: APF 13028500
Contaminants: not listed.

Vehicle: 0.5% aqueous tragacanth.

Test Animal(s): Species: rat
Strain: Wistar BOR: WISW (SPF Cpb)
Source: Winkelman, Borchen
Age: Unspecified
Weight: Document 97439: 195-217g (males); 190-207g (females)
Document 97438: average weight of 200g.

B. Study Design

This study was designed to assess the absorption, tissue distribution,

metabolite patterns, and excretion of HWG 1608 when administered as a single oral dose to rats of both sexes. The study was submitted in two volumes: MRID 409959-11 (Document No. 97438, metabolite patterns) and MRID 409959-12 (Document No. 97439, pharmacokinetics).

Group Arrangements:

For pharmacokinetic studies, as summarized in Table 1, one group of rats was used in a preliminary experiment to study the excretion of radioactivity in expired air, one group of rats with biliary fistulae was used to study gastrointestinal absorption, and six groups of rats (two groups per sex) were used to study tissue distribution and excretion of [phenyl-UL-^{14}C] HWG 1608.

For metabolite characterization studies, six groups of rats (two groups of 5 rats/sex) were administered [phenyl-UL-^{14}C] HWG 1608, according to the same dosing protocol as that shown in Table 1 for the study of tissue distribution and excretion (i.e. low dose, low dose with pretreatment, and high dose). In addition, three groups of rats (two groups of 5 males and one group of 5 females), received a single oral dose of [triazole-3,5-^{14}C] HWG 1608 at 20 mg/kg.

Table 1. Dosing groups for pharmacokinetic studies of HWG 1608.

Test type	Test Group	[^{14}C] HWG-1608 (mg/kg)	Number	Remarks
Excretion of [^{14}C] in expired air	-	20	5 male	Preliminary experiment
Absorption	-	2	5 male	-
Tissue distribution and excretion	Low dose	2	5/sex	-
	Low dose with pretreatment	2	5/sex	Pretreatment with non-radioactive HWG 1608 once a day for 14 days, followed by a single dose of [Phenyl-U-^{14}C] HGW 1608
	High dose	20	5/sex	-

Dosing and sample collection

All doses were given as a suspension in 0.5% aqueous tragacanth in a volume of 10 ml/kg of body weight. The test material was administered by stomach tube

immediately after the preparation of the suspension. The test material was found by TLC to be stable in the suspension for at least 4 hours, however no support data were given. Concentrations of each administration suspension were measured radiometrically; however, no dose-verification data were furnished by the registrant. In addition, it was not reported whether the rats were acclimated to laboratory conditions prior to dosing.

Radioactively-dosed rats were placed in metabolism cages that allowed separate collection of urine and feces.

a. Pharmacokinetic studies

In the preliminary experiment, urine, feces and expired [^{14}C] CO_2 were collected separately and radioassayed at various time points up to 72 hours after dosing, at which time the animals were sacrificed for analysis of residual tissue radioactivity. In the GI absorption experiment, urine, feces and bile were collected separately at various time points up to 48 hours, at which time the rats were sacrificed for determination of residual radioactivity. Bile was collected from bile fistulated rats at 1, 2, 3, 4, 6, 8, 12, 18, 24, 30, 36, 42, and 48 hours after dosing. In the tissue distribution and excretion experiment, blood, urine and feces were collected at various time points up to 72 hours post-dosing, at which time the animals were sacrificed for determination of residual radioactivity in tissues. The following tissues/organs were sampled and radioassayed: liver, spleen, kidney, perirenal fat, testis, ovaries, uterus, muscle, femur, skin, plasma, erythrocytes, heart muscle, brain, lung, residual carcass, GI tract.

b. Metabolite characterization studies

For the animals dosed with [phenyl-UL-^{14}C] HWG 1608, urine and feces were collected at various time points up to 72 hours after dosing, at which time the animals were sacrificed. In the case of the rats dosed with [triazole-3,5-^{14}C] HWG 1608, urine and feces were collected at various time points up to 48 hours for the group of females and one of the male groups; and for up to 72 hours for the remaining male group.

Structural characterization of metabolites was done with urine and feces of the high-dose groups treated with either [phenyl-UL-^{14}C] or [triazole-3,5-^{14}C] HWG 1608. Methanol extracts of lyophilized feces, unextracted urine, and ether extracts of urine were analyzed by micropreparative HPLC. Purified metabolite fractions were examined by gas chromatography/mass spectrometry (GC/MS) and by proton nuclear magnetic resonance spectrometry (NMR). Of nine metabolites thus examined, the structures of only three of them [HWG 2443, HWG 2061, and triazole] were confirmed by comparison with GC/MS and NMR patterns of synthetic reference compounds. Structural characterization of the other six metabolites [ECW Nos. 4393, 4390, 4373, 4908, 4886, and 4882] was limited to interpretation of the GC/MS and NMR patterns, no comparisons with synthetic standards were reported. Quantification of metabolites in urine and feces of the various dose groups was done by analytical HPLC; fractions were identified by co-chromatography with the nine confirmed or putative metabolite markers plus authentic parent compound (HWG 1608) and a non hydroxylated analog, HWG 2251 (i.e. a total of 11 compounds). Up to 6 solvent systems were used in analytical HPLC.

Compliance:

A signed Statement of No Confidentiality Claim was provided for both documents (Nos. 97438 and 97439).

No Statement of Compliance with EPA GLP was included with document 97439 (MRID 409959-12). Instead, a statement indicating that GLP requirements of 40 CFR Part 160 do not apply to the study reported in document 97439 was included. A signed Statement of Compliance with EPA GLP was included with document 97438 (MRID 409959-11); it was indicated, however, that GLP requirements of 40 CFR Part 160 do not apply to the study reported in document 97438.

A signed Quality Assurance Statement was provided for both documents (Nos. 97438 and 97439).

Results

a. Pharmacokinetic studies

Preliminary experiment

Results from a preliminary experiment indicated that in male rats only 0.0304% of the dose was eliminated (as [^{14}C] CO_2) in the expired air. Elimination in the urine accounted for an average 16.2% and elimination in feces accounted for 75.8% of the administered radioactivity over a 72 hour period after dosing.

Absorption

Data for 48-hour [^{14}C] excretion in urine and bile (Table 1) indicated that at least 98.1% of a single oral dose of [phenyl-UL-^{14}C] HWG 1608 (2 mg/kg) was absorbed by bile fistulated male Wistar rats. This value for percent absorption is taken as a lower limit, because an additional 1.49% of the administered radioactivity was recovered in feces and might be attributed to test material being absorbed and then secreted and/or diffused through the GI mucosa. An additional undetermined, but small, fraction of the dose was presumably excreted as exhaled [^{14}C] CO_2. Studies to determine the fraction of dose absorbed were not done for other dose groups.

Table 2. Excretion of radioactivity following a single oral dose of [phenyl-UL-^{14}C] HWG 1608 to male rats with biliary fistulae.[1]

Time after dosing (hours)	Mean excreted radioactivity (as % of dose)			
	Urine	Feces	Bile	Total
1	0.000267	-[2]	15.03	15.03
2	0.000575	-	39.24	39.24
4	2.37	-	61.66	64.03
8	5.53	-	85.82	91.35
24	7.26	1.45	89.64	96.90
36	7.39	-	90.54	97.43
48	7.40	1.49	90.68	99.57

1. Values are means of 4 animals, due to death of one rat after dosing. Data are from Table 12, Document 97439, p. 44.

2. - = No data.

Tissue distribution and excretion

i. Single Low Dose

Seventy-two hours following administration of a single dose of [phenyl-UL-^{14}C] HWG 1608 (2 mg/kg) to rats, approximately 99.2% of the dose was accounted for in males and 96.1% of the dose was accounted for in females (Table 3). Elimination in the urine accounted for about 16.3% of the dose in males and 32.9% in females. Elimination in the feces accounted for about 82.1% of the dose in males and 62.5% in females. Significant sex differences ($p < 0.01$) were found (Table 3) in the amount of radioactive residue present in the body at sacrifice and in the amount of radioactivity excreted in urine or feces over the 72-hour collection period. Most of the radioactivity was eliminated in urine and feces within 48 hours after dosing. Plasma levels of radioactivity were obtained through 72 hours. Total body clearances were found to be 0.71 ml/min for males and 1.35 ml/min for females (based on the AUC values determined from the plasma radioactivity curves), and were significantly lower in males ($p < 0.01$). At sacrifice, total radioactive residue in body (excluding GI tract) amounted to 0.54 and 0.34% of the dose in males and females, respectively. Highest residue levels (Table 4) were noted in liver (0.066 µg/g in males 0.072 µg/g in females). Lower levels were found in kidney, brain, heart, gonads, lungs, spleen, and fat (0.0025 to 0.013 µg/g) for both sexes, with higher values generally found in males.

ii. Low Dose with Pretreatment

Seventy-two hours after a single dose of [phenyl-UL-^{14}C] HWG 1608 (2 mg/kg) following pretreatment with non-radioactive HWG 1608 for 14 days, approximately 94.9% of the dose was accounted for in males and 95.2% of the dose was accounted for in females (Table 3). Values for elimination of radioactivity in feces and

urine were similar to those obtained after the same single dose of [phenyl-UL-^{14}C] HWG 1608 (2 mg/kg) but without pretreatment with non-radioactive HWG 1608.

Table 3. Recovery of radioactivity in tissues and excreta of rats 72 hours after a single oral dose of [Phenyl-UL-^{14}C] HWG 1608.

Matrix	Percent of radioactive dose recovered with					
	2 mg/kg		Pretreatment plus 2 mg/kg		20 mg/kg	
	M[1]	F	M	F	M[2]	F
GI tract	0.25	0.35	0.41	0.96	0.39 (0.39)	0.30
Body minus GI tract	0.54	0.34	0.67	0.42	0.42 (0.63)	0.24
Urine	16.31	32.89	15.00	32.33	14.35 (16.94)	28.80
Feces	82.11	62.48	78.77	61.46	72.11 (78.73)	62.73
Total	99.21	96.06	94.85	95.17	87.28 (96.72)	92.07

1. M = male; F = female.

2. Values in parentheses were obtained after repetition of the trial with a new group of animals. Data were compiled by the reviewer from Tables 2 (p.34) and 3 (p.35) of document 97439.

iii. Single High Dose

Seventy-two hours after a single dose of 20 mg/kg to rats, approximately 87.3-96.7% of the dose was accounted for in males and 92.1% of the dose was accounted for in females (Table 3). Elimination in the urine accounted for about 14.4-16.9% of the dose in males and 28.8% in females. Elimination of radioactivity in the feces accounted for about 72.1-78.7% of the dose in males and 62.7% in females. As in the case of the low-dose rats, significant sex differences were found at 20 mg/kg (Table 3) in the amount of radioactive residue present in the body at sacrifice and in the amount of radioactivity excreted in urine or feces over the 72-hour collection period. Most of the radioactivity was eliminated in urine and feces within 48 hours after dosing. Plasma levels of radioactivity were obtained through 72 hours. Total body clearances were found to be 0.64 ml/min for males and 1.35 ml/min for females (based on the AUC values determined from the plasma radioactivity curves), and were significantly lower in males ($p < 0.01$). At sacrifice, total radioactive residue in the body (excluding the GI tract) amounted to 0.42-0.63 and 0.24% of the dose in males and females respectively. Highest residue levels (Table 4) were noted in GI tract (0.74-0.67 µg/g in males; 0.6 ug/g in females) and in liver (0.53-0.61 ug/g in males; 0.57 µg/g in females). Lower levels were found in kidney, brain, heart, gonads, lungs, spleen, and fat (0.015 to 0.34 µg/g) for both sexes, with higher values generally found in males.

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Table 4. Distribution of radioactivity in rat tissues/organs /2 hours after single oral dosing with [^{14}C] HWG 1608[1].

Tissue/ Organ	Relative concentration of radioactivity[2]					
	2 mg/kg		Pretreatment plus 2 mg/kg		20 mg/kg	
	M[3]	F	M	F	M[4]	F
Liver	0.03300	0.03620	0.03320	0.03980	0.02630 (0.03050)	0.02840
Spleen	0.00517	0.00243	0.00780	0.00279	0.00481 (0.00533)	0.00293
Kidney	0.01290	0.00501	0.01130	0.00681	0.01510 (0.01680)	0.00299
Perirenal fat	0.00511	0.00269	0.01010	0.00451	0.00610 (0.00152)	0.00391
Testis	0.00437	-	0.00515	-	0.00368 (0.00439)	-
Ovaries	-	0.00359	-	0.00530	-	0.01260
Uterus	-	0.00397	-	0.00653	-	0.00077
Muscle (femoral)	0.00275	0.00127	0.00258	0.00155	0.00285 (0.00366)	0.00089
Bone (femur)	0.00236	0.00136	0.00348	0.00127	0.00209 (0.00288)	0.00174
Skin	0.00729	0.00257	0.00488	0.00415	0.00410 (0.00683)	0.00139
Plasma	0.01500	0.00614	0.01470	0.00692	0.00761 (0.01730)	0.00426
Erythrocytes	0.01080	0.00367	0.01000	0.00440	0.01080 (0.01530)	0.00212
Heart	0.00245	0.00263	0.00600	0.00311	0.00741 (0.01040)	0.00181
Brain	0.00208	0.00124	0.00270	0.00141	0.00428 (0.00448)	0.00084
Lung	0.00191	0.00474	0.00973	0.00639	0.01030 (0.01210)	0.00325
Residual carcass	0.00363	0.00186	0.00609	0.00222	0.00377 (0.00536)	0.00137
GI tract	0.02760	0.02590	0.04110	0.09920	0.03680 (0.03330)	0.02980
Body minus GI tct.	0.00605	0.00347	0.00745	0.00423	0.00468 (0.00718)	0.00265

1. Data are means of 5 animals. Data for males at 2 mg/kg (with and without pretreatment) are from Table 7, ,Document 97439 (p.39); data for males at 20 mg/kg are from Tables 7 and 32, Document 97439 (pages 39 and 65, respectively); and all data for females are from Table 8, Document 97439 (p. 40).

2. Relative concentration of radioactivity -
(Radioactivity in tissue per gram of tissue)/(Radioactivity administered per gram of body weight).
Actual ug equivalents of HWG 1608 per gram of tissue are obtained by multiplying the values in Table 3 by the administered dose (i.e. 2 or 20 mg/kg).

3. M - males; F - females.

4. Values in parentheses were obtained from a repetition of the experiment.

In addition to the excretion data obtained in the pharmacokinetic studies and summarized in Table 3, additional excretion data were obtained from the rats dosed with [phenyl-UL-^{14}C] HWG 1608 or [triazole-3,5-^{14}C] HWG 1608 for characterization of metabolites in excreta. Excretion data for rats dosed with [phenyl-UL-^{14}C] HWG 1608 are presented in Table 5, and are very similar to those presented in Table 3; in particular the same sex-dependent patterns in excretion of radioactivity are evident. On the other hand, excretion data for rats dosed with [triazole-3,5-^{14}C] HWG 1608, which are summarized in table 5, suggest that there is no sex dependent pattern in urine/feces excretion of radioactivity for anirals dosed with [triazole-3,5-^{14}C] HWG 1608.

Table 5. Recovery of radioactivity in tissues and excreta of rats 72 hours after single oral dosing with [Phenyl-UL-^{14}C] HWG 1608 for metabolite analysis.

Matrix	Percent of radioactive dose recovered with					
	2 mg/kg		Pretreatment plus 2 mg/kg		20 mg/kg	
	M[1]	F	M	F	M	F
GI tract	0.44	0.30	0.58	0.41	0.88	1.31
Body minus GI tract	0.31	0.27	0.48	0.58	0.49	0.41
Skin	0.07	0.04	0.13	0.13	0.13	0.05
Urine	14.6	33.6	16.8	31.4	14.5	24.1
Feces	77.1	60.6	80.3	65.0	77.2	67.5
Total[2]	92.5	94.8	98.3	97.5	93.2	93.4

1. M = male; F = female.

2. Results rounded to nearest tenth.

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Table 6. Recovery of radioactivity in t ues and excreta of rats after single oral dosing with [triazole-3,5-^{14}C] HWG ? (for metabolite analysis.

Matrix	Percentage of radioactive dose recovered in: Trial 1[1] (Males)	Trial 2 (Males)	Trial 3 (Females)
Body	0.4	5.9	3.0
Urine	19.3	24.0	24.5
Feces	77.2	70.7	72.7
Total	96.9	100.6	100.2

1. Each trial used of the indicated sex. Animals were dosed with a single oral dose [triazole-3,5-^{14}C] HWG 1608 at 20 mg/kg. Excreta were collected for 72 hours for trial 1 and for 48 hours for trials 2 and 3. Data from Table 3, Document 97438 (p. 29).

b. Metabolite characterization studies:

The results of HPLC analysis of feces and urine collected 0 to 48 hours after dosing with [phenyl-UL-^{14}C] HWG 1608 are presented in Table 7. The results in Table 7 are a recalculation by the reviewer expressing the amounts of metabolites as percent of administered dose, based on percentages of metabolites in urine and feces reported by the authors. It is noted that the data in table 7 represent upper boundaries for values, because no data were available for the reviewer to assess independently the fraction of material lost or otherwise unaccounted for.

A total of ten compounds (Table 7 and Appendix 1) were identified in excreta of animals dosed with [phenyl-UL-^{14}C] HWG 1608, amounting to 50.9-58.3% of the dose in males and 67.9-71.3 % of the dose in females. It is noted that the identities of only 3 of these compounds (HWG 2443, HWG 2061, and HWG 1608) were obtained by reference to synthetic standards. The identities of the remaining 6 were obtained by reference to structures tentatively identified by GC/MS and proton NMR without recourse to synthetic standards. It is not clear from the data if the identity of HWG 2251 involved the use of a synthetic standard.

The untransformed parent compound, was present in small amounts (0.5-2.2% of the dose). A large fraction of the identified metabolites corresponded to successive stages in the oxidation of one of the methyl groups in the t-butyl moiety of HWG 1608. Hydroxylated HWG 1608 ("diol") plus its sulfate (ECW 4390) and glucuronide (ECW 4393) amounted to 16.2-20.0% of the dose in males and to 25.7-34.2% of the dose in females; the product of further oxidation to the carboxylic acid ("acid", WWG 2443) amounted to 14.1-32.5% of the dose in males and to 29.7-36.1% of the dose in females. A phenolic compound ("phenol", ECW 4882) was present at 2.4-3.4% of the dose in low-dose males, 3.1-3.2% of the dose in low-dose females, and 4.6-5.2% of the dose in high-dose rats. Compound HWG 2251, an analogue of HWG 1608 with a isopropyl chain instead of a t-butyl chain, was present at levels of 0.3-1.1% of the dose. The authors did not discuss the origin of this compound. No metabolites resulting from the release of the triazole moiety were identified, even though free triazole constitutes 5.4-1.5% of the urinary radioactivity in rats dosed with [triazole-3,5-^{14}C] HWG 1608. A group of 5 metabolites (M1-M5, in Table 7) comprising up to 10.7% of the dose in high-dose males remains to be identified and discussed by the authors.

The results of HPLC analysis of urine collected 0 to 48 hours after dosing with [triazole-3,5-^{14}C] HWG 1608 are presented in Table 8, as percent of total recovered radioactivity (data were not available for recalculation as percent of the dose). Seven metabolites, comprising 13.8-18.0% of the recovered radioactivity were identified. Hydroxylated HWG 1608 ("diol") plus its sulfate (ECW 4390) and glucuronide (ECW 4393) amounted to 2.7% of the recovered radioactivity in males and to 5.9% of the recovered radioactivity in females; the product of further oxidation to the carboxylic acid ("acid", WWG 2443) amounted to 1.6% of the dose in males and to 9.7% of the dose in females. Free triazole (ECW 4895/2, identified with respect to a synthetic standard) was a major urinary metabolite in males, amounting to 5.4% of the recovered radioactivity in males and only 1.5% in females. Approximately 43 and 25% of the urinary radioactivity remained unidentified in male and female rats,

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respectively.

Table 7. Metabolite profiles in excreta of rats dosed orally with [phenyl-UL-^{14}C] HGW 1608.

Compound[2]	Percent of administered dose[1]					
	2mg/kg		Pretreatment plus 2 mg/kg		20 mg/kg	
	M	F	M	F	M	F
HWG 2443 ("acid")	32.5	36.1	26.9	35.2	14.1	29.7
ECW 4393 2/2 ("diol glucuronide")	0.5	4.8	0.3	3.1	0.2	3.7
ECW 4390 ("diol sulfate")	0.0	2.0	0.1	2.1	0.1	2.3
HWG 2061 ("diol")	15.7	18.9	16.8	21.6	19.7	28.2
ECW 4873 ("keto acid")	3.5	1.2	5.7	0.8	2.3	1.0
ECW 4908 ("triol glucuronide")	1.3	0.0	0.7	0.0	1.1	0.0
ECW 4886 ("triol")	1.3	0.5	2.2	0.7	5.5	0.4
ECW 4882 ("phenol")	2.4	3.1	3.4	3.2	4.6	5.2
HWG 2251	0.6	0.7	0.6	0.8	1.1	0.3
HWG 1608 ("parent")	0.5	0.6	0.6	0.5	2.2	0.5
Total identified:	58.3	67.9	57.3	68.0	50.9	71.3
M1	1.4	1.1	1.2	0.9	1.0	0.7
M2	2.0	0.6	1.5	0.6	3.5	0.2
M3	1.7	0.1	1.0	0.2	2.4	0.2
M4	0.9	0.7	1.3	0.7	2.2	0.9
M5	0.5	0.3	0.9	0.3	1.6	0.3
Unassigned	19.7	20.0	25.9	21.4	20.3	13.7
Residual solids	7.0	3.7	7.7	4.3	9.5	4.4
Residue in body	0.8	0.6	1.2	1.1	1.5	1.8
Total unidentified:	34.0	27.1	40.7	29.5	42.0	22.2
Total accounted for[3]:	92.3	95.0	98.0	97.5	92.9	93.5
Lost/unaccounted:	7.7	5.0	2.0	2.5	7.1	6.5
Total:	100.0	100.0	100.0	100.0	100.0	100.0

1. Sum of excretion in urine plus feces. Values were calculated by the reviewer using the data for percent of radioactive dose recovered in urine, feces, and body (Table 3 of this DER), the soluble fraction from feces Table 6, Document 97438 (p32), and the reported percentages of metabolites in urine (Appendix 17 of Document 97438) and feces (Appendix 18 of Document 97438).

2. Formulas depicted in Appendix 1.

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3. Totals may differ slightly (up to 0.2-0.3%) from totals in Table 3 of this DER due to accumulation of roundoff errors.

Table 8. Metabolite profiles in urine of rats dosed orally with [triazole-3,5-^{14}C] HWG 1608.[1]

Compound/matrix	Radioactivity (as % of total recovered) males	females
HWG 2443 ("acid")	1.6	9.7
ECW 4393 (" diol glucuronide")	0.3	2.9
ECW 4390 (" diol sulfate")	0.2	2.7
HWG 2061 ("diol")	2.2	0.3
ECW 4873 ("ketoacid")	3.4	0.7
ECW 4908 ("triol")	0.5	0.2
ECW 4895/2 (triazole)	5.4	1.5
Total identified:	13.6	18.0
Unidentified:	10.2	6.4
Total in urine:	23.8	24.4
Feces	70.3	72.6
Residue in body	5.9	3.0
Total	100.0	100.0

1. One group of 5 males and one group of 5 females received a single oral dose of [triazole-3,5-^{14}C] HWG 1608. Urine and feces were collected for 48 hours after dosing; the animals were sacrificed at 48 hours after dosing. Data from Table 14, Document 97438 (p.40).

Reviewer's comments/conclusions:

Although no statement of compliance with EPA GLP was provided for the pharmacokinetics part of this study (MRID 409959-12), a statement indicating that a GLP requirements of 40 CFR Part 160 do not apply to this study was included.

At least 98.1% of a single oral dose (2 mg/kg) of [phenyl-UL-^{14}C] HWW 1608 administered to bile fistulated male Wistar rats, appeared to have been absorbed, based on 48-hour data for bile and urine excretion. Total recovery of radioactivity 72 hours after dosing accounted for 94 to 100% of the low dose and 87 to 97% of the high dose. Approximately 14 to 33% of the dose was eliminated in the urine and 61 to 82% of the dose was eliminated in feces, with no apparent differences between the two dose groups. Although males dosed with [phenyl-UL-^{14}C] HWG 1608 excreted significantly less radioactivity in the urine (14 to 17% of the dose) than females (29 to 33% of the dose), there does not appear to be a significant sex difference in urinary excretion of radioactivity in rats dosed with [triazole-3,5-^{14}C].

A sacrifice total radioactive residue in the body, excluding the GI tract, amounted to 0.34 to 0.54% of the dose at the low-dose level and to 0.24 to 0.63% of the dose at the high-dose level in animals dosed with [phenyl-UL-^{14}C] HWG 1608. Experiments with male bile-fistulated rats indicated that, at least in low-dose males, the test material (and/or its metabolites) undergo enterohepatic circulation and that radioactivity in feces may be attributed largely to biliary excretion. Elimination of radioactivity in expired air as $^{14}CO_2$ amounted to 0.03% of the dose over a 72-hour collection period.

A total of ten compounds (Table 7) were identified in excreta of animals dosed with [phenyl-UL-^{14}C] HWG 1608, amounting to 50.9-58.3% of the dose in males and 67.9-71.3 % of the dose in females. Only three of those compounds (HWG 2443, HWG 2061,and HWG 1608) were identified with reference to synthetic standards. Of the other seven (9.6-14.9% of the dose), six were identified tentatively based on GC/MS and NMR patterns but without comparison to synthetic standards, and thus remain as putative metabolites. It is not clear whether a synthetic standard was used in the identification of the remaining compound HWG 2251.
Approximately 33.2-40.5% of the radioactivity in male excreta and 20.4-28.4% of the radioactivity in female excreta was left unidentified in rats dosed with [phenyl-UL-^{14}C] HWG 1608. This unidentified radioactivity includes a group of 5 metabolites (M1-M5, in Table 7) comprising up to 10.7% of the dose in high-dose males. The presence of a phenolic compound (ECW 4882) raises the question of the presence of additional phenolic compounds, which may be formed via reactive electrophilic intermediates. Compound HWG 2251, an analogue of HWG 1608 with a isopropyl chain instead of a t-butyl chain, was present at levels of 0.3-1 1% of the dose. The authors did not discuss the origin of this compound, which does not appear to be a metabolite of tebuconazole, but is possibly an impurity present in the test material. Its presence in amounts of up to 1.1% of the dose (Table 7), raises the question of purity of a test material supposedly of >99% purity. No metabolites resulting from the release of the triazole moiety were identified, even though free triazole constitutes 6.1-22.6% of the urinary radioactivity (about 1.5-5.4% of total recovered, Table

8) in rats dosed with [triazole-3,5-^{14}C] HWG 1608.

Examination of Table 7, indicates that the ratio of metabolite HWG 2443 ("acid") to its precursor HWG 2061 ("diol") plus conjugates decreases from values ranging from 1.6-2.0 in low-dose males to 0.7 in high-dose males; in the case of females the ratio decreases from values ranging from 1.3-1.4 in low-dose rats to 0.9. In addition, the phenolic compound ECW 4882 appeared to increase from 2.4-3.4% of the dose in low dose rats to 4.6-5.2 in high-dose animals. These changes could be suggestive of changes of detoxication patterns resulting from metabolic saturation at the high dose; additional data at a higher dose would be required to confirm this apparent trend.

Appendices

Appendix 1. Structures of metabolites and reference compounds.

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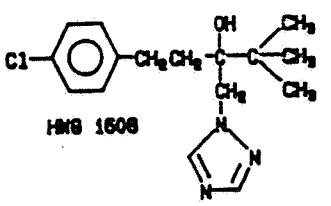
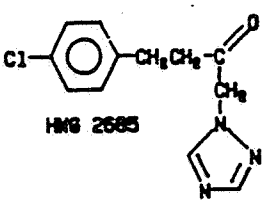
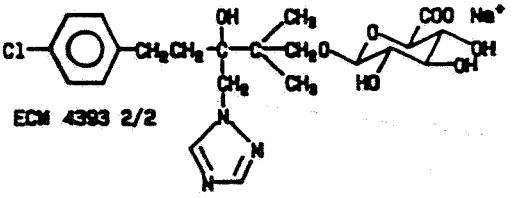
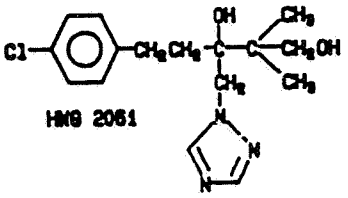
Appendix 1

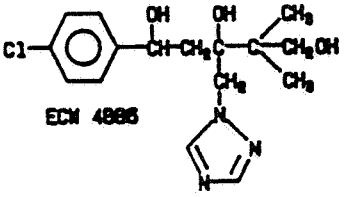
Structures of tebuconazole metabolites and reference compounds. (Copied from p.83 of Document 97438, MRID No. 409959-11)

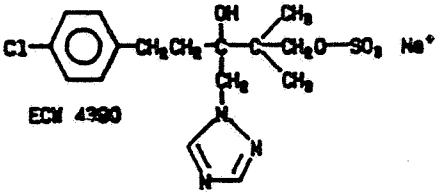


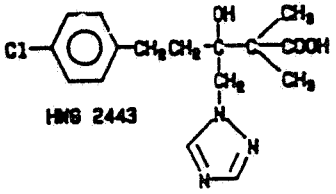


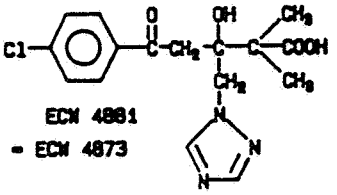


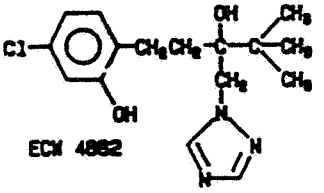


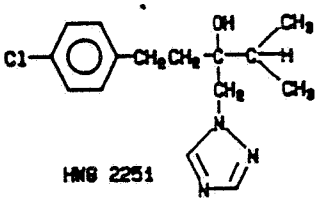


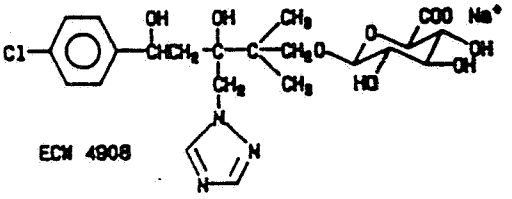












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Page_____ is not included in this copy.

Pages 30 through 42 are not included.

The material not included contains the following type of information:

____ Identity of product inert ingredients.

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Data Evaluation Report

Compound HWG 1608

Citation

Dermal absorption of ^{14}C-HWG 1608 technical in rats. D.A. Eigenberg, Mobay Corporation, Health, Environment and Safety, Corporate Toxicology Department, Study Number 87-721-01, Toxicology report number 1040, Report #97470 Jul 28, 1988, MRID 409959-13

Reviewed by Robert F Zendzian PhD 1/6/90
Senior Pharmacologist

Core Classification Acceptable

Conclusions

Dose distribution following a single dermal dose in ethanol is as follows;

Exposure Duration (hours)	Actual dose ug/cm^2 0.604 Skin	0.604 Absorbed	5.85 Skin	5.85 Absorbed	52.4 Skin	52.4 Absorbed	547 Skin	547 Absorbed
0.5	48.89	0.45	41.05	0.43	56.63	0.48	86.42	0.09
1	40.93	2.22	46.16	2.10	54.66	1.93	76.73	0.46
2	42.49	4.86	42.33	5.48	52.57	3.25	72.10	1.32
4	42.26	8.01	39.15	9.67	48.40	6.49	66.44	1.45
8	34.06	15.55	26.73	22.15	39.97	12.97	64.49	2.53
24	24.70	27.77	24.40	27.06	32.02	23.01	53.11	6.38

Materials

HWG 1608, technical grade
a-[2-(4-Chlorophenyl)ethyl]-a-(1,1-dimetnylethyl)-1H-1,2,4-triazole-1-ethanol
CAS Number 107534-96-3
Batch number 86R00821
Purity 94.7%

HWG 1608, radiolabeled, in ethanol
triazole-^{14}C; uniformed labeled
Reference number 86R138-60
Radiochemical purity 99.66%
Specific activity 19.43 uCi/mg

Adult male Sprague-Dawley derived rats from Sasco Inc.

Experimental Design

Four groups of 24 rats were dosed dermally ar 0.01, 0.1, 1 and 10 mg/rat (0.67, 6.7, 67 and 670 ug/cm^2 respectively). Four rats per dose group were exposed for durations of 0.5, 1, 2, 4, 8 and 24 hours

1. Dose preparation

"The radioactive and non-radioactive HWG 1608 were combined in ethanol to yield the appropriate dose solution concentration." Solutions were analyzed for concentration and stability.

2. Animal preparation and dose administration

Twenty four hours prior to dosing the back of each animal was shaved and wiped with acetone. "The test material, at a dose volume of 0.25 ml/rat in ethanol[1], was applied to a 15 cm^2 area of shaved, intact dorsal skin which was circumscribed by a rubber ring glued to the skin. After the test material had dried, the exposure site was covered with a guaze patch glued to the skin." The animals were placed in individual cages for the duration of the exposure period for the collection of total urine and feces.

Residue on the application device was quantitated to determine the actual dose applied.

"At 0.5, 1, 2, 4, 8 and 24 hours after dosing , urine and feces were collected from four animals per dose group and these animals were anesthetized with halothane --------, bled (cardiac puncture) and sacrificed by cutting the diaphram. Urine in the bladder was collected and added to the urine sample for that animal. The rubber ring and gauze were removed and the exposure area was excised with its underlying muscle layers. The treated area of skin from each animal was rinsed, but not scrubbed, with 25 ml of a 5% aqueous Contrad solution followed by several water rinses to a total volume of 100 ml. The rubber ring was rinsed with 25ml of a 5% aqueous Contrad solution."

The following samples were analyzed for radioactivity;

Whole blood	Carcass
Urine	Application device
Feces	Rubber ring
Skin	Gauze patch

Results

Mean applied doses ranged from 78 to 90 % of nominal.

Mean Percent Recovery of ^{14}C was as follows (from Table 2 of the report);

"1. Due to the physical nature of the test compound, i.e. octanol water partition coefficient of 5000, an aqueous water vehicle could not be used"

Exposure Time (Hr)	Actual Dose (ug/cm^2)			
	0.604	5.86	52.4	547
0.5	102	102	105	101
1.0	99	104	105	102
2.0	197	98	105	100
4.0	97	104	102	99
8.0	98	100	102	97
24.0	48	91	93	91

The dose distribution, in mg, is persented in Table 1 and in percent of dose applied for selected values in Table 2.

Discussion

1) Comments on the study

This study, one of a series performed in the Mobay Laboratory, shares two common problems with the other studies; 1) the test compound is applied in ethanol and 2) the tables in the report are very poorly presented and incomplete.

The physical state in which a compound is applied to the skin significantly effect it penetration. If a compound such as HWG 1608 is suspended in water it is essentialy presented as a solid and can be expected to show very little penetration. If, as in this study, it is dissolved in ethanol it is essentially presented as an organic liquid and its penetration can be expected to be enhanced. Also, ethanol itself has been shown to enhance dermal penetration.

The tables are incomplete in that there are no individual animal data. Individual animal data are always required for all studies. They allow allow the review scientist to check the data manipulation in the report and to manipulate subsets of the data.

On Wednesday Jan 31, 1990 a meeting was held with representatives of MOBAY to discuss the writing of this and other dermal absorption study reports. The registrant indicated that all such reports would be rewritten for completeness and clarity.

2) Comments on the data

This ccmpound is unusual in that the percent of the dose which remains on the application site after the soap and water wash increases with increasing dose. Table 3 summarizes this data. With the majority of compounds, that have been tested with this protocol, the percent of dose that remains after washing decreases with increasing dose as does the percent of the dose that is absorbed. Since the skin residue is potentially absorbable, this unusual relationship may have significant effects on the total dose absorbed following a washing by the applicator.

Table 1. Dose distribution of HWG 1608 following a single dermal dose to male rats. Values are means of 4 animals. Data from Appendix VIII of the report.

Dose ug/cm^2 Nominal (actual)	Actual Dose/ Rat(mg)	Exposure Duration (hours)	Skin Wash (mg)	Gauze+ Ring(mg)	Skin(mg)	Carcass (mg)	Blood (mg)	Urine (mg)	Feces (mg)	Absorbed[1] mg	Absorbed[1] % dose
0.67	0.00898	0.5	0.00442	0.00034	0.00439	0.00004	0.00000	0.00000	0.00000	0.00004	0.45
(0.604)	0.00899	1	0.00443	0.00057	0.00368	0.00020	0.00000	0.00000	0.00000	0.00020	2.22
	0.00906	2	0.00399	0.00044	0.00385	0.00044	0.00000	0.00000	0.00000	0.00044	4.86
	0.00911	4	0.00381	0.00051	0.00385	0.00072	0.00000	0.00001	0.00000	0.00073	8.01
	0.00913	8	0.00373	0.00048	0.00331	0.00137	0.00000	0.00005	0.00000	0.00142	15.55
	0.00911	24	0.00237	0.00139	0.00225	0.00123	0.00000	0.00033	0.00097	0.00253	27.77
6.7	0.08796	0.5	0.05015	0.00271	0.03611	0.00038	0.00000	0.00000	0.00000	0.00038	0.43
(5.85)	0.08752	1	0.04507	0.00341	0.04040	0.00184	0.00000	0.00000	0.00000	0.00184	2.10
	0.08803	2	0.04022	0.00413	0.03726	0.00477	0.00001	0.00004	0.00000	0.00482	5.48
	0.08758	4	0.04284	0.00597	0.03428	0.00833	0.00001	0.00013	0.00000	0.00847	9.67
	0.08830	8	0.03973	0.00501	0.02360	0.01875	0.00002	0.00075	0.00004	0.01956	22.15
	0.08815	24	0.02386	0.01104	0.02151	0.01230	0.00002	0.00274	0.00879	0.02385	27.06
67	0.78620	0.5	0.33031	0.05034	0.44519	0.00376	0.00001	0.00000	0.00000	0.00377	0.48
(52.4)	0.78206	1	0.42745	0.06399	0.42745	0.01512	0.00001	0.00000	0.00000	0.01513	1.93
	0.78388	2	0.33549	0.04826	0.41128	0.02534	0.00003	0.00013	0.00000	0.02550	3.25
	0.78488	4	0.30187	0.06895	0.37988	0.05017	0.00006	0.00074	0.00002	0.05097	6.49
	0.78782	8	0.31160	0.07801	0.31487	0.09943	0.00011	0.00228	0.00039	0.10221	12.97
	0.78716	24	0.11610	0.15908	0.25206	0.13130	0.00015	0.02239	0.04729	0.18113	23.01
670	8.21612	0.5	1.08788	0.14357	7.10005	0.00770	0.00002	0.00000	0.00000	0.00772	0.09
(547)	8.19947	1	1.82292	0.23281	6.29125	0.03777	0.00006	0.00004	0.00006	0.03793	0.46
	8.20064	2	1.94590	0.23325	5.91299	0.10705	0.00012	0.00090	0.00002	0.10809	1.32
	8.18515	4	2.20870	0.34568	5.43806	0.11645	0.00011	0.00170	0.00010	0.11836	1.45
	8.21729	8	2.18377	0.32671	5.29959	0.19969	0.00018	0.00555	0.00235	0.20777	2.53
	8.21084	24	1.91869	0.63056	4.36065	0.37549	0.00025	0.04583	0.10240	0.52397	6.38

1. Absorbed is the total of carcass, blood, urine and feces

Table 2. Dose distribution, as percent of actual dose, for selected parameters of HWG 1608 following a single dermal dose to male rats. Values are means of 4 animals.

Dose ug/cm^2 Nominal (actual)	Actual Dose/ Rat(mg)	Exposure Duration (hours)	Not absorbed[1]	Skin	In body[2]	Excreted[3]	Absorbed[4]
0.67	0.00898	0.5	53.01	48.89	0.45	0.00	0.45
(0.604)	0.00899	1	55.62	40.93	2.22	0.00	2.22
	0.00906	2	48.90	42.49	4.89	0.00	4.86
	0.00911	4	47.42	42.26	7.90	0.11	8.01
	0.00913	8	46.11	34.06	15.01	0.55	15.55
	0.00911	24	41.27	24.70	13.50	14.27	27.77
6.7	0.08796	0.5	60.10	41.05	0.43	0.00	0.43
(5.85)	0.08752	1	55.39	46.16	2.10	0.00	2.10
	0.08803	2	50.37	42.33	5.43	0.05	5.48
	0.08758	4	55.73	39.15	9.52	0.15	9.67
	0.08830	8	50.68	26.73	21.26	0.89	22.15
	0.08815	24	39.59	24.40	13.98	13.08	27.06
67	0.78620	0.5	48.42	56.63	0.48	0.00	0.48
(52.4)	0.78206	1	62.84	54.66	1.93	0.00	1.93
	0.78388	2	48.96	52.57	3.24	0.02	3.25
	0.78488	4	47.25	48.40	6.40	0.10	6.49
	0.78782	8	49.39	39.97	12.63	0.34	12.97
	0.78716	24	34.96	32.02	16.70	8.85	23.01
670	8.21612	0.5	15.00	86.42	0.09	0.00	0.09
(547)	8.19947	1	25.07	76.73	0.46	0.01	0.46
	8.20064	2	26.57	72.10	1.31	0.01	1.32
	8.18515	4	31.21	66.44	1.42	0.02	1.45
	8.21729	8	30.55	64.49	2.43	0.10	2.53
	8.21084	24	31.05	53.11	4.58	1.81	6.38

1. Not absorbed is total of wash, gauze and ring.
2. In body is total of carcass and blood.
3. Excreted is total of urine and feces
4. Absorbed is the total of carcass, blood, urine and feces

Table 3. Effect of dose remaining on the skin on the potential for total absorption. Values are percent of applied dose. Data from table 2

Dose ug/cm^2 Nominal (actual)	Exposure Duration (hours)	Not absorbed$_1$	Skin	Absorbed$_2$	Total of skin and Absorbed
0.67	0.5	53.01	48.89	0.45	49.34
(0.604)	1	55.62	40.93	2.22	43.15
	2	48.90	42.49	4.86	47.35
	4	47.42	42.26	8.01	50.27
	8	46.11	34.06	15.55	49.61
	24	41.27	24.70	27.77	52.47
6.7	0.5	60.10	41.05	0.43	41.48
(5.85)	1	55.39	46.16	2.10	48.26
	2	50.37	42.33	5.48	47.81
	4	55.73	39.15	9.67	47.82
	8	50.68	26.73	22.15	48.87
	24	39.59	24.40	27.06	51.46
67	0.5	48.42	56.63	0.48	57.11
(52.4)	1	62.84	54.66	1.93	56.59
	2	48.96	52.57	3.25	55.52
	4	47.25	48.40	6.49	54.89
	8	49.39	39.97	12.97	52.94
	24	34.96	32.02	23.01	55.03
670	0.5	15.00	86.42	0.09	86.51
(547)	1	25.07	76.73	0.46	77.19
	2	26.57	72.10	1.32	73.42
	4	31.21	66.44	1.45	67.89
	8	30.55	64.49	2.53	67.02
	24	31.05	53.11	6.38	59.49

1. Not absorbed is total of wash, gauze and ring.
2. Absorbed is the total of carcass, blood, urine and feces