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DATA EVALUATION RECORD

STUDY TYPE: Metabolism - Rat; OPPTS 870.7485; OECD 417.

PC CODE: 128101 **DP BARCODE:** 341456

TEST MATERIAL (PURITY): [^{14}C] - 5-chloro-2-methyl-3(2H) isothiazolone (99.9%)

SYNONYMS: 4,5-^{14}C]-RH-651), [^{14}C]-RH-651

CITATION: Kim-Kang, H. and D. Wu (2005). Metabolism of ^{14}C-RH-651 in the biliary cannulated rat. Xenobiotic Laboratories, Inc., Plainsboro, NJ 08536. Report Number RPT01229, August 4, 2005. MRID 47154008. Unpublished.

SPONSOR: Rohm and Haas Company, 727 Norristown Road, Springhouse, PA 19477-0904

EXECUTIVE SUMMARY: In a 24-hour metabolism study (MRID 47154008), [^{14}C]-RH-651, (Lot number 1018.0012) was administered to bile duct cannulated Sprague Dawley rat. A single oral dose of 3.75 mg/kg was administered to a group of 3 female rats with excretion collections for 24 hours. During the 24 hours an average of 4.74% of the administered dose was excreted in bile. The dose recovered as measured by the amount of radioactivity in the urine, cage rinse, and feces were 44.09%, 7.96%, and 24.72%, respectively. Total recovery during the 24-hour period in bile, urine, cage rinse, and feces averaged 81.5%. At least 20 metabolites were observed in urine and feces. Among these N-methyl-malonamic acid (M1A-1) was detected in urine as the major metabolite for RH-651 (26.3% of dose). Parent compound was not detected in either urine or feces sample.

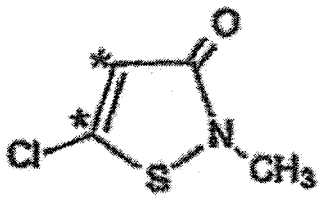
This metabolism study in the bile duct cannulated rats is classified **ACCEPTABLE-GUIDELINE** for a tier 2 metabolism study and satisfies only the guideline requirement for a metabolism study characterizing metabolites [OPPTS 870.7485, OECD 417] in rats.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

I. MATERIALS AND METHODS

A. MATERIALS:

1. **Test compound:**

Radiolabelled test material:	[^{14}C] - 5-chloro-2-methyl-3(2H) isothiazolone white solid
Description:	white solid
Radiochemical purity:	99.9% determined by HPLC (XBL ref.#1564:10A)
Specific activity:	51.65 mCi/g
Lot/batch #:	1018.0012
Non-Radiolabelled test material:	Kathon 886-F (contains 10.45% RH-651, 3.66% RH-573)
Description:	Amber liquid
Lot/batch #:	Kathon 886-F: 0000371525 RH-573:8001J123(TD#01-119)
Purity:	RH-573:51.4% a.i.
Contaminants:	Not reported
CAS # of TGAI:	Not provided
Structure:	

2. **Vehicle and/or positive control:** NANOPure® water

3. **Test animals:**

Species:	Rats
Strain:	Sprague-Dawley
Age/weight at study initiation:	Females: 10 weeks of age body weights ranged from 286-300 g
Source:	Hilltop Lab Animals, Inc. (Scottdale, PA)
Housing:	One/cage in polycarbonate cages and changed to Nalgene metabolism cages
Diet:	Certified Purina Rodent Chow #5002 was available *ad libitum*; feed analyzed by manufacturer for nutritional contents and contamination
Water:	Fresh water with electrolyte supplements was available *ad libitum*; water samples analyzed by International Hydronics Corp. (Rocky Hill, NJ) for selected organophosphates and chlorinated hydrocarbons
Environmental conditions:	**Temperature:** 19-25°C **Humidity:** 30.0-70.0% **Air changes:** **Photoperiod:** ~12 hrs dark/~12 hrs light
Acclimation period:	4 days to the facilities ~24 hr acclimation in study cages

B. STUDY DESIGN AND METHODS:

1. **Group arrangements:** Three female rats were assigned to a single test group noted in Table 1.

TABLE 1: Dosing groups for metabolic characterization studies for RH 651 in a biliary cannulation study in rat			
Test group	**Dose of labeled material (mg/kg)**	**Number/sex**	**Remarks**
Oral dose	3.75	3 Females	Sacrificed 24 hr post-dose

2. Dosing and sample collection:

Dose Solution Preparation: Dose solution was prepared as follows: 0.00165 g of RH-573, 0.03369 g of Kathon 886F, and ~122 µCi of ^{14}C-RH-651 were added into the dose bottle, and a sufficient amount of NANOPure® water was added and mixed well until dissolved to achieve a target concentration of 0.5 mg RH-651 and 0.18 mg RH-573 per gram dose solution.

Dose Solution Concentration Assay: Weighing duplicate aliquots of 100 µL dosing solution into 10-mL volumetric flasks and diluting to 10 mL with water, samples were assayed as pre- and post-dose concentrations. The samples were thoroughly mixed and duplicate aliquots of 100 µL were analyzed using a liquid scintillation spectrometer.

Dose Administration: Each treated rat received a single dose by oral gavage at the nominal dose based upon individual body weights taken prior to dosing. The actual amount of dose solution given to each animal was determined by weighing the loaded dose syringe before dose administration and the emptied syringe after dose administration.

Sample Collection: At pre-dose and 0-24 hr post-dose bile, urine, and feces were collected in metabolism cages. Pre-dose bile was collected at ~0.5-0 hr. The pre-dose urine, cage rinse and feces were collected at –24-0 hr. The urine and feces samples were collected into tared sample cups and freeze-trapped using dry ice to avoid atmospheric oxidation, evaporation and bacterial degradation. Cages were thoroughly washed with IPA/water at the end of the study. All cage rinse/wash samples were collected in tared sample containers.

a. Metabolite characterization studies:

Sample Preparation For Metabolite Profiling: Matrix samples from each group were generally pooled by gender and one time interval.

Urine: For each individual rat, 0-24-hr urine samples were pooled proportionally and were LSC analyzed as duplicate aliquots.

Feces: Samples of 0-24-hr of homogenized feces were proportionally pooled. Combusting triplicate aliquots of homogenized samples determined the total radioactive residue (TRR) levels in pooled feces. For extraction, a subsample from the pooled sample was used.

The pooled feces samples were extracted and concentrated before HPLC analysis by the following method:

Each pooled feces sample was mixed with ~5x v/w CH_3OH in a 50 mL centrifuge tube, and placed on a Wrist Action shaker for 20 min at high speed. The samples were centrifuged at 4°C for 10 min at 11,000 rpm, and the supernatant decanted into another tube. Using methanol, the volumes of the supernatants were adjusted to 25 mL, and aliquots were taken for LSC determination. To determine the radioactivity, triplicate aliquots (~50 mg) of dried post extraction solids (PES) were combusted with a Harvey biological oxidizer and radio-assayed by LSC.

3. **Statistics:** At least duplicate samples were analyzed. Statistical analysis was limited to arithmetic mean and standard deviation and % CV, which seems to be appropriate for the test.

4. **Preparation of dosing solutions:**

   a. **Bile, Urine, Cage Rinse and Feces:** Bile, urine, and cage rinse were thoroughly mixed; duplicate aliquots (~0.025 g for bile, ~0.1 g for urine, ~1 g for cage rinse) were weighed into scintillation vials, mixed with scintillation cocktail, and assayed directly by LSC. Feces were homogenized with 3-5x (w/v) NANOPure® water and triplicate aliquots of homogenate equal to ~100 mg fresh feces weight and were combusted in a Harvey Biological Sample Oxidizer and counted by LSC.

   b. **Radioactivity Analysis:** Counting aliquots directly in a liquid scintillation counter (LSC) determined levels of radioactivity in bile, urine, cage rinse and feces extract samples. Combusting aliquots of homogenized samples in a Harvey OX-500 or OX-300 Biological Sample Oxidizer determined total radioactive residue (TRR) levels in rat feces or post-extractions solid (PES) samples. The evolved $[^{14}C]O_2$ was counted in 15 mL of Harvey Scintillation Carbon-14 Cocktail. Samples analyzed to produce excretion data were either counted in triplicate (combustion analysis) or duplicate (direct counting). Depending on sample availability, samples analyzed for metabolite profiling and product identification were usually limited to single or duplicate analysis. Samples were regularly assayed with a Beckman Liquid Scintillation Counter for 10 min or until the 2-sigma error was less than or equal to 2%, whichever occurred first. The counting time was 2 min. for HPLC fractions collected. The counting time was 5 min. for TopCount fractions. An external standard method was used to perform quench correction. Combusting a known amount of $[^{14}C]$-mannitol validated oxidizer efficiencies.

   The scintillation spectrometer was set to zero background for total radioactive residue (TRR) levels in rat bile, urine, cage rinse, and feces. Pre-dose and treated samples were counted for each matrix, and counts per minute (cpm) were automatically converted to disintegrations per minute (dpm). From the treated sample, the dpm from the pre-dose sample was subtracted; for subsequent calculations, the net dpm per aliquot was used.

II. RESULTS:

A. EXCRETION:

A summary of the percent of the doses that were recovered from pooled urine, bile, and feces collections, as well as the amount of dose that had adhered to the cage as a rinse can be seen in the Table 3.

TABLE 3: Recovery of radioactivity in excreta of rats after administration of C^{14}-labeled RH 651 orally [a]

	Percent of radioactive dose recovered			
	Oral dose			
	GA-001-F	GA-002-F	GA-003-F	Mean
Bile	4.60	5.38	4.23	4.74
Urine	46.87	45.56	39.83	44.09
Feces	20.27	21.29	32.61	24.72
Cage Rinse	6.30	9.16	8.41	7.96
Total	**78.04**	**81.39**	**85.08**	**81.50**

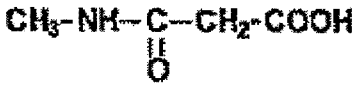
[a] Data obtained from page 39 in the study report.

a. Oral dose: As summarized in Table 3 a majority of radioactivity was recovered in urine and cage rinse, and a lesser amount was recovered in feces. A small amount of the dosed radioactivity was recovered in bile, indicating that bile was not the primary excretion route. Within 24 hour after dosing an average of 44.09%, 7.96%, 24.72%, and 4.74% of dosed radioactivity were recovered in urine, cage rinse, feces, and bile respectively. Therefore, total recovery of C^{14}-radioactivity within 24 hour averaged 81.50% of administered dose.

B. **METABOLITE CHARACTERIZATION STUDIES:** Twenty five metabolites were detected from rat urine, bile, and feces samples during the initial HPLC radioprofiling. All the metabolites accounting for >5% of the dose in at least one of the urine or bile samples. Further analyses of the metabolites structures were performed by LC/MS and LC/MS/MS. LC/MS was used to analyze the structure of metabolites accounting for less than 5% of the dose. Radio HPLC coupled with mass spectrometry analyzed the urine and bile. Molecular ions corresponding to individual radioactive peaks were obtained. The proposed structures were drawn from MS/MS analysis for most of the metabolites. The resulting data for LC/MS and MS/MS were compared to data from reference standards. After RH-651 discussion, the metabolites were discussed by order of elution from HPLC Condition 2. LC/UV/RAM/(+)ESI-MS also analyzed pre-dose urine and bile samples (control urine and bile), and metabolites were distinguished from the matrix using the data.

The protonated molecular ion ($[M+H]^+$) was observed at *m/z* 150 (HPLC R_t ca. 38 min). At *m/z* 133, 132, 114, and 105 characteristic fragment ions were observed. Unaffected RH-651 was not found in urine or bile. No detectable RH-651 was found in either urine or bile samples under the same conditions (LC/MS Condition 1) as those used for the analysis of the reference standard.

1. **Metabolite M1A:** Metabolite M1A was the major metabolite and it is primarily observed in the urine (Table 4). Radioprofiling detected **M1A** at retention time (R_t) ~3.7 min in the urine sample (HPLC Condition 2); HPLC Condition 3 was used to isolate the radioactive peak, and NP-HPLC analyzed the isolate. Only one distinctive radioactive peak is shown. LC/MS (LC/MS Condition 2) also analyzed the isolate, showing that **M1A** eluted at R_t ~3.7 min, yielding a mass ion peak at *m/z* 118 corresponding to $[M+H]^+$ by NP-HPLC. It indicated the MW of the compound is 117. The HPLC retention time and molecular weight of **M1A** were consistent with those of the reference standard, *N*-Methyl malonamic acid. LC/(+)ESI-MS/MS analysis of **M1A** also resulted in similar product ions to those of *N*-Methyl malonamic acid. Thus, **M1A** was identified as *N*-Methyl malonamic acid. Based on the data, the structure of **M1A** was confirmed as follows:

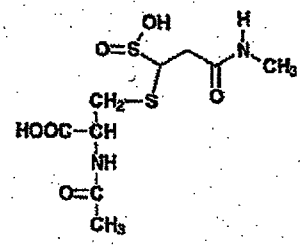


M1A

2. **Metabolite M15:** The next more prevalent metabolite is **M15**, which is found solely in the feces (Table 4). Radioprofiling at R_t ~18 min in bile detected **M15** as a major compound in the feces extract. **RP-HPLC** isolated **M15** from the feces extract, and the isolate was analyzed by LC/MS using LC/MS Condition 2. LC/RAM/(+)ESI-MS analysis of the compound in the isolate showed a distinctive peak corresponding to the mass ion peak at *m/z* 313 for $[M+H]^+$ under LC/MS Condition 2, suggesting a MW of 312. LC/RAM/(+)ESI-MS/MS of **M15** yielded major fragment ions at *m/z* 282 (loss of CH_3NH_2) and 231. **M15** was also detected as a major compound in the feces during the previous study (MRID 47154007)[1].

   During the radioprofiling of urine, **M15** was not detected. However, a direct LC/RAM/(+)ESI-MS analysis of the compound in urine showed a distinctive peak corresponding to the mass ion peak at *m/z* 313 for $[M+H]^+$ under LC/MS Condition 1, indicating that the compound was present in urine at a low level, therefore, no further analysis was conducted with the compound in urine. The structure of **M15** was more extensively investigated during the previous rat metabolism study (MRID 47154007).

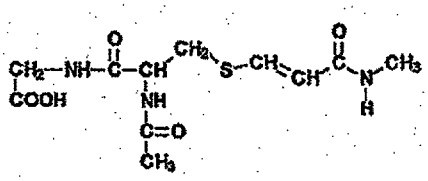
   Based on the results, the structure of **M15** is proposed as follows:



M15

3. **Metabolite M24: M24** is prevalent in urine, but can be found in fecal and bile as noted in Table 4. Radioprofiling at R_t ~29 min in urine detected **M24** as a minor component. A direct LC/RAM/(+)ESI-MS analysis of the compound in urine showed two distinctive peaks corresponding to the mass ion peaks at *m/z* 304 and 394 for $[M+H]^+$ under LC/MS Condition 1, respectively, suggesting a MW of 303 and 393, respectively. The two peaks were assigned as **M24-A** and **M24-B**. **M24-A** eluted slightly earlier than **M24-B**, which co-eluted as a broad peak during the radioprofiling. **M24-A** and **M24-B** were extensively analyzed during the previous metabolism study (MRID 47154007). The LC/MS/MS analyses of the two compounds yielded similar fragment ions as detected in the previous study (MRID 47154007). The structure of **M24-A** was proposed as follows; however, there were not sufficient evidence to propose a structure for **M24-B**:

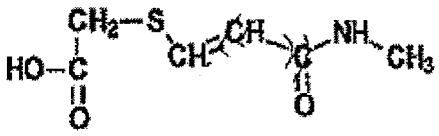
[1] Kim-Kang, H. and D. Wu (2005) Metabolism of ^{14}C-RH-651 in the rat. XenoBiotic Laboratories, Inc., Plainsboro, NJ. XBL Report No. RPT01224, August 4, 2005. MRID 47154007. Unpublished.



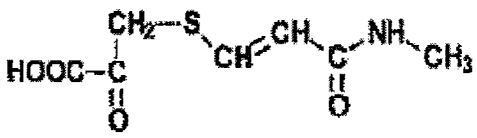
M24-A

4. **Metabolite M1B:** Radioprofiling at R_t ~4 min detected **M1B** as one of the major components in the feces extract. HPLC isolated the metabolite using HPLC Condition 3 and NPP-HPLC analyzed the isolate using Condition 4. Two radioactive peaks, which were assigned as **M1B-1** (~35 min) and **M1B-4** (~30 min), resulted from the fraction. **M1B-1** was detected from the radioprofiling of the **M1B** isolate during the previous study of metabolism. During the previous rat metabolism study, **M1B-4** was not detected in the **M1B** isolate. LC/MS analyzed the isolate using LC/MS Condition 2. During LC/MS analysis, the isolate was shown to contain two compounds, which were assigned as **M1B-1A** and **M1B-1B**. The two compounds co-eluted as one broad radioactive peak.

M1B-1A and **M1B-1B** yielded the molecular ions $[M+H]^+$ at *m/z* 176 and 204 in positive ion mode, showing the MW of each compound as 174 and 203 daltons, respectively. The parent compound can go through reductive ring cleavage followed by glutathione conjugation, which can be further metabolized to form a cystein conjugate. *S*-substitued cysteins may undergo transamination yielding the corresponding thiopyruvic acids, which are further metabolized to thiolactic and thioacetic (thioglycolic) acids. Although the conjugation position and stereo confirmation could not be assigned from limited MS/MS data, the positions is most likely to occur on the C_5 position rather than the C_4 position, according to the published findings that glutathione conjugation favors the β-position of an α, β-unsaturated carbonyl group. Based on the data, the structures for **M1B-1A** and **M1B-1B** were proposed as follows:



M1B-1A



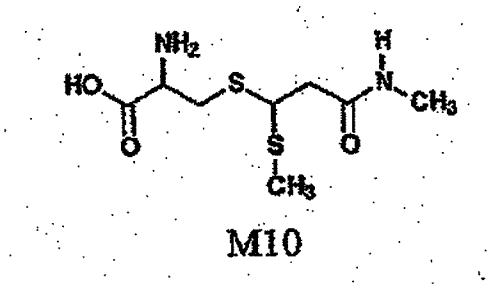
M1B-1B

The compounds were identified as major components in feces from the rat metabolism study of RH-573 (MRID 47154009)[2], in which the compounds were assigned as **M2B** and **M2C**.

5. **Metabolite M33:** Radioprofiling at R_t ~18 min in bile a d some in the feces detected **M33** (Table 4). LC/RAM/(+)ESI-MS analysis of **M33** in bile produced an intense molecular ion $[M+H]^+$ at *m/z* 231 under LC/MS Condition 1, suggesting a MW of 230. LC/ (+)ESI-MS/MS of **M33** yielded major fragment ions at *m/z* 200 (loss of NH_2CH_3) and 174 (loss of 57 amu). The LC/MS/MS/MS analysis of the product ion at *m/z* 200yielded a major fragment ion at *m/z* 143 (loss of 57 amu, possible loss of CH_3NCO) and that of the product ion at *m/z* 174 yielded major fragment loss at *m/z* 143 (loss of NH_2CH_3) and 117 (loss of 57 amu, possible loss of CH_3NCO). The same mass unit loss, i.e., loss of NH_2CH_3 and 57 amu, from the product ions indicated that the compound might have contained a repetition of the same functional moieties.

6. **Metabolite M10:** Radioprofiling at R_t ~13 min in bile detected **M10** (Table 4). LC/RAM/)+)ESI-MS analysis of **M10** produced an intense molecular ion $[M+H]^+$ at *m/z* 253 under LC/MS Condition 1, suggesting a MW of 252. LC/(+)ESI-MS/MS of **M10** yielded major fragment ions at *m/z* 235, 205, and 132. The LC/MS/MS/MS analysis of the product ion at *m/z* 132 yielded major fragment ions at *m/z* 101 and 86. The fragmentation pattern and retention time of the compound were similar to those obtained with **M29**, identified in bile during the rat metabolism study of RH-573 (MRID 47154009). None of the other bile metabolites detected in the bile during the rat metabolism study of RH-573 were detected during this study (MRID 47154009).

   Based on the results, the structure of **M10** was proposed as follows:



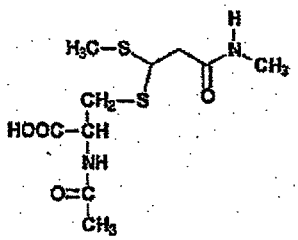
M10

7. **Metabolite M20:** Radioprofiling did not detect **M20**. However, a direct LC/RAM/(+)ESI-MS analysis of the compound in urine showed a distinctive peak corresponding to the mass ion peak at *m/z* 295 for $[M+H]^+$ under LC/MS Condition 1, suggesting a MW of 294. LC/MS/MS analysis of **M20** yielded fragment ions similar to those detected in the previous rat metabolism study (MRID 47154007). A portion

[2] Kim-Kang, H., L. Cai, and D. Wu (2005) Metabolism and pharmacokinetics of ^{14}C-RH-573 in the rat. XenoBiotic Laboratories, Inc., Plainsboro, NJ. XBL Report No. RPT01057, June 13, 2005. MRID 47154009. Unpublished.

of the compound could have been derived from RH-573, which was one of the components in the dosing solution.

The structure of **M20** was thoroughly investigated during the rat metabolism study of RH-573 (MRID 47154009) and confirmed as follows:



M20

The proposed metabolic pathway of RH-651 is as follows:

Proposed Metabolic Pathways of RH-651 in Biliary Cannulated Rats

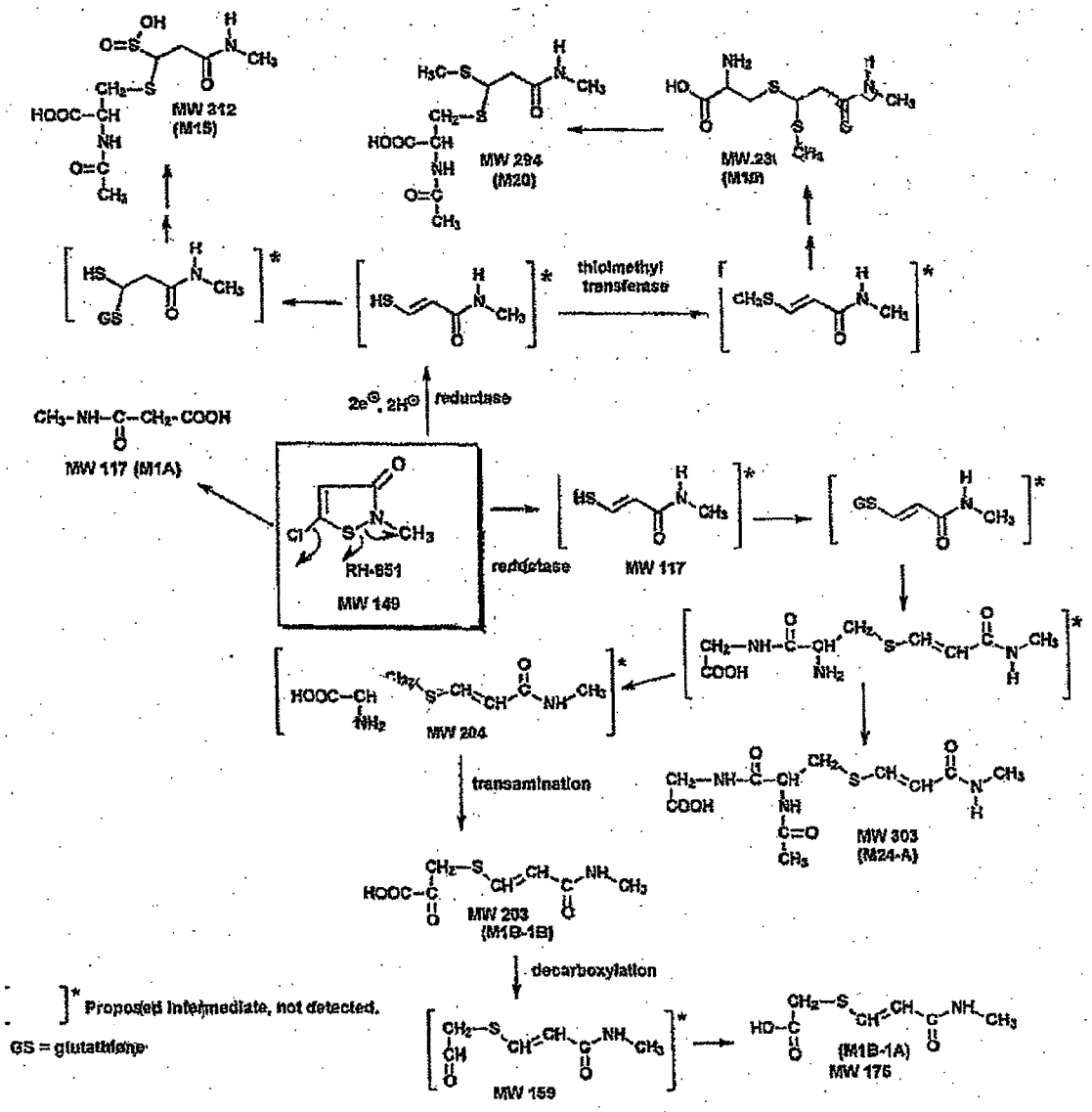


Table 4. Percent Distribution of ^{14}C-RH-651 Metabolites in Urine, Bile, and Feces Expressed as % Dose[a]					
Metabolite ID	**Rt (min) Range**	**Bile GA-F-B24 % Dose**	**Urine GA-F-U24 % Dose**	**Feces GA-F-F24 % Dose**	**Total % Dose**
M1A	~3.70	ND	26.26	ND	26.26
M1B	~3.41	0.75	ND	2.10	2.85
M2	4.59-5.18	0.18	3.17	0.36	3.71
M4	6.06-6.64	ND	2.01	0.27	2.28
M5	~6.95	ND	2.80	ND	2.80
M6	7.82-7.84	ND	1.53	0.14	1.67
M7	8.41-8.43	ND	1.88	0.32	2.20
M8	9.32-9.89	ND	1.73	0.17	1.90
M10	~13.44	0.76	ND	ND	0.76
M12	~14.9	ND	ND	0.28	0.28
M15	~17.86	ND	ND	8.83	8.83
M18	~22.87	ND	ND	0.26	0.26
M22	26.71-26.74	0.47	ND	0.34	0.81
M23	~27.92	0.44	ND	ND	0.44
M24	29.07-29.69	0.25	3.86	0.24	4.35
M26	~30.56	ND	0.86	ND	0.86
M27	32.02	ND	ND	0.36	0.36
M28	~32.90	ND	ND	0.32	0.32
M29	~34.70	0.36	ND	ND	0.36
M32	~37.33	ND	ND	0.50	0.50
M33	38.51-38.54	1.22	ND	0.42	1.65
M35	~39.69	ND	ND	0.27	0.27
M36	~40.89	0.08	ND	ND	0.08
M37	~42.93	ND	ND	0.22	0.22
M38	~47.09	0.23	ND	ND	0.23
Total		**4.74**	**44.09**	**15.41**	**64.24**

[a] Data obtained from pages 42 in the study report.
ND = Not Detected

TABLE 5. Metabolite Profile in Excreta of Rats Dosed with C^{14}-labeled RH 651 [a].	
Dose	Percent of Administered Dose (Oral)
Parent	
Identified metabolite 1 (M1A)	26.26
Identified metabolite 2 (M1B)	2.85
Identified metabolite 3 (M2)	3.71
Identified metabolite 4 (M4)	2.28
Identified metabolite 5(M5)	2.80
Identified metabolite 6 (M6)	1.67
Identified metabolite 7 (M7)	2.20
Identified metabolite 8 (M24)	4.35
Other metabolites	18.12
Total identified	46.12
Unidentified metabolite M15	8.83
Unidentified metabolite M20	X
Total unidentified	8.83+X
Total accounted for [b]	64.24
Lost/unaccounted for [c]	35.76
Total	100

[a] Data obtained from pages 30-35 in the study report.

[b] Total accounted for = (Total identified) + (Total unidentified)

[c] 100 - (Total accounted for)

III. CONCLUSIONS:

A. CONCLUSIONS:

- The study author concluded that the test material was rapidly excreted from the rat and that by 24 hours greater than 81% of the dose was eliminated. A majority of the dose was excreted via the urine with lesser amounts in the bile, feces and cage rinse.

- RH-651 was extensively metabolized and excreted mainly in the urine following a single oral dose to the rat. Intact RH-651 was not found in urine, bile, or feces.

- N-methyl malonamic acid (M1A) was the major component of the 0-24 hour urine sample and accounted for about 26.3% of the dose. The 24-hour bile sample contained a large number of compounds, each accounted for less than 1% of the dose. Only M-33 accounted for 1.2% of the dose.

- The initial HPLC radio-chromatography revealed the presence of at least 5 components derived from RH-651. All the metabolites accounting for greater than 5% of the administered dose were identified and/or characterized by LC/MS and LC/MS/MS. Some of the minor metabolites accounting for less than 5% of the dose were also

identified and/or characterized by LC/MS and LC/MS/MS.

- The metabolites of RH-651 are comprised of a variety of Phase I metabolites consisting of reductive and oxidative cleavage products of RH-651, and Phase II metabolites consisting of glutathione-derived conjugates of Phase I metabolites of RH-651, in addition to glutathione conjugates. However, no data were presented to indicate glutathione conjugation is a metabolic pathway.

- Since the non-cannulated rat passes the bile back to the intestinal tract, which has the effect of microbial metabolism, these further metabolized products can in a large number of instances be reabsorbed back into the animal body. They may well be metabolites to which the body is ultimately exposed and not just the "25" metabolites that were found in this study. As a result, the metabolism could also include the exhalation of ^{14}C-carbon dioxide metabolites.

B. STUDY DEFICIENCIES: The following major study deficiency is noted:

- The study did not evaluate non-cannulated female rats, or males to see if any differences between the sexes did occur in metabolism of the RH-651. However, MRID 47154007 found no difference in sex absorption, distribution, or excretion.

The following minor deficiencies are noted:

- Rationale for the dose of unlabelled RH-651 was not provided.

- The mineral supplementation of the drinking water was not provided in detail or the rationale for it.

C. STUDY CLASSIFICATION: This metabolism study in the rat is **ACCEPTABLE - GUIDELINE** and satisfies only the guideline requirement for the metabolite characterization portion of a metabolism study (870.7485).