DATA EVALUATION RECORD

STUDY 2

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FORMULATION--00--ACTIVE INGREDIENT

STUDY ID 44387455
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CONCLUSIONS

Laboratory Accumulation - Fish

1. This study is not scientifically valid and does not provide useful information on the bioaccumulation of cloqiontocet-mexyl (CGA-185072) residues in bluegill sunfish. The concentration of the parent compound was not constant throughout the study and the level of degradates in the exposure water was unacceptably high. In addition, the concentration of total [^{14}C]residues in the treatment water was not constant throughout the study.

2. This study does not meet Subdivision N Guidelines for the fulfillment of EPA data requirements on bioaccumulation in fish for the following reasons:

   (i) extractable [^{14}C]residues which exceeded 50 ppb were not adequately identified;

   (ii) the exposure concentration of the parent compound was not constant throughout the study, and the level of degradates in the water was unacceptably high; and

   (iii) frozen storage stability data for fish tissue were not provided.

3. Radiolabeled residues accumulated in bluegill sunfish that were exposed to nonradiolabeled plus quinoline ring-labeled [3-^{14}C]cloqiontocet-mexyl, at a nominal concentration of 100 µg/L, under flow-through aquarium conditions. Data were reported for two separate exposure tanks. Maximum bioconcentration factors (reviewer-calculated), based on total radioactivity, were 153X and 128X for edible, 680X and 655X for nonedible, and 439X and 747X for whole tissues, respectively. Mean total [^{14}C]residues were highest in nonedible tissues (35.8 and 36.3 ppm) compared with the edible (4.3 and 4.6 ppm) and whole fish (21.8 and 30.3 ppm) tissues. Maximum total [^{14}C]residues were 12.7 and 11.1 ppm in the edible tissues, 57.1 and 57.0 ppm in the nonedible tissues, and 38.2 and 65.0 ppm in the whole fish tissues. Data were variable over time; therefore, a plateau or steady state could not be determined. Radiolabeled [^{14}C]residues were characterized only in the edible and nonedible tissues collected at exposure days 3 (both tanks) and 17 (one tank); data reported for degradates are in parent equivalents. In edible and nonedible fish tissues, the parent compound was not detected at exposure days 3 or 17. The major metabolite CGA 153433 was present at mean concentrations of 9.6 ppm and 3.3 ppm in the edible tissue, and was 35.4 ppm and 24.3 ppm in the nonedible tissue at days 3 and 17, respectively. The unidentified major metabolite M5 was present at 0.28 ppm and 0.46 ppm in the edible tissue, and was 1.48 ppm and 0.46 ppm in the nonedible tissue at exposure days 3 and 17, respectively. The unidentified major metabolite M6 was present only in the nonedible tissue, at 1.1 ppm on exposure day 3. During the depuration period, ≥98.0% of the [^{14}C]residues (both tanks) accumulated in the edible, nonedible, and whole fish tissues were eliminated by 7 days.

METHODOLOGY

Bluegill sunfish (*Lepomis macrochirus*; length not specified; weight approximately 1.8 grams; age not specified) were acclimated to the laboratory environment for four weeks prior to the initiation of the study; conditions were not reported. Flow-through aquatic exposure systems were prepared using three temperature-controlled tanks (two exposure and one control; tank material not reported) maintained at 19 ± 1°C (Figure 3, p. 68; p. 27.). Each aquarium contained 100 L of well water (hardness 44.0 fr.H°, alkalinity 28.2 fr.H°, pH 7.6-8.2, conductivity 720.0 µS/cm; Table 2, p. 50; pp. 42, 102; see Comment #8). The aerated test water was continuously supplied at a measured flow rate of approximately three turnovers per day (p. 27). Twenty-four hours prior to the introduction of fish into the aquaria, the exposure tanks were treated with nonradiolabeled plus quinoline ring-labeled [3-^{14}C]cloqiontocet-mexyl (5-chloro-8-quinolinoxy-acetic acid-1-methyl-hexylester; radiochemical purity 99.6 ± 0.2%, specific activity 52.2 µCi/mg, p. 24), dissolved in acetone and mixed with Tween 80, at a nominal concentration of 100 µg/L (approximately 1/1000 of the reported 96-hour LC_{50}; see Comment #7). The test compound was introduced into the exposure water with a Hamilton dispenser. The control aquarium was treated only with the untreated application solution (p. 27).

Bluegill sunfish (199) were placed in each of the two exposure aquaria and the control aquarium (p. 26). The flow-through systems were continuously aerated to maintain a dissolved oxygen content of 6.2-9.5 mg/L, and the temperature was maintained at 19 ± 1°C (Table 2, p. 50). The tanks were subjected to a light/dark cycle of 16 hours/8 hours throughout the exposure period. During the exposure period, duplicate water samples were collected from the treated aquaria on days 0, 1, 2, 3, 6, 10, 14, and 17 for the determination of total [^{14}C]residues; water samples were collected on exposure days 0, 1, 3, 10, 14 and 17 for the characterization of [^{14}C]residues (p. 32). During the exposure period, three fish were collected from each treated aquarium at 0, 1, 3, 6, 10, 14, and 17 days to determine total [^{14}C]residues in edible (fillet and skin) and nonedible (head, fins, viscera, and skeleton) tissues (p. 34). Two additional fish were collected from each tank at each sampling interval and stored at -20°C. A single fish from each treated aquarium was collected for the analysis of whole fish tissue samples (see Comment #10). Four fish were collected from the control aquarium at the initiation and termination of the exposure period. Additional fish (10 and 12 fish from the two treated aquaria) were collected at day 17 for possible further analysis (p. 32). Upon removal, fish were rinsed, sacrificed, dissected, and stored at -20°C for an unspecified length of time prior to analysis.

Following the 17-day exposure period, the remaining fish from the two treated aquaria were temporarily transferred to clean tap water while treatment tanks were cleaned prior to the 14-day depuration period (p. 29). Duplicate water samples were collected from the two aquaria on depuration days 0, 1, 7, 10, and 14 for the determination of total [^{14}C]residues (p. 32). During the depuration period, three fish were collected from each

treated aquarium at 1, 3, 7, 10, and 14 days to determine total [^{14}C]residues in edible and nonedible tissues; a single fish was also collected for the analysis of whole fish tissue samples (p. 34). Two additional fish were collected from each tank at each sampling interval and stored at -20°C. Water temperature, pH and the dissolved oxygen content were monitored daily in each tank throughout the exposure and depuration periods (Table 2, p. 50).

At each sampling interval, duplicate water samples from the treated aquaria were analyzed for total radioactivity by LSC; the limit of quantitation was reported as twice the background (Table 12, p. 60). Aliquots of samples collected for characterization were acidified (pH 1) with hydrochloric acid and extracted 1-3 times with ethyl acetate (p. 33). The ethyl acetate extracts were concentrated with sodium sulfate, evaporated, redissolved in acetone, and analyzed by TLC using silica gel and RP-18 plates developed with one of the following solvent systems: trichloromethane (100%), n-hexane:ethyl acetate (20:40, v:v) and trichloromethane:methanol:acetic acid:water (75:20:4:2, v:v:v:v; p. 37). Areas of radioactivity were detected by an autoradioimaging scanner. Samples were co-chromatographed with nonradiolabeled reference standards which were visualized under UV light (254 or 366 nm). The aqueous fractions remaining after partitioning were concentrated by freeze-drying, dissolved in methanol, re-concentrated, centrifuged, and analyzed by TLC as described previously, but were developed with trichloromethane: methanol:acetic acid:water (75:20:4:2).

Whole fish samples were cut, weighed, and solubilized with Soluene® for 48-96 hours at 50°C. Duplicate subsamples were analyzed for total radioactivity by LSC (p. 34). Edible and nonedible fish tissues were pooled, weighed, and solubilized as described previously. Homogenized samples were extracted in sequence with dichloromethane:acetonitrile (1:1, v:v; twice), dichloromethane, dichloromethane:hexane (1:1, v:v), dichloromethane: acetonitrile (2:8, v:v), acetonitrile (twice), acetonitrile:methanol (2:8, v:v), and methanol (p. 35). Following extraction, the last four extracts were pooled, concentrated and analyzed by TLC using silica gel and RP-18 plates developed with one of the following solvent systems: trichloromethane (100%), n-hexane:ethyl acetate (20:40, v:v) and trichloromethane:methanol:acetic acid:water (75:20:4:2, v:v:v:v; p. 37). Areas of radioactivity were detected by an autoradioimaging scanner. Samples were co-chromatographed with nonradiolabeled reference standards which were visualized under UV light (254 or 366nm). The post-extracted fish tissues were air dried and homogenized and triplicate samples were analyzed for total radioactivity by LSC following combustion.

DATA SUMMARY

Radiolabeled residues accumulated in bluegill sunfish that were exposed to nonradiolabeled plus quinoline ring-labeled [3-^{14}C]cloqiontocet-mexyl (radiochemical purity 99.6 ± 0.2%), at a nominal concentration of 100 µg/L, under flow-through

aquarium conditions. Mean total [^{14}C]residues (reviewer-calculated means of days 1-17 data from Tables 8, 9; pp. 56, 57) were highest in nonedible tissues (35.8 and 36.3 ppm) compared with the edible (4.3 and 4.6 ppm) and whole fish (21.8 and 30.3 ppm) tissues (Figures 5, 6; pp. 70, 71). Data were variable over time; therefore, an accumulation plateau or steady state could not be determined (see Comment #2). Maximum total [^{14}C]residues were 12.7 and 11.1 ppm in the edible tissues (day 3), 57.1 and 57.0 ppm in the nonedible tissues (day 1), and 38.2 ppm (day 6) and 65.0 ppm (day 3) in the whole fish tissues.

Radiolabeled [^{14}C]residues were characterized only in the edible and nonedible tissues collected at 3 and 17 days of exposure; data reported for degradates are in parent equivalents. Fish tissues from both tanks were combined on day 3 to obtain enough material for analysis; day 17 data were obtained from a single tank. Total radiolabeled [^{14}C] residues were 9.9 ppm and 3.4 ppm in the edible tissue, and 38.0 ppm and 24.8 ppm in the nonedible tissue at 3 and 17 days, respectively (Tables 14, 15; pp. 62, 63). The parent compound was not detected at exposure days 3 and 17. The major metabolite

5-chloro-8-quinolinoxyacetic acid (CGA 153433)

was present at concentrations of 9.6 ppm and 3.3 ppm in the edible tissue, and was 35.4 ppm and 24.3 ppm in the nonedible tissue at exposure days 3 and 17, respectively (Tables 16, 17; pp. 64, 65). The unidentified major metabolite

M5 (chemical name and structure not reported)

was present at 0.284 ppm and 0.461 ppm in the edible tissue, and was 1.48 ppm and 0.461 ppm in the nonedible tissue at exposure days 3 and 17, respectively. The unidentified major metabolite

M6 (chemical name and structure not reported)

was present only in the nonedible tissue, at 1.1 ppm at day 3 of the exposure period.

Maximum bioconcentration factors (BCF; calculated by reviewer as described in Comment #4), based on total radioactivity, were 153X and 128X for the edible, 680X and 655X for the nonedible, and 439X and 747X for the whole tissues in the two exposure tanks. Depuration percentages were calculated by the reviewer using reported tissue concentration (total radioactivity) in Tables 8 and 9 (pp. 56, 57). During the depuration period, ≥98.0% of the [^{14}C]residues (both tanks) accumulated in the edible, nonedible, and whole fish tissues were eliminated by 7 days.

The concentration of total [^{14}C]residues (as parent equivalents) in the exposure aquaria water ranged from 79-112 µg/L and 83-118 µg/L in each tank (Table 3, p. 51). The

parent compound was present at 0.038-0.079 µg/mL and 0.049-0.079 µg/mL in tanks two and three, respectively (Tables 10, 11; pp. 58, 59); concentrations were variable throughout the exposure period. Three metabolites (CGA 153433, M2, and M4) were detected in the exposure tanks. CGA 153433 was detected in tank two at a range of 33.5-63.8% of the radioactivity initially present in the water, and in tank three at a range of 29.5-50.5% of the initially present radioactivity (Table 7, p. 55). An unidentified metabolite (M2) was detected at ranges of 5.6-11.1% and 2.7-4.5% of the radioactivity initially present in the water in tanks two and three, respectively. Another unidentified metabolite (M4) was detected at ranges of 0.9-7.3% and 2.6-5.0% of the radioactivity initially present in the water in tanks two and three, respectively.

Nonextractable [^{14}C]residues were present at 1.0 ppm and 0.63 ppm in the edible tissue, and were 2.9 ppm and 2.4 ppm in the nonedible tissue at days 3 and 17, respectively (Tables 14, 15; pp. 62, 63).

Water quality measurements (pH, temperature, and dissolved oxygen) were obtained daily; data were only reported as two sets of ranges for both the exposure and depuration periods. During the exposure and depuration periods, the temperature of the water in the exposure and control tanks was 19-20°C, the pH ranged from 7.6-8.3, and the dissolved oxygen content ranged from 6.2-9.5 mg/L (Table 2, p. 50).

COMMENTS

1. Exposure to the parent compound was not constant and the level of degradates in the water was unacceptably high (Tables 10, 11; pp. 58, 59). In addition, the concentration of total [^{14}C]residues in the water was not constant throughout the study. The study author reported that the instability of the parent compound in the exposure water may have been a result of the compound's high hydrolytic and microbial instability, and variation in the residual radioactivity may have been due to an increasing high metabolic activity of the fish (as reported in additional literature; pp. 43, 44). The reviewer also notes that the exposure water was reported to be turbid on day 2 (p. 103). Subdivision N Guidelines require that the exposure water be free of degradates which may provide a stressful environment for the metabolism of the parent in the fish. The number of water volume turnovers per day may need to be increased for compounds which rapidly metabolize in the test water.

2. Metabolites present at concentrations greater than 50 ppb (0.05 ppm) were not identified. The unidentified major metabolite M5 was present at 0.284 ppm and 0.461 ppm in the edible tissue, and was 1.48 ppm and 0.461 ppm in the nonedible tissue at exposure days 3 and 17, respectively. The unidentified major metabolite M6 was present in the nonedible tissue at 1.1 ppm at exposure day 3. Subdivision N Guidelines require that all extractable residues present at ≥50 ppb be identified. Additionally, nonextractable [^{14}C]residues

were unacceptably high, at up to 1.0 ppm and 2.9 ppm in edible and nonedible tissues, respectively (Tables 14, 15; pp. 62, 63).

3. Frozen storage stability data for the parent and degradates in fish tissue samples were not reported, and the length of frozen storage of tissue samples was not reported. For samples stored for longer than thirty days, storage stability studies should be conducted using both water and fish tissues that have been fortified separately with the parent compound and its degradates and stored for a duration of time equal to the longest interval for which the test samples were stored.

4. Bioconcentration factors (BCF) for edible (filet and skin), nonedible (head, fins, viscera, and skeleton), and whole fish tissues at each sampling interval were calculated by the reviewer by dividing the mean measured concentration of [^{14}C]residues in the fish tissues at each sampling interval by the mean measured water concentration up to and including the respective sampling day. This method enabled the reviewer to determine the maximum mean bioconcentration factor. In contrast, the registrant-calculated values were determined using the mean [^{14}C]residues in the water at each individual sampling interval (rather than a running mean calculated through the sampling interval; p. 40). The BCF's reported by the study author were 255X and 218X for the edible, 1241X and 1083X for the nonedible, and 802X and 1274X for whole tissue in the two exposure tanks (Tables 10, 11; pp. 58, 59).

5. Throughout the study, a total of 9 mortalities were observed in the 199 fish used. The study author reported that on day 8 the fish were "too thin" and, as a result, the amount of daily food increased from 2% to 4% of the total fish body weight per tank for the remainder of the exposure period (p. 41). The average weight of the fish at the initiation of the study was approximately 1.8 grams; the weight of the fish at the termination of the study was not reported.

6. Growth/weight patterns of fish throughout the study were not provided. At a minimum, the length and weight of the fish remaining at the end of the study should be reported.

7. The study author reported that the LC_{50} of cloqiontocet-mexyl was >51 mg/L for bluegill sunfish (p. 23). The intended nominal concentration was 0.5 mg/L (1/100 of the LC_{50} data). However, preliminary tests indicated that a homogeneous solution could not be obtained at that concentration and the nominal exposure concentration used in this study was 0.1 mg/L.

8. Clarification by the registrant may be required for the units of measurement used to report the water hardness and alkalinity (fr.H^0). The reviewer is not familiar with these units.

9. The aqueous solubility of cloqiontocet-mexyl was reported as 0.8 mg/L at 20°C (pH not specified; p. 23).

10. Replicate whole fish tissue samples from separate fish were not utilized for analysis at each sampling interval; instead, only single fish were collected for analysis. Data obtained from single fish may not adequately represent the fish population.

Table 1: Names and structures of reference compounds.

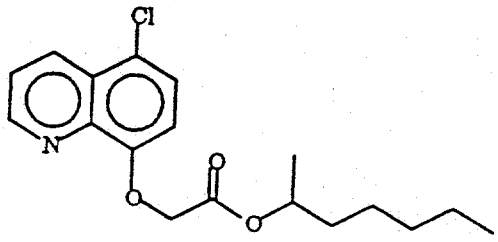
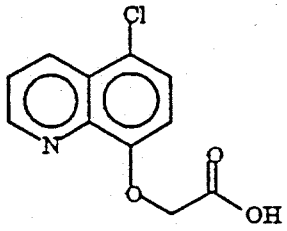
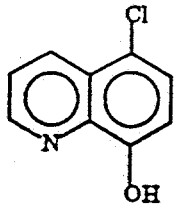
Name	Structure
CGA 185072 (PARENT) (Batch: AMS 261/101)	
CGA 153433 (Batch: RV-2110)	
C 18469 (Batch: RV-2285)	

Table 2: Temperature, pH and oxygen values in control and exposure tanks.

Time interval (days)		Tank								
		1 (control)			2 (treated)			3 (treated)		
		Temp. (°C)	pH	O_2 mg/l	Temp. (°C)	pH	O_2 mg/l	Temp. (°C)	pH	O_2 mg/l
A	0-7	20.0-20.0	8.1-8.3	8.4-9.3	19.0-19.0	7.9-8.2	7.8-9.3	19.0-19.0	7.9-8.2	8.2-9.3
A	8-17	20.0-20.0	7.9-8.2	8.1-9.2	19.0-19.5	7.8-8.1	7.0-8.9	19.0-19.0	7.6-8.1	6.2-8.8
B	18-24	20.0-20.0	8.0-8.2	8.5-9.0	19.0-19.0	7.9-8.2	8.7-9.0	19.0-19.0	7.9-8.2	8.7-9.0
B	25-31	20.0-20.0	8.0-8.1	8.5-9.4	19.0-19.0	8.0-8.1	8.8-9.5	19.0-19.0	8.0-8.1	8.8-9.5

A : Accumulation.

B : Depuration.

Table 7: Partitioning behaviour and pattern of degradates in exposure water of tanks 2 and 3 (values given in percent of the radioactivity initially present in exposure water).

Metabolite Code *	Tank 2					Tank 3				
	Days of Exposure									
	0	1	3	14	17	0	1	3	10	14
Organic										
Parent (CGA 185072)	97.3	58.7	60.0	21.4	37.5	93.3	65.5	60.8	42.8	55.6
M2	n.d.	n.d.	5.6	11.1	n.d.	4.1	n.d.	n.d.	2.2	n.d.
M3 (CGA 153433)	n.d.	4.3	3.5	22.6	18.5	n.d.	3.1	2.7	4.5	4.1
M4	2.7	6.3	0.9	3.7	7.3	2.6	5.0	4.8	4.5	3.4
Subtotal	100.0	69.3	70.0	58.8	63.3	100.0	73.6	68.3	54.0	63.1
Aqueous										
M3 (CGA 153433**)	n.d.	30.7	30.0	41.2	36.7	n.d.	26.4	31.7	46.0	36.9
T O T A L	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
Subtotal M3	n.d.	35.0	33.5	63.8	55.2	n.d.	29.5	34.4	50.5	41.0

* : For the TLC-behaviour of the identified and the unknown metabolite fractions, see Figures 10-29.

Identity of the radioactive metabolite fraction with the corresponding reference compound was proven by TLC (see corresponding Figures).

** : Exclusively M3 was measured in selected samples (days 1, 14 and 17 of tank 2, Figures 28 and 29). Based on these results, for all other aqueous fractions, the same metabolite pattern was assumed.

n.d. : Not detected.

Table 8: Residues in edible and non-edible parts of fish and in the whole fish during accumulation/depuration of 14C-CGA 185072 at an average dose level of 92 µg/l in tank 2 (all values were corrected for background and expressed in parent equivalents on a fresh weight basis in µg/g).

Phase	Time Interval (Days) I	Time Interval (Days) II	Residues** (µg/g = ppm) Edibles	Non-edibles	Whole fish
A	0*	---	1.547*	4.854*	3.727*
A	1	---	4.555	57.071	36.888
A	3	---	12.732	50.325	19.592
A	6	---	2.750	39.895	38.200
A	10	---	1.000	23.014	13.207
A	14	---	0.891	17.296	11.129
A	17	0	4.018	27.114	11.971
B	18	1	0.443	3.826	1.562
B	20	3	0.443	0.579	0.284
B	24	7	0.082	0.327	0.130
B	27	10	0.093	0.207	0.152
B	31	14	0.126	0.229	0.152

I : Days after the start of accumulation.

II : Days after the start of depuration.

* : About one hour after starting the daily dose.

** : All values were corrected for respective background levels of 0.279 (edibles), 0.307 (non-edibles) and 0.296 mg/kg (whole fish).

A : Accumulation.

B : Depuration.

Table 9: Residues in edible and non-edible parts of fish and in the whole fish during accumulation/depuration of 14C-CGA 185072 at an average dose level of 93 µg/l in tank 3 (all values were corrected for background and expressed in parent equivalents on a fresh weight basis in µg/g).

Phase	Time Interval (Days) I	Time Interval (Days) II	Residues** (µg/g = ppm) Edibles	Non-edibles	Whole fish
A	0*	---	1.274*	4.252*	2.995*
A	1	---	2.968	57.049	21.953
A	3	---	11.124	55.234	64.987
A	6	---	4.346	34.166	29.169
A	10	---	4.007	34.625	16.793
A	14	---	2.815	21.078	33.444
A	17	0	2.422	15.743	15.524
B	18	1	0.738	4.362	1.814
B	20	3	0.136	0.382	0.229
B	24	7	0.027	0.218	0.185
B	27	10	0.049	0.207	0.152
B	31	14	0.071	0.163	0.163

I : Days after the start of accumulation.

II : Days after the start of depuration.

* : About one hour after starting the daily dose.

** : All values were corrected for respective background levels of 0.279 (edibles), 0.307 (non-edibles) and 0.296 mg/kg (whole fish).

A : Accumulation.

B : Depuration.

Table 10: BCF-estimation based on concentrations of CGA 185072 in water and residue levels in fish in tank 2.

Time Interval (Days)	Parent equiv. in µg/l in water	% Parent in water	Parent in µg/ml in water	Residues in fish in µg/g (I)	BCF	Calculated BCF value**
EDIBLES						
0	81	97.3	0.079	1.547*	20	131
1	79	58.7	0.046	4.555	99	
3	84	60.0	0.050	12.732	255	(k = 1.85)
14	98	21.4	0.021	0.891	42	(R^2= 0.72)
17	102	37.5	0.038	4.018	106	
NON-EDIBLES						
0	81	97.3	0.079	4.854*	61	944
1	79	58.7	0.046	57.071	1241	
3	84	60.0	0.050	50.325	1007	(k = 4.56)
14	98	21.4	0.021	17.296	824	(R^2= 0.95)
17	102	37.5	0.038	27.114	714	
WHOLE FISH						
0	81	97.3	0.079	3.727*	47	508
1	79	58.7	0.046	36.888	802	
3	84	60.0	0.050	19.592	392	(k = 5.23)
14	98	21.4	0.021	11.129	530	(R^2= 0.88)
17	102	37.5	0.038	11.971	315	

I : Based on the assumption that only CGA 185072 (Parent) was accumulated.

* : About one hour after starting the daily dose.

** : For calculation, see section 2.7.

BCF: Bioconcentration factor.

k : Constant of the BCF calculation.

R^2 : Correlation coefficient.

Table 11: BCF-estimation based on concentrations of CGA 185072 in water and residue levels in fish in tank 3.

Time Interval (Days)	Parent equiv. in µg/l in water	% Parent in water	Parent in µg/ml in water	Residues in fish in µg/g (I)	BCF	Calculated BCF value**
EDIBLES						
0	85	93.3	0.079	1.274*	16	
1	83	65.5	0.054	2.968	55	112
3	84	60.8	0.051	11.124	218	(k = 1.29)
10	118	42.8	0.051	4.007	79	(R^2= 0.72)
14	88	55.6	0.049	2.815	57	
NON-EDIBLES						
0	85	93.3	0.079	4.252*	54	
1	83	65.5	0.054	57.049	1056	810
3	84	60.8	0.051	55.234	1083	(k = 4.55)
10	118	42.8	0.051	34.625	679	(R^2= 0.90)
14	88	55.6	0.049	21.078	430	
WHOLE FISH						
0	85	93.3	0.079	2.995*	38	
1	83	65.5	0.054	21.953	407	733
3	84	60.8	0.051	64.987	1274	(k = 1.30)
10	118	42.8	0.051	16.793	329	(R^2= 0.79)
14	88	55.6	0.049	33.444	683	

I : Based on the assumption that only CGA 185072 (Parent) was accumulated.

* : About one hour after starting the daily dose.

** : For calculation, see section 2.7.

BCF: Bioconcentration factor.

k : Constant of the BCF calculation.

R^2 : Correlation coefficient.

Table 12: Background levels in edible and non-edible parts of untreated fish and in the whole untreated fish during incubation (values given as dpm per 100 mg fish and expressed in parent equivalents on a fresh weight basis, taking into account the respective specific radioactivity).

Time Interval (Days)	Edibles		Non-edibles		Whole fish	
	dpm per 100mg	spec.radioact. (µCi/mg) 0.412 µg/g	dpm per 100mg	spec.radioact. (µCi/mg) 0.412 µg/g	dpm per 100mg	spec.radioact. (µCi/mg) 0.412 µg/g
0	27	0.295	36	0.394	33	0.361
17	24	0.262	20	0.219	21	0.230
MEANS		0.279		0.307		0.296

Table 14: Balance of radioactivity after extraction of pooled edible parts of fish after 3 and 17 days of exposure to 14C-CGA 185072 at an average dose level of 93 µg parent equivalents/l.

	Exposure (Days)			
	3 (Tanks 2+3)		17 (Tank 2)	
	I	II	I	II
Extractable				
- CH_2Cl_2/ACN (1+1, v/v)	5.0	0.546	5.5	0.221
- CH_2Cl_2	n.d.	---	---	---
- CH_2Cl_2/hexane (1+1, v/v)	0.5	0.055	---	---
- CH_2Cl_2/ACN (2+8, v/v)	n.d.	---	5.4	0.217
- ACN	53.1	5.803	45.7	1.836
- ACN/MeOH (2+8, v/v)	23.7	2.590	18.6	0.747
- MeOH	8.4	0.918	9.2	0.370
Subtotal	90.7	9.912	84.4	3.391
Non-Extractables	9.3	1.016	15.6	0.627
T O T A L	100.0	10.928*	100.0	4.018

I : Values in % of the radioactivity recovered in the edible parts of fish.

II : Values expressed in mg parent equivalents per kg (ppm) of edible parts.

n.d. : Not determined.

* : Measured ppm-value of the pooled edible parts (tanks 2 and 3) of day 3 (for initial values: see Tables 8 and 9).

Table 15: Balance of radioactivity after extraction of pooled non-edible parts of fish after 3 and 17 days of exposure to 14C-CGA 185072 at an average dose level of 93 µg parent equivalents/l.

	Exposure (Days)			
	3 (Tanks 2+3)		17 (Tank 2)	
	I	II	I	II
Extractable				
- CH_2Cl_2/ACN (1+1, v/v)	2.2	0.900	2.4	0.651
- CH_2Cl_2	n.d.	---	2.4	0.651
- CH_2Cl_2/hexane (1+1, v/v)	4.3	1.759	1.5	0.407
- CH_2Cl_2/ACN (2+8, v/v)	n.d.	---	0.4	0.108
- ACN	55.8	22.828	60.0	16.268
- ACN/MeOH (2+8, v/v)	20.9	8.551	16.8	4.555
- MeOH	9.6	3.928	7.8	2.115
Subtotal	92.8	37.966	91.3	24.755
Non-Extractables	7.2	2.946	8.7	2.359
T O T A L	100.0	40.912*	100.0	27.114

I : Values in % of the radioactivity recovered in the non-edible parts of fish.

II : Values expressed in mg parent equivalents per kg (ppm) of non-edible parts.

n.d. : Not determined.

* : Measured ppm-value of the pooled non-edible parts (tanks 2 and 3) of day 3 (for initial values: see Tables 8 and 9).

Table 16: Metabolite pattern in extracts of edible parts of fish during exposure to 14C-CGA 185072.

Meta-bolite	Identity **	Rf-values * in			Exposure (Days)			
					3		17	
		SS 1	SS 2	SS 4	I	II	I	II
M3	CGA 153433	0.02	0.01	0.47	88.1	9.628	81.1	3.258
M5	Unknown	0.02	0.01	0.25	2.6	0.284	3.3	0.133
T O T A L					90.7	9.912	84.4	3.391

I : Values in % of the radioactivity recovered in edible parts.

II : Values expressed in mg parent equivalents per kg of edible parts.

* : As obtained from day 17.

** : The identity of metabolite fraction M3 and CGA 153433 was proven by co-chromatography (Figure 31).

Table 17: Metabolite pattern in extracts of non-edible parts of fish during exposure to 14C-CGA 185072.

Metabolite	Identity **	Rf-values * in			Exposure (Days) 3		17	
		SS 1	SS 2	SS 4	I	II	I	II
M3	CGA 153433	0.01	0.01	0.43	86.5	35.389	89.6	24.294
M5	Unknown	0.01	0.01	0.26	3.6	1.473	1.7	0.461
M6	Unknown	0.01	0.98	0.97	2.7	1.104+	n.d.	---
T O T A L					92.8	37.966	91.3	24.755

I : Values in % of the radioactivity recovered in non-edible parts.

II : Values expressed in mg parent equivalents per kg of non-edible parts.

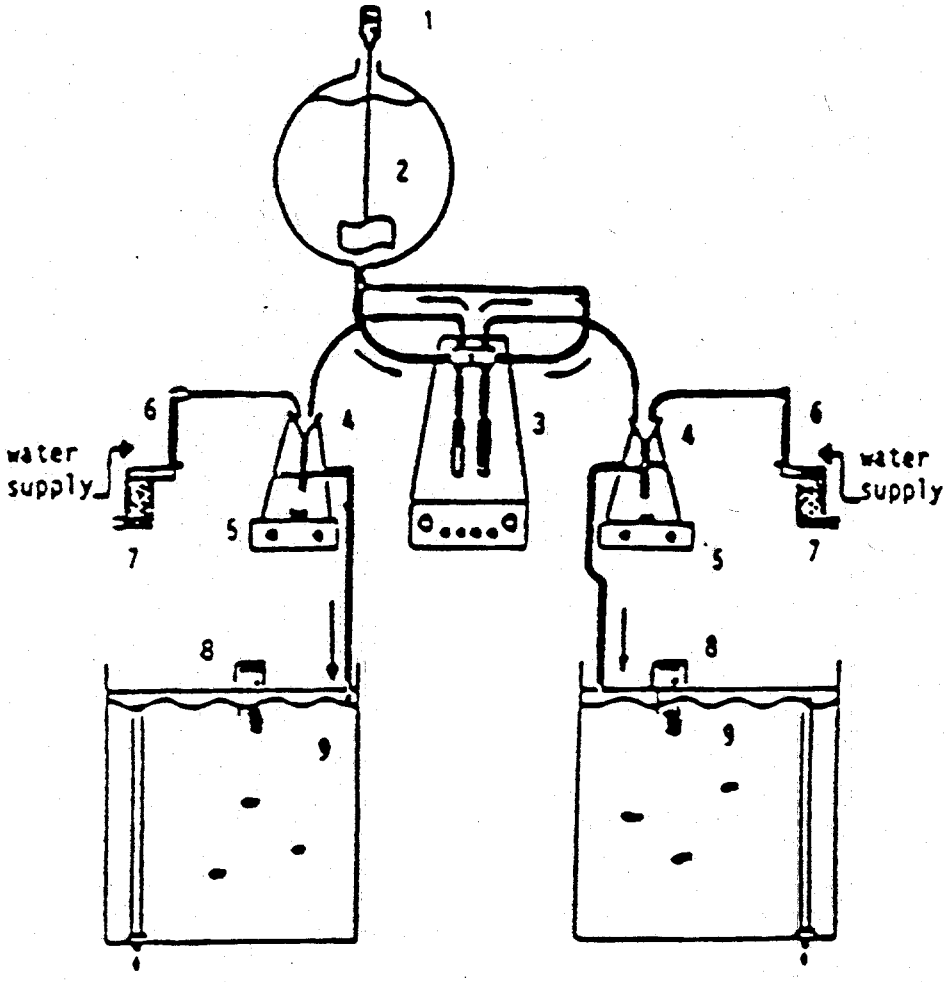
* : As far as possible obtained from day 17.

** : The identity of metabolite fraction M3 and CGA 153433 was proven by co-chromatography (Figures 30 and 31).

\+ : Rounded to 1.104 to obtain totally 37.966.

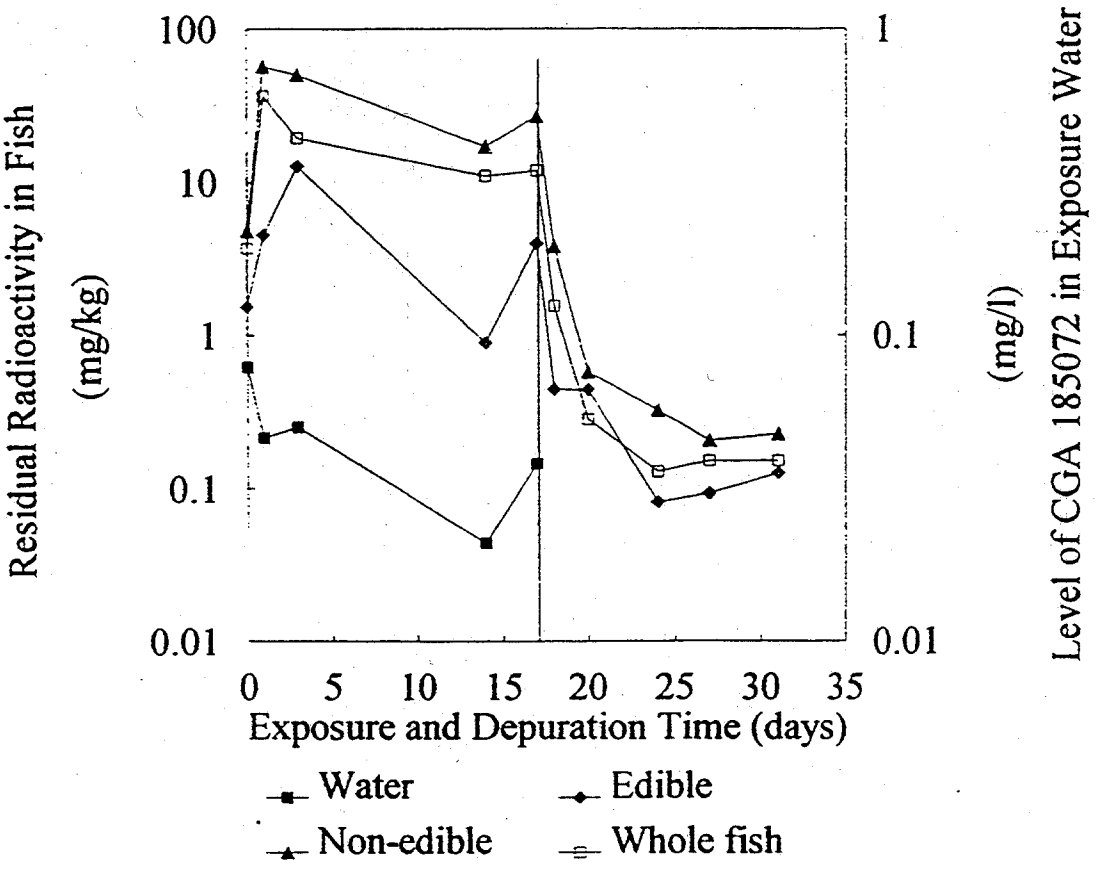
n.d.: Not detectable.

Figure 3: Test system.



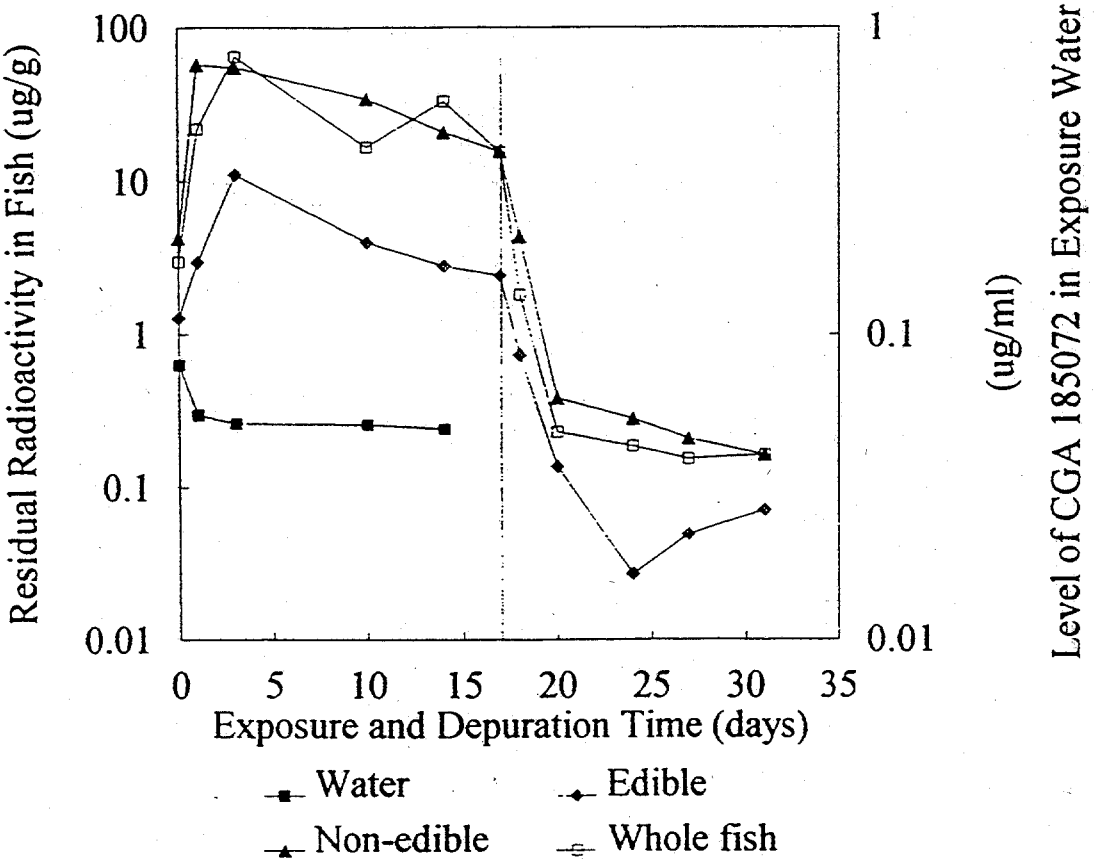
1 Stirrer
2 Stock solution
3 Dispenser
4 Mixing flask
5 Magnetic stirrer
6 Flow-meter
7 Activated charcoal filter
8 Thermostat
9 Test water tank

Figure 5: Concentration of 14C-CGA 185072 or its equivalents in exposure water and fish/fish parts (tank 2).



- Accumulation data of Table 10 and depuration data of Table 8 presented as graph.

Figure 6: Concentration of 14C-CGA 185072 or its equivalents in exposure water and fish/fish parts (tank 3).



- Accumulation data of Table 11 and depuration data of Table 9 presented as graph.

DP BARCODE: D252023

CASE: 062169 DATA PACKAGE RECORD DATE: 01/07/99
SUBMISSION: S553898 BEAN SHEET Page 1 of 1

* * * CASE/SUBMISSION INFORMATION * * *

CASE TYPE: REGISTRATION ACTION: 101 RESB NC-FOOD/FEED USE
RANKING : 0 POINTS ()
CHEMICALS: 125203 Propanoic acid, 2-{4{(5-chloro-3-fluoro-2-pyridiny 93.0000%

ID#: 000100-ONO CLODINAFOP-PROPARGYL TECHNICAL
COMPANY: 000100 NOVARTIS CROP PROTECTION, INC.
PRODUCT MANAGER: 23 JOANNE MILLER 703-305-6224 ROOM: CM2 237
PM TEAM REVIEWER: SUSAN STANTON 703-305-5218 ROOM: CM2 237
RECEIVED DATE: 12/22/98 DUE OUT DATE: 06/30/99

* * * DATA PACKAGE INFORMATION * * *

DP BARCODE: 252023 EXPEDITE: N DATE SENT: 01/07/99 DATE RET.: / /
CHEMICAL: 125203 Propanoic acid, 2-{4{(5-chloro-3-fluoro-2-pyridinyl)oxy}phe
DP TYPE: 001 Submission Related Data Package
CSF: N LABEL: N

ASSIGNED TO	DATE IN	DATE OUT
DIV : EFED	1/7/99	/ /
BRAN: ERB3	1/7/99	/ /
SECT: IO	1/7/99	/ /
REVR : John Jordan	1/7/99	/ /
CONTR:	/ /	/ /

ADMIN DUE DATE: 05/07/99
NEGOT DATE: / /
PROJ DATE: / /

* * * DATA REVIEW INSTRUCTIONS * * *

Attention: Dan Rieder/John Jordan

Novartis has submitted additional data to fill data gaps for clodinafop-propargyl (fish bioaccumulation and a reference on a rapid method of total lipid extraction and purification). Please review along with the data previously submitted and routed to EFED under data packages DP 244333, 246528, 247992 and 249455. The new studies are:

MRID # 44719-6-01 and -02.

Thanks,
Susan Stanton

* * * DATA PACKAGE EVALUATION * * *

No evaluation is written for this data package

* * * ADDITIONAL DATA PACKAGES FOR THIS SUBMISSION * * *

DP BC	BRANCH/SECTION	DATE OUT	DUE BACK	INS	CSF	LABEL

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Tel 336 632 6000

447196-00

NOVARTIS

To: Jim Breithaupt
on 1/14/99

December 10, 1998

Document Processing Desk (PETN)
Office of Pesticide Programs (H7504C)
U.S. Environmental Protection Agency
401 M. Street, S.W.
Washington, D.C. 20460

Attn: Ms. JoAnne Miller, PM 23

SUBJECT: PESTICIDE PETITION 7F4924
CGA-184927 TECHNICAL (CLODINAFOP-PROPARGYL)
SUBMISSION OF FISH BIOCONCENTRATION STUDY

In accordance with commitments made earlier by Novartis Crop Protection, Inc. to provide data to fill identified data gaps for clodinafop-propargyl (CGA-184927) prior to its registration in the U.S., enclosed are three copies of three volumes which include a Transmittal Document (Volume 1) results of a fish bioconcentration study (EPA Guideline 165-4 - Volume 2) and a reference on a rapid method of total lipid extraction and purification (Volume 3).

Although CGA-184927 was found to initially bioaccumulate in the fish, it was immediately metabolized to CGA-193469 and rapidly eliminated from the fish. This would indicate that the initial uptake of CGA-184927 in the bluegill sunfish was highly reversible.

Sincerely,

Karen S. Stumpf

Karen S. Stumpf
Senior Regulatory Manager
Regulatory Affairs

Enclosures

VOLUME 1 OF 3 OF SUBMISSION
(TRANSMITTAL DOCUMENT)

1. Name and Address of Submitter

Novartis Crop Protection, Inc.
P.O. Box 18300
Greensboro, NC 27419

2. Regulatory Action in Support of which this Package is Submitted

Clodinafop - Propargyl/CGA-184927
Pesticide Petition 7F4924 - Submission of Fish Bioconcentration

3. Transmittal Date

12/10/1998

4. List of Submitted Studies

MRID NUMBER	VOLUME NUMBER	STUDY TITLE	EPA GUIDELINE NUMBER
	1 of 3	TRANSMITTAL DOCUMENT	NOT APPLICABLE
44719601	2 of 3	UPTAKE, DEPURATION AND BIOCONCENTRATION OF 14C-CGA-184927 IN BLUEGILL SUNFISH (LEPOMIS MACROCHIRUS) UNDER FLOW-THROUGH TEST CONDITIONS (STUDY NO. 98070) (352/61-98/91392)	165-4
44719602	3 of 3	A RAPID METHOD OF TOTAL LIPID EXTRACTION AND PURIFICATION (STUDY NO. NA) (352/61-98/92034)	NOT APPLICABLE

Company Official: Stumpf, Karen S. Karen S. Stumpf
(Name) **(Signature)**

Company Name: NOVARTIS CROP PROTECTION, INC.

Company Contact: Stumpf, Karen S. 336-632-2169
(Name) **(Phone)**