PC 999999

Data Evaluation Report on the hydrolysis of halcomid

PMRA Submission Number {.....} EPA MRID Number 45369732

Data Requirement: PMRA Data Code:
EPA DP Barcode: D284964
OECD Data Point:
EPA Guideline: 161-1

Test material:
Common name: Halcomid.
Chemical name
IUPAC: N,N-Dimethyldecanoic acid amide.
CAS name: Not reported.
CAS No: Not reported.
Synonyms: None.
SMILES string: O=C(CCCCCCCCC)N(C)C.

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CITATION: Burri, R. 1995. Hydrolysis determination of [1-^{14}C]N,N-dimethyldecanoic acid amide at pH 5, 7 and 9. Unpublished study performed by RCC Umweltchemie AG, Itingen/BL, Switzerland, sponsored by Bayer AG, Leverkusen, Germany, and submitted by C. P. Hall Company, Chicago, IL. RCC Project No.: 340290. Study experimental start date April 27, 1993 and experimental end date July 28, 1993 (p. 13). Final report issued on May 23, 1995.

ADMINISTRATIVE CONCLUSIONS

1) This study is scientifically valid, and satisfies Subdivision N Guideline criteria for hydrolysis (§161-1). No additional hydrolysis data are needed at this time.

2) The submitter should note the criticisms and comments given in Sections III and IV of this Data Evaluation Report, and consider their applicability to the acceptability of future submissions.

SCIENTIFIC CONCLUSIONS

The hydrolysis of [1-^{14}C]-labeled N,N-dimethyldecanoic acid amide (halcomid), at 0.79-0.81 µg/mL, was studied in the dark at 25.0 ± 0.2°C in sterile pH 5 (0.01M acetate), pH 7 (0.01M TRIS), and pH 9 (0.01M borate) aqueous buffered solutions for up to 30 days. Under these conditions, halcomid was essentially ***stable*** for environmental assessment purposes (half-lives indeterminately long in a test period lasting only 30 days). (There is some evidence that minor hydrolysis may have occurred at pH 9, with an extrapolated regression half-life of 269 days with a 95% confidence range of 174 to 591 days.)

EXECUTIVE SUMMARY

The hydrolysis of [1-^{14}C]-labeled N,N-dimethyldecanoic acid amide (halcomid), at 0.79-0.81 µg a.i./mL, was studied in the dark at 25.0 ± 0.2°C in sterile pH 5 (0.01M acetate), pH 7 (0.01M TRIS), and pH 9 (0.01M borate) aqueous buffered solutions for up to 30 days. The study was performed in accordance with US EPA Pesticide Assessment Guidelines, Subdivision N §161-1, and in compliance with USEPA Good Laboratory Practices. The test system consisted of three 3-neck pyrex glass flasks (250-mL capacity) each containing 200 mL of treated buffer solution; there was one flask for each buffer solution. The flasks were held in a water bath that was covered with a steel cover in order to maintain darkness. Air was drawn through a flask, then through NaOH and ethylene glycol trapping solutions. Duplicate aliquots of each buffer solution were collected at 0, 3, 7, 10, 14, 17, 21, 24, and 30 days posttreatment and analyzed using LSC. Adsorbed [^{14}C]residues were washed from the vessels with acetone and quantified by LSC. Aliquots of the samples were analyzed via one-dimensional TLC. Areas of radioactivity on the plates were identified by comparison to the location of a halcomid reference standard that was cochromatographed with the samples. The following reference compounds for possible transformation products were included in the study: N,N-dimethyloctanoic acid amide, decanoic acid, decanedioic acid, nonanoic acid, nonanedioic acid, octanoic acid, octanedioic acid, heptanoic acid, heptanedioic acid, hexanoic acid, hexanedioic acid, pentanoic acid, pentanedioic acid, butanoic acid, and butanedioic acid. Further analysis via HPLC was employed to confirm the identification of halcomid.

The overall [^{14}C]residue recoveries were 96.9 ± 3.1% of the applied (range 92.2-102.3%) from the pH 5 buffer, 95.6 ± 2.8% (range 90.0-100.0%) from the pH 7 buffer, and 94.5 ± 2.9% (range 88.9-100.0%) from the pH 9 buffer. There was no significant loss of material from any buffer solution with time.

In the pH 5 buffer solution, [^{14}C]halcomid was 97.2% of the applied at 0 days posttreatment, ranged from 93.3-100.7% at 3-21 days with no pattern of decline, and was 93.7% at 30 days (study termination). In the pH 7 buffer solution, [^{14}C]halcomid declined from 97.0% at 0 days posttreatment to 91.7% at 30 days. In the pH 9 buffer solution, [^{14}C]halcomid declined from 97.0% at 0 days posttreatment to 88.6% at 30 days.

No major transformation products were isolated and no minor transformation products were identified in any of the buffer solutions. Three minor unidentified transformation products (M2, M3, and M4) were each ≤3.4% of the applied. Volatilized $^{14}CO_2$ totaled ≤1.4% of the applied, and volatile organics were not detected.

Based on first order linear regression analysis (Excel 2000), halcomid degraded with half-lives of 462-495 days in the pH 5 and 7 solutions and 266 days in the pH 9 solution. These half-lives are of uncertain value because they are extrapolated well beyond the duration of the study. Also, the r^2 values associated with the pH 5 and 7 calculations are 0.206 and 0.311, respectively, and with the pH 9 calculation is 0.6256.

A transformation pathway was not provided. Halcomid was stable in neutral and acidic buffers and relatively stable in the alkaline buffer.

RESULTS SYNOPSIS:

	Half life	**Major and minor transformation products**
pH 5	Stable (extrapolated to 479 days or 1.31 years).	None
pH 7	Stable (extrapolated to 476 days or 1.30 years).	None
pH 9	Stable (extrapolated to 269 days or 0.74 years).	None

Study Acceptability: This study is classified as **acceptable** and satisfies the guideline requirement for a hydrolysis study.

I. MATERIALS AND METHODS

GUIDELINE FOLLOWED: This study was conducted in accordance with USEPA Pesticide Assessment Guideline Subdivision N §161-1 and amendments (pp. 1, 14). No significant deviations from Subdivision N guidelines were noted.

COMPLIANCE: This study was conducted in compliance with USEPA, OECD, and Swiss Good Laboratory Practices (1989; 1981; 1986, respectively; pp. 3, 14). Signed and dated Data Confidentiality, GLP, Certificate of Authenticity, and Quality Assurance statements were provided (pp. 2-3, 6-7).

A. MATERIALS:

1. Test Materials [1-^{14}C]Halcomid (pp. 18-19).

Chemical Structures: See DER Attachment.

Description: Colorless liquid (nonradiolabeled; p. 18).

Purity: Radiochemical purity: >98% (p. 19).
Batch No.: A 387.
Analytical purity: Not reported.
Specific activity: 100.5 µCi/mg (3.72 MBq/mg).
Location of the radiolabel: 1-Carbon (carbonyl carbon).

Storage conditions: The test substance was stored in the dark at *ca.* -20°C (p. 19).

Physico-chemical properties of halcomid.

Parameter	Values	Comments
Molecular Formula	Not reported.	
Molecular weight	199.4 g/mole	
Water solubility	270 mg/L.	At 20°C and pH 5.5.
Vapor pressure	Not reported.	
UV absorption	Not reported.	
pK_a	Not reported.	
K_{ow}/log K_{ow}	Not reported.	
Stability of compound at room temperature	Not reported.	

Data obtained from pp. 18-19 of the study report.

2. Buffer Solution: The following buffer solutions were prepared:

Table 1: Description of buffer solutions.

pH	Type and final molarity of buffer	Composition
5	0.01M Acetate	67.8 mL of sodium acetate was combined with *ca.* 32.2 mL of acetic acid. The resulting buffer (0.1M) was diluted 10 fold, and the pH was adjusted to ± 0.1 units.
7	0.01M TRIS	50.0 mL of TRIS was combined with *ca.* 50.0 mL of 0.1N HCl. The resulting buffer (0.1M) was diluted 10 fold, and the pH was adjusted to ± 0.1 units.
9	0.01M Borate	70.0 mL of boric acid was combined with *ca.* 22.7 mL of 0.1N NaOH. The resulting buffer (0.1M) was diluted 10 fold, and the pH was adjusted to ± 0.1 units.

Data obtained from p. 21 of the study report. Bidistilled water was used.

B. EXPERIMENTAL CONDITIONS

1. Preliminary Studies: A preliminary study was performed in order to determine the stability of the test material in the pH 9 borate buffer solution (p. 23). A 70-µL aliquot (10.2 µg) of the [^{14}C]halcomid stock solution was transferred to a 10-mL volumetric flask. After the acetone was evaporated, the test material was dissolved in 10 mL of the 0.01M borate buffer (pH 9). The radioactivity of the solution was determined immediately (100% of the applied radioactivity) and after 24 hours at room temperature (99.2% of the applied). At 24 hours, halcomid was the only [^{14}C]compound that was detected. Consequently, the study author determined that the test solutions were appropriate for the test material.

Also, a preliminary study (not described) was also conducted to determine the stability of the pH of the buffer solution upon addition of the test substance (p. 21).

2. Experimental conditions

Table 2: Experimental parameters

Parameters		Details
Duration of the study		30 days.
Test concentrations	Nominal:	1 µg a.i./mL
	Measured:	pH 5: 0.80 µg a.i./mL pH 7: 0.81 µg a.i./mL pH 9: 0.79 µg a.i./mL
No. of replications		None. One solution was prepared for each buffer solution, and these bulk solutions were subsampled at each sampling interval.
Preparation of the test medium	Volume used/treatment	Aliquots (*ca.* 250 µg a.i./aliquot) of the halcomid stock solution were evaporated to dryness, then dissolved in 250 mL of buffer solution. A portion (200 mL) of these solutions were used in bulk in the study and repeatedly subsampled.
	Method of sterilization	The treated test solutions were sterilized by filtration (0.45 µm). Application devices and glassware were sterilized by autoclaving for at least 30 minutes at 120°C.
	Co-solvent	None. The acetone solvent was evaporated prior to the addition of the buffer.
Test apparatus (type/material/volume)		Pyrex glass flasks (250-mL capacity; 3-neck; one flask per pH) containing 200 mL of treated buffer solution were sealed with rubber septa and placed in a water bath. The water bath was covered with a steel cover in order to maintain darkness.
Details of traps for volatile, if any		Filter-sterilized humidified air was drawn through the sample flask (30 mL/minute), then through single tubes of 2N NaOH and ethylene glycol (50 mL/trap). The test apparatus is illustrated on p. 22 of the study report.
If no traps were used, is the test system closed/open?		Volatile traps were used.
Is there any indication of the test material adsorbing to the walls of the test apparatus?		Yes, 0.7- 0.9% of the applied radioactivity was rinsed from the flask walls at study termination.
Experimental conditions Temperature (°C) Lighting pH Ranges		25.0 ± 0.2°C (range, 25.0-25.2°C). Dark. pH 5: 5.0; pH 7: 7.0-7.1; and pH 9: 8.6-9.1.

Parameters	Details
Other details, if any	Water lost from the test vessels during the study was replaced with sterile water.

Details obtained from pp. 21-25 and Tables 1-5, pp. 37-41 of the study report.

3. Supplementary Experiments: No supplementary experiments were reported.

4. Sampling:

Table 3: Sampling details.

Criteria	Details
Sampling intervals	0, 3, 7, 10, 14, 17, 21, 24, and 30 days.
Sampling method	At each sampling interval, two 4-mL aliquots of the treated buffer solutions were removed from each sample flask.
Sampling methods for the volatile compounds, if any	The NaOH trap solution was collected and replaced with fresh solution at every sampling interval. The ethylene glycol trap was not collected at each sampling interval since the radioactivity remained <0.05% of the applied.
Sampling intervals/times for: pH measurement Sterility check	 At each sampling interval. At the beginning and end of the experiment.
Sample storage before analysis	Aliquots of samples were analyzed immediately via LSC and TLC. Samples were stored at *ca.* - 20°C for ≤ 1 month prior to HPLC analysis.
Other observation, if any:	LSC analysis was performed for all sampling intervals; however, TLC and HPLC analyses were only performed on aqueous samples from 0, 3, 7, 14, 21, and 30 days.

Details obtained from pp. 24-25 of the study report.

C. ANALYTICAL METHODS

Extraction/clean up/concentration methods, if used: Test solutions were analyzed by LSC, TLC, and HPLC as collected, without manipulation or modification. At experiment termination, the flasks were washed with acetone (p. 24). The acetone wash was analyzed by LSC for total radioactivity.

Volatile residue determination: Aliquots of the NaOH and ethylene glycol solutions were analyzed by LSC for total radioactivity (p. 26). The residues in the NaOH were identified as $^{14}CO_2$ via precipitation with barium carbonate.

Total ^{14}C measurement: Total [^{14}C]residues were calculated by summing the measured

radioactivity in the aqueous solution, volatile traps, and acetone wash.

Derivatization method, if used: A derivatization method was not employed.

Identification and quantification of the parent: [^{14}C]Residues in the 0-, 3-, 7-, 14-, 21-, and 30-day posttreatment samples were separated, quantified, and identified by one-dimensional TLC on silica gel plates (5 cm x 20 cm; 0.25 mm thickness; 60 F_{254}) developed in chloroform:acetonitrile (50:50, v:v; solvent system code: SS 6; p. 27). The samples were cochromatographed with an unlabeled reference standard of halcomid (R_f 0.77 and 0.82; purity 98.8%; **pp**. 18, 27-28). The plates were visualized by exposure to iodine (parent and Ref. A), bromocresol green/bromophenol blue/potassium permanganate (Ref. B to O), and autoradiography. Radioactive residues were quantified by measuring their surface area via the Gaussian fit method.

The identity and quantity of halcomid in the buffer solutions (0, 3, 7, 14, 21, and 30 days) were confirmed via HPLC (pp. 29-30). The HPLC system consisted of a Lichrospher RP 18 column (250 mm x 4.0 mm; 5 µ), a mobile gradient phase consisting of (A) acetonitrile and (B) bidistilled water [A:B, v:v; 0-5 minutes 0:100, 25-30 minutes 100:0, and 30.1-40 minutes, 0:100], and UV (205 nm) and radioactive flow detection. Halcomid was identified by comparison of the retention time of the unlabeled reference standard of halcomid (purity 98.8%; Rt 25.23 minutes; **pp**. 18, 29-30).

Identification and quantification of transformation products: The transformation products were isolated and quantified via TLC using the same method as described for the parent (pp. 27-28). The transformation products were identified by comparison to the retention time of the following unlabeled reference standards; only Ref A was cochromatographed with the samples (pp. 20, 28).

Reference Compound	Ref. Code	Purity (%)	Rf-TLC	Reference Compound	Ref. Code	Purity (%)	Rf-TLC
N,N-Dimethyldeeanoic acid amide	None	98.8	0.77 0.82*	Heptanoic acid	H	>99	0.52
N,N-Dimethyloctanoic acid amide	A	97.0	0.74 0.80*	Heptanedioic acid	I	>98	0.05
Decanoic acid	B	>98	0.64	Hexanoic acid	J	>98	0.59
Decanedioic acid	C	>98	0.12	Hexanedioic acid	K	>99	0.04
Nonanoic acid	D	97	0.64	Pentanoic acid	L	>99	0.49
Nonanedioic acid	E	*ca.* 88	0.03	Pentanedioic acid	M	>99	0.05
Octanoic acid	F	>99	0.59	Butanoic acid	N	>99	0.51
Octanedioic acid	G	>99	0.05	Butanedioic acid	O	>99	0.04

*Second determination.

The identities of transformation products were confirmed via HPLC using the same method as described for the parent (pp. 29-30). The retention times of transformation products were compared to the retention times of the following selected unlabeled reference standards (pp. 20, 29-30):

Reference Compound	Ref. Code	Purity (%)	Retention time- HPLC
N,N-Dimethyldecanoic acid amide	None	98.8	25.23 minutes
N,N-Dimethyloctanoic acid amide	A	97.0	22.21 minutes
Decanoic acid	B	>98	24.15 minutes
Decanedioic acid	C	>98	17.21 minutes

Detection limits (LOD, LOQ) for the parent: The Limits of Detection were not reported. The counting error of the LSC reported to be <5%; more specific data were not provided (p. 26). The value of <0.05% was reported as a LOQ for the LSC in Tables 3-5, pp. 39-41. The Limits of Quantification for the TLC and HPLC were ≥0.8% and 3.3% of the applied radioactivity, respectively (pp. 27, 29).

Detection limits (LOD, LOQ) for the transformation products: The Limits of Detection were not reported. The Limits of Quantification were the same as those for the parent.

II. RESULTS AND DISCUSSION

A. TEST CONDITIONS: The incubation temperatures were reported as 25.0 ± 0.2°C (range, 25.0-25.2°C) during the study (pp. 22, 24-25, 31; Table 2, p. 38). The pH ranges were 5.0 (pH 5), 7.0-7.1 (pH 7), and 8.6-9.1 (pH 9). The sterility of the test solutions was determined at the beginning and end of each experiment. After 48 hours of incubation at 37°C on agar plates, 1 colony was observed on the day-0 pH 5 plate, 13 colonies on the day-30 pH 9, and none on the remaining plates (p. 30).

B. MASS BALANCE: The overall [^{14}C]residue recoveries were 96.9 ± 3.1% of the applied (range 92.2-102.3%) from the pH 5 buffer, 95.6 ± 2.8% (range 90.0-100.0%) from the pH 7 buffer, and 94.5 ± 2.9% (range 88.9-100.0%) from the pH 9 buffer (Tables 3-5, pp. 39-41). There was no significant loss of material from any buffer solution with time.

Table 4a. Hydrolysis of [^{14}C]halcomid, expressed as percentage of the applied radioactivity (mean ± s.d.; n = 2), at pH 5 and 25°C.*

Compound	Sampling times (days)								
	0	3	7	10	14	17	21	24	30
Parent (M1; halcomid; Rf 0.88)[1]	97.2 ± 0.3	94.8 ± 3.5	100.7 ± 1.3	NA	93.3 ± 2.1	NA	93.9 ± 3.4	NA	93.7 ± 3.4
Unknown M2 (Rf 0.77)[1]	ND	ND	ND	NA	ND	NA	ND	NA	1.3 ± 0.1
Unknown M3 (Rf 0.70)[1]	1.2 ± 0.2	1.6 ± 0.2	ND	NA	ND	NA	ND	NA	1.1 ± 0.0
Unknown M4 (Rf 0.96)[2]	1.7 ± 0.1	1.5 ± 0.3	ND	NA	ND	NA	ND	NA	ND
Total % recovery (aqueous solution)	100.0 ± 0.0	97.8 ± 3.4	100.7 ± 1.3	95.5 ± 0.8	93.3 ± 2.1	96.6 ± 0.6	93.9 ± 3.4	92.7 ± 0.6	96.1 ± 3.5
Volatiles	NS	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05
Acetone wash[3]	--[3]	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.7
Total % recovery (overall)	100.0 ± 0.0	98.5 ± 3.4	101.4 ± 1.3	96.2 ± 0.8	94.0 ± 2.1	97.3 ± 0.6	94.6 ± 3.4	93.4 ± 0.6	96.8 ± 3.5

* Data obtained from Table 3, p. 39 and Table 6, p. 42 of the study report.

NA = Not analyzed. Aqueous samples from 10, 17, and 24 days posttreatment were not analyzed via TLC in order to quantify the parent and its transformation products.

ND = Not detected, below the limit of detection.

NS = Not sampled, volatiles were not collected from day 0.

1 The retention time was obtained from the day 30, sample A.

2 The retention time was obtained from the day 3, sample A.

3 The measured radioactivity from the acetone wash of the test vessel at the end of the experiment was added completely to all samples, except day 0 (p. 24).

Table 4b. Hydrolysis of [^{14}C]halcomid, expressed as percentage of the applied radioactivity (mean ± s.d.; n = 2), at pH 7 and 25°C.*

Compound	Sampling times (days)								
	0	3	7	10	14	17	21	24	30
Parent (M1; halcomid; Rf 0.90)[1]	97.0 ± 0.5	93.4 ± 1.4	94.2 ± 3.4	NA	90.4 ± 2.2	NA	92.6 ± 2.7	NA	91.7 ± 0.8
Unknown M2 (Rf 0.78)[1]	ND	ND	1.4 ± 0.1	NA	1.5 ± 0.1	NA	1.6 ± 0.5	NA	1.8 ± 0.5
Unknown M3 (Rf 0.67)[1]	1.6 ± 0.4	ND	1.3 ± 0.4	NA	1.5 ± 0.3	NA	ND	NA	ND
Unknown M4 (Rf 0.96)[2]	1.5 ± 0.1	ND	ND	NA	ND	NA	ND	NA	ND
Total % recovery (aqueous solution)	100.0 ± 0.0	93.4 ± 1.4	96.9 ± 2.8	93.4 ± 3.5	93.3 ± 2.5	95.2 ± 0.3	94.2 ± 2.2	89.2 ± 1.7	93.5 ± 0.4
Volatiles	NS	<0.05	<0.05	0.2 ± 0.0	0.4 ± 0.0	0.6 ± 0.0	0.8 ± 0.0	1.1 ± 0.0	1.4 ± 0.0
Acetone wash[3]	--[3]	0.9	0.9	0.9	0.9	0.9	0.9	0.9	0.9
Total % recovery (overall)	100.0 ± 0.0	94.3 ± 1.4	97.8 ± 2.8	94.5 ± 3.5	94.6 ± 2.5	96.7 ± 0.3	95.9 ± 2.2	91.2 ± 1.7	95.8 ± 0.4

* Data obtained from Table 4, p. 40 and Table 8, p. 44 of the study report.
NA = Not analyzed. Aqueous samples from 10, 17, and 24 days posttreatment were not analyzed via TLC in order to quantify the parent and its transformation products.
ND = Not detected, below the limit of detection.
NS = Not sampled, volatiles were not collected from day 0.
1 The retention time was obtained from the day 30, sample A.
2 The retention time was obtained from the day 0, sample A.
3 The measured radioactivity from the acetone wash of the test vessel at the end of the experiment was added completely to all samples, except day 0 (p. 24).

Table 4c. Hydrolysis of [^{14}C]halcomid, expressed as percentage of the applied radioactivity (mean ± s.d.; n = 2), at pH 9 and 25°C.*

Compound	Sampling times (days)						
	0	3	7	10	14	17	21
Parent (M1; halcomid; Rf 0.90)[1]	97.0 ± 0.4	92.0 ± 1.1	92.6 ± 0.1	NA	88.7 ± 0.9	NA	88.9 ±
Unknown M2 (Rf 0.78)[1]	1.6 ± 0.0	2.2 ± 0.0	3.3 ± 0.1	NA	3.4 ± 0.2	NA	3.2 ±
Unknown M3 (Rf 0.66)[2]	1.5 ± 0.4	ND	ND	NA	ND	NA	ND
Total % recovery (aqueous solution)	100.0 ± 0.0	94.2 ± 1.1	95.8 ± 0.1	91.3 ± 1.0	92.0 ± 1.1	93.9 ± 1.3	92.1 ±
Volatiles	NS	<0.05	0.1 ± 0.0	0.1 ± 0.0	0.3 ± 0.0	0.4 ± 0.0	0.5 ±
Acetone wash[3]	--[3]	0.9	0.9	0.9	0.9	0.9	0.9
Total % recovery (overall)	100.0 ± 0.0	95.1 ± 1.1	96.8 ± 0.1	92.3 ± 1.0	93.2 ± 1.1	95.2 ± 1.3	93.5 ±

* Data obtained from Table 5, p. 41 and Table 10, p. 46 of the study report.
NA = Not analyzed. Aqueous samples from 10, 17, and 24 days posttreatment were not analyzed via TLC in order to quantify the parent and its transformation products.
ND = Not detected, below the limit of detection.
NS = Not sampled, volatiles were not collected from day 0.
1 The retention time was obtained from the day 30, sample A.
2 The retention time was obtained from the day 0, sample A.
3 The measured radioactivity from the acetone wash of the test vessel at the end of the experiment was added completely to all samples, except day 0 (p. 24).

C. TRANSFORMATION OF PARENT COMPOUND: In the pH 5 buffer solution, [^{14}C]halcomid was 97.2% of the applied at 0 days posttreatment, ranged from 93.3-100.7% at 3-21 days with no pattern of decline, and was 93.7% at 30 days (study termination; Table 6, p. 42). In the pH 7 buffer solution, [^{14}C]halcomid declined from 97.0% at 0 days posttreatment to 94.2% at 7 days and 91.7% at 30 days (Table 8, p. 44). In the pH 9 buffer solution, [^{14}C]halcomid declined from 97.0% at 0 days posttreatment to 92.6% at 7 days and 88.6% at 30 days (Table 10, p. 46).

HALF-LIVES: Halcomid was relatively stable (<5% or *ca.* 5% degradation over 30 days) in the pH 5 and 7 buffer solutions, with calculated half-lives of greater than 1 year. The r^2 values associated with these calculations are 0.206 and 0.311 for the pH 5 and 7 experiments, respectively. In the pH 9 buffer solution, halcomid displayed a slightly faster degradation (*ca.* 10% degradation over 30 days), with a calculated half-life of 266.60 days (0.73 years) and associated r^2 value of 0.6256. These half-lives are of uncertain value because they are extrapolated well beyond the 30-day duration of the study.

The reviewer-calculated half-lives were similar to those that were calculated by the study author using zero-order and first-order regression kinetics (p. 33).

Half-lives

pH	First-order linear kinetics [time (x-axis) vs log of % parent radioactivity (y-axis)]		
	Half-life*	Regression equation	r^2
pH 5	479 days (1.31 years)	y = -0.00145x + 4.5775	0.206
pH 7	476 days (1.30 years)	y = -0.00146x + 4.5526	0.311
pH 9	269 days (0.74 years)	y = -0.00258x + 4.5455	0.6256

* Half-lives were calculated by the reviewer using data obtained from Table 6, p. 42, Table 8, p. 44, and Table 10, p. 46 of the study report. Half-lives reported by the study author are on p. 33 of the study report (the study author's decay curves were illustrated in Figure 20, p. 67 of the study report).

TRANSFORMATION PRODUCTS: No major transformation products were isolated and no minor transformation products were identified. Three minor unidentified transformation products (M2, M3, and M4) were each ≤3.4% of the applied at all sampling intervals (Table 6, p. 42; Table 8, p. 44; Table 10, p. 46).

VOLATILIZATION: Volatiles were measured at maxima of > 0.05%, 1.4%, and 1.0% in the pH 5, 7, and 9 buffer solutions (Table 6, p. 42; Table 8, p. 44; Table 10, p. 46). Volatilized $^{14}CO_2$ composed 98.6% of the measured volatile radioactivity (quantified via barium carbonate precipitation; p. 35).

TRANSFORMATION PATHWAY: A transformation pathway was not provided. Halcomid was relatively stable in the buffer solutions; no transformation products were identified.

Table 5: Chemical name and CAS number for the transformation products of halcomid.

Applicant's Code Name	CAS Number	Chemical Name	Chemical formula	Molecular weight (g/mol)	SMILES string
No transformation products were identified.					

D. SUPPLEMENTARY EXPERIMENT-RESULTS: No supplementary experiments were reported.

III. STUDY DEFICIENCIES:

1. The agar plate on which the pH 9 test solution was plated had a plate count of 13 colonies at study termination. It is unlikely that this level of contamination is high enough to have caused any significant degradation of the test substance, and may have occurred during analysis. Since the concentration of halcomid in the pH 9 buffer solution is very similar to that in the pH 5 and 7 solutions, microbial activity clearly had no significant impact on the study results.

2. In the pH 9 solution, the material balance for replicate B at 24 days posttreatment was 88.9% of the applied. Since the material balance of replicate A was 92.3%, the average material balance at 24 days was 90.6%.

IV. REVIEWER'S COMMENTS:

1. The study author assumed that the adsorption of the test material to the walls of the test vessels occurred during "the first hours of the study" (p. 24). Therefore, the radioactivity which was measured in the acetone wash at study termination was added to every sampling interval after day 0. Since the acetone wash solution contained <1% of the applied, this assumption does not affect the interpretation of the study.

2. The results of the HPLC analyses are provided in the following table:

Concentration of halcomid (% of applied radioactivity)						
Sampling times (days)	**0**	**3**	**7**	**14**	**21**	**30**
pH 5	100.0	97.8	100.7	93.3	93.9	96.1
pH 7	100.0	93.4	96.9	93.3	94.2	93.5
pH 9	100.0	94.2	95.8	92.0	92.1	91.5

Data obtained from Table 7, p. 43, Table 9, p. 45, and Table 11, p. 47 of the study report.

3. The study author concluded that the test material was stable in the application solution because the radiochemical purity was 98.1% of the applied before application and 97.0-97.3% after application (p. 31).

4. The study author did not explain why the reference compounds other than N,N-dimethyloctanoic acid amide (Ref A) were not co-chromatographed with the aqueous solutions, especially in cases where the R_f of an unidentified transformation product was close to that of a reference compound. However, the identification of these transformation products was not necessary since they did not exceed 3% of the applied radioactivity.

5. The aliquots of the aqueous solutions which were taken for sterility determinations (0.5-mL) and HPLC analysis (unspecified) were stored at - 20°C for 10 days to 1.5 months (pp. 24, 30). No storage data was provided by the study author; the study author noted that the HPLC storage was irrelevant because this data was not used for quantification (p. 24).

6. The Limits of Detection for the LSC, TLC, and HPLC method were not provided. LODs should be reported to allow the reviewer to evaluate the adequacy of the test method. The reviewer also noted that ≥0.8% (greater than or equal to 0.8%) is not a logical LOQ.

7. Physico-chemical properties such as the molecular formula, vapor pressure, UV adsorption, pK_a, and K_{ow} were not reported.

8. The application rate used in the study was not justified by the study author.

9. Representative TLC chromatograms were presented in Figures 1-13, pp. 48-60 of the study report. Representative HPLC chromatograms were presented in Figure 1, p. 48 and Figures 14-19, pp. 61-66 of the study report. Figure 1 contained the TLC and HPLC chromatograms of the nonradiolabeled halcomid reference material.

V. REFERENCES:

1. U.S. Environmental Protection Agency. 1982. Pesticide Assessment Guidelines, Subdivision N, Chemistry: Environmental Fate, Section 161-1. Hydrolysis studies. Office of Pesticide and Toxic Substances, Washington, DC. EPA 540/9-82-021.

2. U.S. Environmental Protection Agency. 1989. FIFRA Accelerated Reregistration, Phase 3 Technical Guidance. Office of the Prevention, Pesticides, and Toxic Substances, Washington, DC. EPA 540/09-90-078.

3. U.S. Environmental Protection Agency. 1993. Pesticide Registration Rejection Rate Analysis - Environmental Fate. Office of the Prevention, Pesticides, and Toxic Substances, Washington, DC. EPA 738-R-93-010.

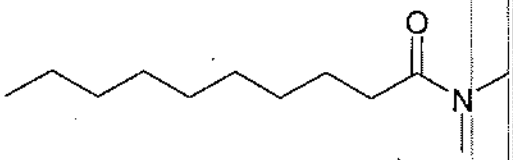
ATTACHMENT

Chemical Structure of Parent
and
Names of Unidentified Reference Compounds

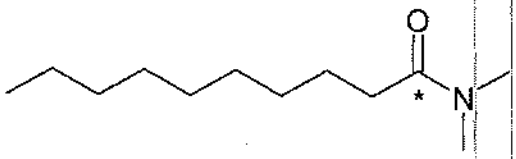
Halcomid

IUPAC name: N,N-Dimethyldecanoic acid amide.
CAS name: Not reported.
CAS No: Not reported.
SMILES string: O=C(CCCCCCCCC)N(C)C

Unlabeled



[1-^{14}C]Halcomid



* Position of radiolabel

Unidentified Reference Compounds

N,N-Dimethyloctanoic acid amide
Structure not provided.
Decanoic acid
Structure not provided.
Decanedioic acid
Structure not provided.
Nonanoic acid
Structure not provided.
Nonanedioic acid
Structure not provided.
Octanoic acid
Structure not provided.
Octanedioic acid
Structure not provided.
Heptanoic acid
Structure not provided.
Heptanedioic acid
Structure not provided.
Hexanoic acid
Structure not provided.
Hexanedioic acid
Structure not provided.
Pentanoic acid
Structure not provided.
Pentanedioic acid
Structure not provided.
Butanoic acid
Structure not provided.
Butanedioic acid
Structure not provided.

Attachment 1

Excel Spreadsheets

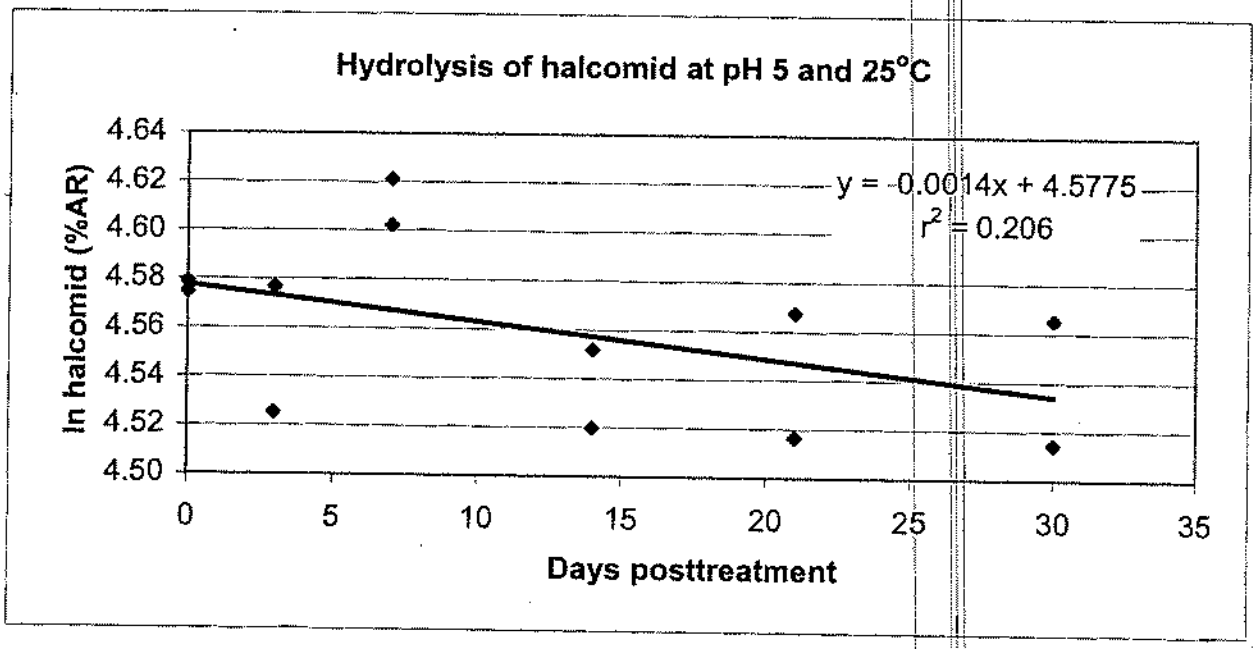
Chemical Name: Halcomid
PC Code: 999999
MRID: 45369732
Guideline No.: 161-1

Half-life: 495.11 days
1.36 years

pH 5

Days	Halcomid (% AR)	ln Halcomid (%AR)
0	97.0	4.5747
0	97.4	4.5788
3	92.3	4.5250
3	97.2	4.5768
7	99.7	4.6022
7	101.6	4.6210
14	94.8	4.5518
14	91.8	4.5196
21	96.3	4.5675
21	91.5	4.5163
30	91.3	4.5142
30	96.1	4.5654

Data obtained from Table 6, p. 42 of the study report.



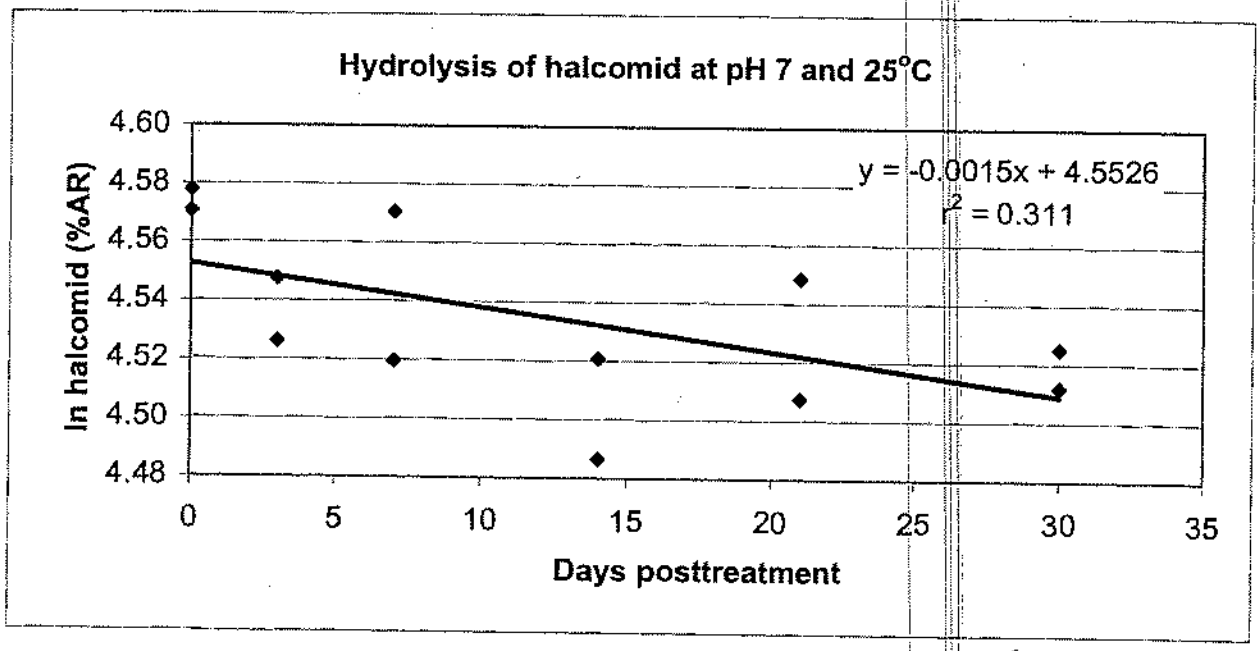
Chemical Name: Halcomid
PC Code: 999999
MRID: 45369732
Guideline No.: 161-1

Half-life: 462.10 days
1.27 years

pH 7

Days	Halcomid (% AR)	ln Halcomid (%AR)
0	97.3	4.5778
0	96.6	4.5706
3	92.4	4.5261
3	94.4	4.5475
7	91.8	4.5196
7	96.6	4.5706
14	91.9	4.5207
14	88.8	4.4864
21	94.5	4.5486
21	90.7	4.5076
30	92.3	4.5250
30	91.1	4.5120

Data obtained from Table 8, p. 44 of the study report.



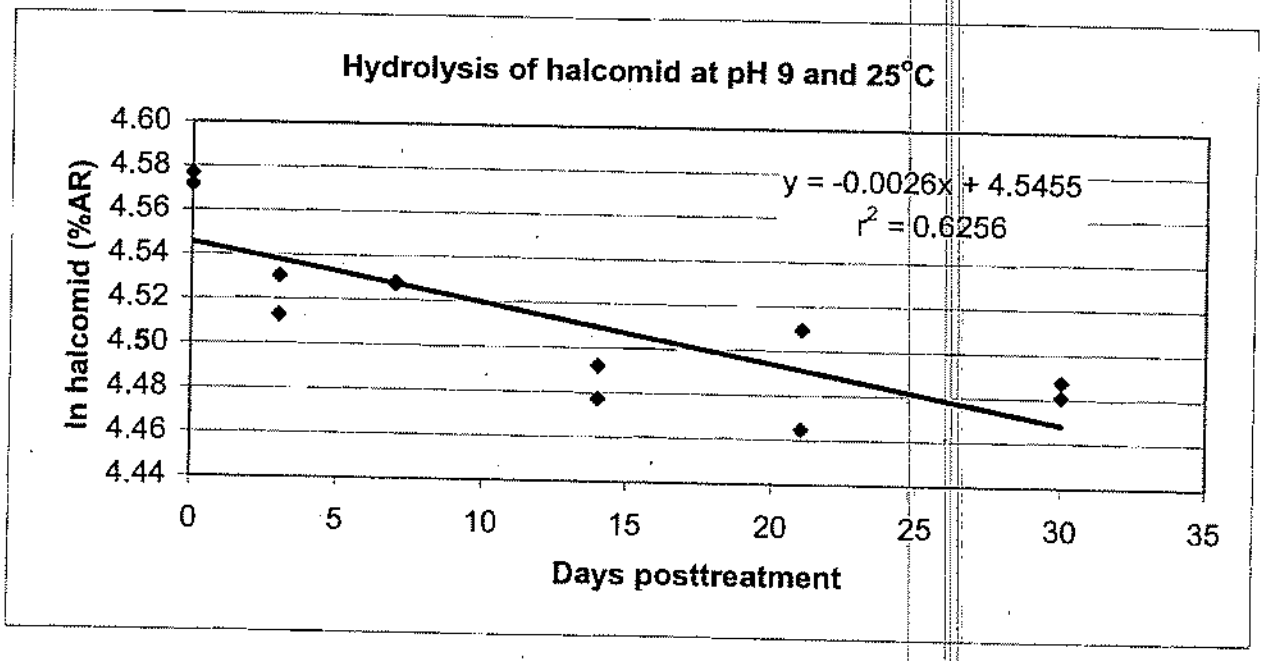
Chemical Name: Halcomid
PC Code: 999999
MRID: 45369732
Guideline No.: 161-1

Half-life: 266.60 days
0.73 years

pH 9

Days	Halcomid (% AR)	ln Halcomid (%AR)
0	97.2	4.5768
0	96.7	4.5716
3	91.2	4.5131
3	92.8	4.5304
7	92.6	4.5283
7	92.5	4.5272
14	89.3	4.4920
14	88.0	4.4773
21	90.9	4.5098
21	86.9	4.4648
30	88.9	4.4875
30	88.3	4.4807

Data obtained from Table 10, p. 46 of the study report.



Chemical Name: Halcomid
PC Code: 999999
MRID: 45369732
Guideline No.: 161-1

Mass Balance in % of applied radioactivity
Data obtained from Table 3, p. 39 of the study report.

pH 5 25°C

Days	Aqueous	Mean	SD	Volatiles	Mean	SD	Acetone Wash	Mean	SD	Total	Mean	SD
0	100.0	100.0	0.0	0.0			0.0	0.0	0.0	100.0	100.0	0.0
0	100.0			0.0			0.0			100.0		
3	95.4	97.8	3.4	<0.05			0.7	0.7	0.0	96.1	98.5	3.4
3	100.2			<0.05			0.7			100.9		
7	99.7	100.7	1.3	<0.05			0.7	0.7	0.0	100.4	101.4	1.3
7	101.6			<0.05			0.7			102.3		
10	96.0	95.5	0.8	<0.05			0.7	0.7	0.0	96.7	96.2	0.8
10	94.9			<0.05			0.7			95.6		
14	94.8	93.3	2.1	<0.05			0.7	0.7	0.0	95.5	94.0	2.1
14	91.8			<0.05			0.7			92.5		
17	96.1	96.6	0.6	<0.05			0.7	0.7	0.0	96.8	97.3	0.6
17	97.0			<0.05			0.7			97.7		
21	96.3	93.9	3.4	<0.05			0.7	0.7	0.0	97.0	94.6	3.4
21	91.5			<0.05			0.7			92.2		
24	92.2	92.7	0.6	<0.05			0.7	0.7	0.0	92.9	93.4	0.6
24	93.1			<0.05			0.7			93.8		
30	93.6	96.1	3.5	<0.05			0.7	0.7	0.0	94.3	96.8	3.5
30	98.6			<0.05			0.7			99.3		
										96.9	Mean	
										3.1	SD	

Chemical Name: Halcomid
PC Code: 999999
MRID: 45369732
Guideline No.: 161-1

Distribution of Radioactivity in % of applied radioactivity
Data obtained from Table 6, p. 42 of the study report.

pH 5 25°C

Days	Parent (M1)	Mean	SD	Unknown M2	Mean	SD	Unknown M3	Mean	SD	Unknown M4	Mean	SD
0	97.0	97.2	0.3	0.0	0.0	0.0	1.3	1.2	0.2	1.7	1.7	0.1
0	97.4			0.0			1.0			1.6		
3	92.3	94.8	3.5	0.0	0.0	0.0	1.4	1.6	0.2	1.7	1.5	0.3
3	97.2			0.0			1.7			1.3		
7	99.7	100.7	1.3	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
7	101.6			0.0			0.0			0.0		
14	94.8	93.3	2.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
14	91.8			0.0			0.0			0.0		
21	96.3	93.9	3.4	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
21	91.5			0.0			0.0			0.0		
30	91.3	93.7	3.4	1.2	1.3	0.1	1.1	1.1	0.0	0.0	0.0	0.0
30	96.1			1.4			1.1			0.0		

Chemical Name: Halcomid
PC Code: 999999
MRID: 45369732
Guideline No.: 161-1

Mass Balance in % of applied radioactivity
Data obtained from Table 4, p. 40 of the study report.

pH 7 25°C

Days	Aqueous	Mean	SD	Volatiles	Mean	SD	Acetone Wash	Mean	SD	Total	Mean	SD
0	100.0	100.0	0.0	0.0			0.0	0.0	0.0	100.0	100.0	0.0
0	100.0			0.0			0.0			100.0		
3	92.4	93.4	1.4	<0.05			0.9	0.9	0.0	93.3	94.3	1.4
3	94.4			<0.05			0.9			95.3		
7	94.9	96.9	2.8	<0.05			0.9	0.9	0.0	95.8	97.8	2.8
7	98.9			<0.05			0.9			99.8		
10	95.8	93.4	3.5	0.2	0.2	0.0	0.9	0.9	0.0	96.9	94.5	3.5
10	90.9			0.2			0.9			92.0		
14	95.1	93.3	2.5	0.4	0.4	0.0	0.9	0.9	0.0	96.4	94.6	2.5
14	91.5			0.4			0.9			92.8		
17	95.4	95.2	0.3	0.6	0.6	0.0	0.9	0.9	0.0	96.9	96.7	0.3
17	95.0			0.6			0.9			96.5		
21	95.7	94.2	2.2	0.8	0.8	0.0	0.9	0.9	0.0	97.4	95.9	2.2
21	92.6			0.8			0.9			94.3		
24	90.4	89.2	1.7	1.1	1.1	0.0	0.9	0.9	0.0	92.4	91.2	1.7
24	88.0			1.1			0.9			90.0		
30	93.7	93.5	0.4	1.4	1.4	0.0	0.9	0.9	0.0	96.0	95.8	0.4
30	93.2			1.4			0.9			95.5		
										95.6	Mean	
										2.8	SD	

Chemical Name: Halcomid
PC Code: 999999
MRID: 45369732
Guideline No.: 161-1

Distribution of Radioactivity in % of applied radioactivity
Data obtained from Table 8, p. 44 of the study report.

pH 7 25°C

Days	Parent (M1)	Mean	SD	Unknown M2	Mean	SD	Unknown M3	Mean	SD	Unknown M4	Mean	SD
0	97.3	97.0	0.5	0.0	0.0	0.0	1.3	1.6	0.4	1.4	1.5	0.1
0	96.6			0.0			1.9			1.5		
3	92.4	93.4	1.4	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
3	94.4			0.0			0.0			0.0		
7	91.8	94.2	3.4	1.5	1.4	0.1	1.5	1.3	0.4	0.0	0.0	0.0
7	96.6			1.3			1.0			0.0		
14	91.9	90.4	2.2	1.5	1.5	0.1	1.7	1.5	0.3	0.0	0.0	0.0
14	88.8			1.4			1.3			0.0		
21	94.5	92.6	2.7	1.2	1.6	0.5	0.0	0.0	0.0	0.0	0.0	0.0
21	90.7			1.9			0.0			0.0		
30	92.3	91.7	0.8	1.4	1.8	0.5	0.0	0.0	0.0	0.0	0.0	0.0
30	91.1			2.1			0.0			0.0		

Chemical Name: Halcomid
PC Code: 999999
MRID: 45369732
Guideline No.: 161-1

Mass Balance in % of applied radioactivity
Data obtained from Table 5, p. 41 of the study report.

pH 9 25°C

Days	Aqueous	Mean	SD	Volatiles	Mean	SD	Acetone Wash	Mean	SD	Total	Mean	SD
0	100.0	100.0	0.0	0.0			0.0	0.0	0.0	100.0	100.0	0.0
0	100.0			0.0			0.0			100.0		
3	93.4	94.2	1.1	<0.05			0.9	0.9	0.0	94.3	95.1	1.1
3	95.0			<0.05			0.9			95.9		
7	95.9	95.8	0.1	0.1	0.1	0.0	0.9	0.9	0.0	96.9	96.8	0.1
7	95.7			0.1			0.9			96.7		
10	92.0	91.3	1.0	0.1	0.1	0.0	0.9	0.9	0.0	93.0	92.3	1.0
10	90.6			0.1			0.9			91.6		
14	92.8	92.0	1.1	0.3	0.3	0.0	0.9	0.9	0.0	94.0	93.2	1.1
14	91.2			0.3			0.9			92.4		
17	94.8	93.9	1.3	0.4	0.4	0.0	0.9	0.9	0.0	96.1	95.2	1.3
17	93.0			0.4			0.9			94.3		
21	94.1	92.1	2.8	0.5	0.5	0.0	0.9	0.9	0.0	95.5	93.5	2.8
21	90.1			0.5			0.9			91.5		
24	90.7	89.0	2.4	0.7	0.7	0.0	0.9	0.9	0.0	92.3	90.6	2.4
24	87.3			0.7			0.9			88.9		
30	91.7	91.5	0.4	1.0	1.0	0.0	0.9	0.9	0.0	93.6	93.4	0.4
30	91.2			1.0			0.9			93.1		
										94.5	Mean	
										2.9	SD	

Chemical Name: Halcomid
PC Code: 999999
MRID: 45369732
Guideline No.: 161-1

Distribution of Radioactivity in % of applied radioactivity
Data obtained from Table 10, p. 46 of the study report.

pH 9 25°C

Days	Parent (M1)	Mean	SD	Unknown M2	Mean	SD	Unknown M3	Mean	SD
0	97.2	97.0	0.4	1.6	1.6	0.0	1.2	1.5	0.4
0	96.7			1.6			1.7		
3	91.2	92.0	1.1	2.2	2.2	0.0	0.0	0.0	0.0
3	92.8			2.2			0.0		
7	92.6	92.6	0.1	3.3	3.3	0.1	0.0	0.0	0.0
7	92.5			3.2			0.0		
14	89.3	88.7	0.9	3.5	3.4	0.2	0.0	0.0	0.0
14	88.0			3.2			0.0		
21	90.9	88.9	2.8	3.2	3.2	0.0	0.0	0.0	0.0
21	86.9			3.2			0.0		
30	88.9	88.6	0.4	2.8	2.9	0.1	0.0	0.0	0.0
30	88.3			2.9			0.0		

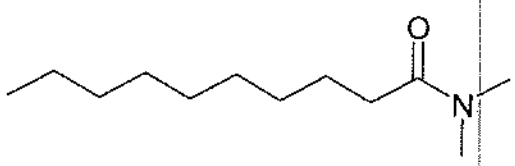
Attachment 2

Structures of Parent and Transformation Products

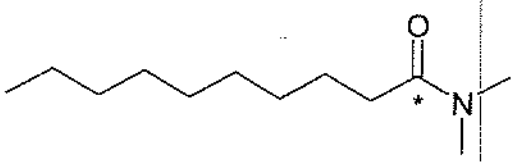
Halcomid

IUPAC name: N,N-Dimethyldecanoic acid amide.
CAS name: Not reported.
CAS No: Not reported.
SMILES string: O=C(CCCCCCCCC)N(C)C

Unlabeled



[1-^{14}C]Halcomid



* Position of radiolabel.

Unidentified Reference Compounds

N,N-Dimethyloctanoic acid amide
Structure not provided.
Decanoic acid
Structure not provided.
Decanedioic acid
Structure not provided.
Nonanoic acid
Structure not provided.
Nonanedioic acid
Structure not provided.
Octanoic acid
Structure not provided.
Octanedioic acid
Structure not provided.
Heptanoic acid
Structure not provided.
Heptanedioic acid
Structure not provided.
Hexanoic acid
Structure not provided.
Hexanedioic acid
Structure not provided.
Pentanoic acid
Structure not provided.
Pentanedioic acid
Structure not provided.
Butanoic acid
Structure not provided.
Butanedioic acid
Structure not provided.

Attachment 3

Illustration of Test System

2.2.2 Experimental Set Up

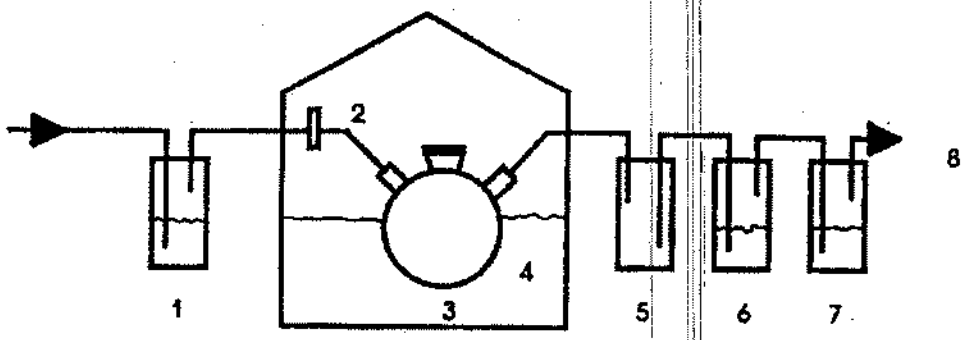
Test System:

Aliquots of 200 ml sterile buffer (pH 5, 7 or 9) solution containing the test article were incubated in pyrex glass flasks in a waterbath at the desired temperature of 25 °C (± 0.2 °C).

The incubations were performed in the dark in a waterbath which was covered with a steel cover to protect the samples from occasional light.

The flasks were ventilated with moistened air through a sterile filter (about 30 ml/min.). The outcoming air was passed through a CO_2-trapping system (2N NaOH) and through ethylene glycol for absorption of volatiles.

Diagram of the incubation apparatus:



1	Gas washing bottle with water to moisten the incoming air
2	Filter to sterilize the incoming air
3	Incubation flask (three necks, 250 ml)
4	Waterbath
5	Empty gas washing bottle for collection of condensation water
6	Gas washing bottle containing 50 ml 2N NaOH to absorb $^{14}CO_2$
7	Gas washing bottle containing 50 ml ethylene glycol for absorption of volatiles
8	Vacuum pump