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

8-17-2000

OFFICE OF
PESTICIDES AND
TOXIC
SUBSTANCES

MEMORANDUM

Chemical: 108800
DPBarcode: D236884

SUBJECT: Agency Review of Registrant's (Novartis) Rebuttal Comments to the Environmental Fate and Ground Water Branch Review (April 22, 1997) for Metolachlor and S-Metolachlor (MRID 44303502) and The K_{oc} Section in the Document Entitled *Equivalency of Pesticides Metolachlor and S-Metolachlor with Respect to Ground Water Contamination (Docket Number OPP-36190A, 4/21/20000)*

FROM: Kevin Costello, Risk Assessment Process Leader Kevin A Costello 8/17/2000
James Hetrick, Ph D., Senior Physical Scientist James A. Hetrick 8/16/2000

THRU: Sidney Abel, Acting Chief Sidney Abel 8/17/2000
Environmental Risk Branch 1
Environmental Fate and Effects Division (7507C)

TO: Joanne Miller, PM 23
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and

Arthur-Jean Williams, Branch Chief
Environmental Field Branch
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Please find attached the Agency review to Novartis' rebuttal comments on the Environmental Fate and Ground Water Branch Review (April 22, 1997) for Metolachlor and S-Metolachlor and the K_{oc} section in *Equivalency of Pesticides Metolachlor and S-Metolachlor with Respect to Ground Water Contamination (Docket Number OPP-36190A, 4/21/20000)*. Based on the Agency's review, the bridging studies for metolachlor and S-metolachlor should be upgraded to fulfill the photodegradation in water (161-2), photodegradation on soil (163-1), aerobic soil metabolism (162-1), anaerobic soil metabolism (162-2), anaerobic aquatic metabolism (162-3), and aerobic aquatic metabolism (162-4) data requirements. These data indicate that metolachlor and S-metolachlor are expected to have similar degradation pathways and rates in soil and water environments.

The Agency believes that there is no difference in soil sorption affinity between metolachlor and S-metoachlor. Although the comparison of non-paired batch equilibrium data indicate there is a significant difference in Koc coefficients for metolachlor (mean K_{oc}=69.288) and S-metolachlor (mean K_{oc}= 219.556), the difference can be attributed to higher average soil organic content (SOC) content in the test soils used in the S-metolachlor sorption studies rather than an actual increase in the sorption affinity of S-metolachlor. Similar Koc coefficients for metolachlor (mean K_{oc}=249.250) and S-metolachlor (mean K_{oc}=265.875) were observed in paired batch equilibrium studies. These data suggest that metolachlor and S-metolachlor are expected to be highly mobile to mobile in soil and water environments.

INTRODUCTION

This document is EPA's rejoinder to Novartis Crop Protection, Inc. response to the Environmental Protection Agency (EPA) review (dated April 28, 1997) of bridging data submitted in support of the registration of CGA-77102 (common name *S*-metolachlor; chemical name; (S)-2-chloro-N-(2-ethyl-6-methyl-phenyl)-N-(2-methoxy-1-methyl-ethyl) acetamide) for new formulations of metolachlor enriched with this isomer. Also, the Agency addresses the registrant's assessment of soil:water partitioning coefficients for metholachlor and CGA-77102 as presented in the document entitled *Equivalency of Pesticides Metolachlor and S-Metolachlor with Respect to Ground Water Contamination (Docket Number OPP-36190A, 4/21/2000)*. The format used in this response first presents EPA comments from the review, followed by the Novartis response, followed by EFED's rejoinder.

General Agency Concerns:

The registrant submitted environmental fate data comparing racemic metolachlor and S- metolachlor. The basic approach was to compare half-lives as well as the type and quantities of transformation products between racemic metolachlor and S-metolachlor. Althought this approach is reasonable, it is complicated because the experimental conditions were not similar among the various environmental fate studies. The Agency notes that future studies on metolachlor and S-metolachlor should report the enantiomeric ratio during the study. These data are expected to directly assess preferential degradation, sorption, or bioconcentration of the R-and S- enantiomer of metolachlor.

EPA'S COMMENTS/RESPONSES - NOVARTIS RESPONSES (MRID 44303502)

Photodegradation on Soil (161-3, MRID# 40430203, MRID# 43928935)[1,2]

EPA Comment:

The photodegradation on soil study is scientifically valid, and can be used as supplemental data. However, it is not acceptable to fulfill the photodegradation on soil data requirement (161-3) for the following reasons:

a. There is a discrepancy in previous metolachlor soil photolysis data (GT; 02/25/93) and these bridging soil photolysis data for metolachlor (half-life = 8 days vs. 78.8 days, respectively).

Novartis Response to EPA Comment "a":

The previously accepted soil photolysis study (MRID# 40430203, 1987[1]) supported the registration of metolachlor. The bridging photolysis study (MRID# 43928935, 1995[2]) provided data that compared the soil photolysis of metolachlor and CGA-77102.

Several aspects of these two studies were similar; for example, topically dosed soil and natural sunlight intensities. However, there were also differences between the two; percent organic matter of the test soil, soil moisture level, temperature ranges and dosing solvents, which are discussed below.

The percent organic matter of the test soils was significantly different. The organic matter of the soils used in the first (1987) study and the bridging study was 5.0% and 2.9%, respectively (Table I). According to Miller and Herbert[3] (Appendix B), the organic (humic) substances in the soil can behave as sensitizers. The faster irradiated half-life (8 days) reported in the first (1987) study could be attributed to a higher amount of organic matter.

All samples generated in the first (1987) study (MRID# 40430203) were dried at 35°C overnight before dosing. The temperature of the naturally irradiated samples varied from 15 to 52°C. The samples were not moistened or measured for viability during the course of the thirty day study. Acetone, a known light sensitizer, was used as the dosing solvent. This sensitizer may have contributed to a faster irradiated half-life. The higher amount of organic matter, the absence of moisture, the wide range of temperature, and the use of acetone as the dosing solvent attributed to the shorter, irradiated half-life (8 days). The recently submitted bridging soil photolysis study (MRID# 43928935) used moist, viable soil maintained at 25 ± 1°C for the thirty day incubation period. The dose solvent was acetonitrile, which is not classified as a sensitizing solvent.

For these reasons, Novartis believes the half-life of metolachlor (8 days) in the previous study (MRID# 40430203) was affected by the above discussed study parameters. Therefore, half-lives (78.8 and 95.1 days for metolachlor and CGA-77102, respectively) determined in the bridging soil photolysis study (MRID# 43928935) provide a better comparison to determine the behavior of metolachlor and CGA-77102 on irradiated soils.

EFED Rejoinder to Novartis' Response to Comment "a":

The Agency agrees with the registrant that the discrepancy in photodegradation on soil half-lives appears to be more dependent on the experimental conditions. The Agency pointed out the possible discrepancy between the reported half-lives of metolachlor in the photodegradation on soil studies (MRID 43928935 and MRID 40430203). The registrant believes the differences in half-lives can be attributed to the experimental design such as soil properties, pesticide dosing procedures, and temperature control.

An examination of the photodegradation on soil studies indicates that the experimental methods were different (Table 1). For example, the bridging photodegradation on soil studies (MRID 43928935) were conducted using a Maryland soil as a 2mm soil layer[1] while the original photodegradation on soil study (MRID 40430203) was conducted on an Iowa soil as a thin section. The bridging data from the photodegradation on soil study (MRID 43928935) indicate the half-lives of racemic and S- metolachlor are very similar. However, when compared with the different experimental conditions used in the original photodegradation on soil studies (MRID 40430203) the half-lives were very different. An qualitative analysis of the data suggests that experimental methods used in the photodegradation on soil studies caused greater differences in half-lives than the enantiomeric ratio (the ratio of the R- and S- enantiometers of metolachlor).

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[1] The registrant indicates the soil layer used in the photodegradation on soil study (MRID 43928935) was 2 cm. Based on the Agency review of the material and methods, the soil layer depth was 2 mm instead of 2 cm.

Table 1. Photodegradation on Soil

Study	MRID	Metolachlor	Test Conditions	Linear Half-life (days)		Non-Linear Half-life (days)		Transformation Products	
				Light	Dark	Light	Dark	Light	Dark
Photodegradation in Soil	40430203	racemic	thin section soil film artificial light (Hg Arc) 1-D TLC Iowa soil continuous	34.8[A] 38.4		30.6 33.8		51202 37735 41638 40919 41507 37913	None
Photodegradation in Soil	40430203	racemic	thin section soil film natural light 1-D TLC Iowa soil	6.83 8.99		7.99 9.37		51202 37735 41638 40172 40919 41507 37913	None
Photodegradation on Soil	43928935	racemic	Maryland soil 2mm soil layer Xenon light 12 hour days 2-D TLC and HPLC 25C 1.3 ppm	94.95 76.6	41.01 39.7	93.66 77.01	41.75 40.29	51202 40172 40919 46129 48087 50720	40172 40919 50720 51202 46129 48087
Photodegradation on Soil	43928935	S-metolachlor	Maryland soil 2 mm soil layer Xenon light 12 hour days 2D TLC and HPLC 25C 1.3 ppm	94.95 93.3	50.22 49.9	93.66 92.41	50.59 50.96	51202 40172 40919 46129 48087 50720 24705	77102 40172 40919 50720 51202 46129 48087 24705

A=Half-lives in artificial light were corrected for 24 hour day (half-life for continuous light*2)
B=Nonlinear Model [$C=C0e^{-kt}$ where C0= Concentration at time zero; C=Concentration at any time; k=rate constant (days-1); and time (days)]

EPA Comment:

b. There is a discrepancy in these bridging soil photolysis data (half-lives = 78.8 and 95.1 days for metolachlor and CGA-77102, respectively) and the bridging aerobic soil metabolism data (half-life = ~8 days for metolachlor and CGA-77102). All these half-lives were based on day 0 to 21 test samples of data.

<u>Novartis Response to EPA Comment "b"</u>:

The aerobic soil metabolism study (MRID# 43928936[4]) and bridging soil photolysis study (MRID# 43928935[2]) are similar in several ways: soil collection from the same area, dose rate (1.3 ppm), temperature range maintained at 25 ± 1°C and extraction methods. However, the differences in half-lives (aerobic soil metabolism half-life for metolachlor and CGA-77102 = approx. 8 days, irradiated soil photolysis half-lives for metolachlor and CGA-77102 = 78.8

days and 95.1 days, respectively; dark control half-lives for metolachlor and CGA-77102 in the soil photolysis study = 40.9 days and 50.2 days, respectively) are attributed to the following differences: method of dosing, lack of soil binding (organic matter content), and study duration. The major route of degradation for the parent compound (metolachlor or CGA-77102) was microbial degradation. In the aerobic soil metabolism study, the test substances were dosed and homogenized (roller mixed) throughout the moist, viable soil. This exposed the test substances to the majority of the microbial population present in the soil, producing shorter and similar half-lives (~8 days) for metolachlor and CGA-77102. In the soil photolysis study, the test substances were topically applied (by syringe) to the surface of the soil sample layers. This reduced the microbial population that was exposed to the test substances, and therefore, produced longer, similar half-lives (78.8 and 95.1 days, metolachlor and CGA-77102, respectively). The longer half-lives in the irradiated photolysis samples compared to the dark controls and the aerobic metabolism samples, indicate that what little photolytic degradation may occur is minor compared to microbial degradation.

Homogenization (roller mixing) of the test substances in the aerobic soil metabolism study exposed the test substances to a higher amount of organic matter present in the soil. For the soil photolysis study, samples were topically dosed, which concentrated the test substance on to the thin layer of soil surface (approximately 2 cm). Under conditions of irradiation (12 hour light cycle), there is partial drying of the soil surface. This reduces the amount of test substance which is solubilized. Loss of solubilized test material reduces both interaction with organic components of the soil and degradation by soil microbes. The rate of degradation is further slowed considerably during the 12 hour light cycle. During the 12 hour dark cycle, two things can occur: rehydration of the soil surface (by water sealed in the test vessels) and resolubilization of the test substance. This can cause possible further degradation.

Over time, the binding of the test substance to the soil limited the rate of aerobic soil metabolism (six month study duration) causing a secondary degradation rate (metolachlor and CGA-77102, half-lives = 30.6 days and 28.8 days, respectively) (Figure 1) and therefore, a biphasic half-life in the degradation profile. For the soil photolysis study, the binding of the test substances to the soil was less significant. Due to the minimal binding of the test substance to the soil and the short, required length of the study (thirty days), biphasic half-lives were not observed in the soil photolysis study.

EFED Rejoinder to Novartis' Response to Comment "b":

The Agency pointed out there appears to be a discrepancy between the half-life of metolachlor in photodegradation on soil study (MRID 43928935) and the aerobic soil metabolism study (MRID 43928936). The registrant believes the aerobic soil metabolism studies yielded shorter half-lives for metolachlor because of soil mixing, better control of soil moisture, and the biphasic degradation pattern of metolachlor beyond the thirty-day duration of the soil photolysis study.

The Agency believes the reported half-lives for metolachlor and S-metolachlor in photodegradation on soil and aerobic soil metabolism studies are consistent with "normal" variation reported in the open literature. The reported first-order aerobic soil metabolism degradation half-lives for metolachlor range from 7.33 to 37.87 days depending on the half-life estimation method (Table 2). The photodegradation on soil half-lives in the dark controls range from 39.7 to 50.96 days depending on the half-life estimation method.(Table 1). This range of half-lives is consistent with soil persistence data ($t_{1/2}$= 15 to 70 days) presented in the Extension Toxicology Network (EXTONET) (http://ace.orst.edu/info/extoxnet/pips/metolach.htm).

The Agency believes the photodegradation on soil study (MRID 43928935) should be upgraded to acceptable bridging data for linking the racemic metolachlor and S-metolachlor. These data illustrate that metolachlor and S-metolachlor are not expected to photodegrade quickly on soil.

Table 2. Aerobic Soil Metabolism

Study	MRID	Metolachlor	Test Conditions	Linear Half-life (days)	Non-Linear Half-life (days)	Transformation Products
Aerobic Soil Metabolism	41309801		Iowa soil 10.6 ppm 1-D TLC & 2-DTLC oxic conitions	66	27	51202 37735 41638
Aerobic Soil Metabolism	43928936	racemic	Maryland soil 1.3 ppm 1-D TLC/2-TLC/HPLC	37.87	7.33	46129 40172 50720 41638 40919 48087 51202 354743 322966 37735 77102
Aerobic Soil Metabolism	43928936	S-metolachlor	Maryland soil 1.3 ppm 1-D TLC/2-TLC/HPLC	37.87	9.21	46129 40172 50720 41638 40919 48087 51202 354743 322966 37735 77102

Aerobic Soil Metabolism (162-1 MRID# 43928936, MRID# 41309801A and B[4,5])

EPA Comment:

a. There is a discrepancy in the half-life reported in the previous metolachlor data (GT; 02/25/93) and these bridging data. A half-life of 67 days was reported in previous metolachlor data. These data reported biphasic half-lives of 8/67.9 and 7.8/69.7 for metolachlor and CGA-77102, respectively.

Novartis Response to EPA Comment "a":

The perceived discrepancy between the older metolachlor study and the bridging data is a result of advanced changes in the calculation of half-lives from 1989 (MRID# 41309801 A and B[5]) to 1995 (MRID# 43928936[4]). When the 1989 studies were conducted, it was typical to calculate the half-life by obtaining a "best linear fit" (log % parent) to the exponential curve, thereby calculating a single half-life. The study submitted for the bridging data conducted in 1995 included calculations using the Excel trend analysis to calculate primary and secondary half-lives for the exponential curve. Within the last year, Novartis has gained the capability to evaluate an exponential curve more accurately using a two compartment model (Origin software, version 4.0). Figure 1 represents re-calculation of the data points from Agrisearch study number 1258 (1989) and Ciba study number 338-94 (1995) to evaluate each exponential curve using the more advanced two compartment model of Origin. Using this curve fit, the primary half-lives for the 1989 and the 1995 studies are 7.4 and 6.9 days, respectively. Also similar were the metolachlor secondary half-lives of 30.1 days (1989 study) and 30.6 days (1995 study). The CGA-77102 primary and secondary half-lives were 6.9 days and 28.8 days, respectively. All of the exponential curves seen in the 1989 and the 1995 studies confirm the same rates for biphasic degradation of metolachlor and CGA-77102.

EFED Rejoinder to Novartis' Response to Comment "a":

The Agency agrees that the degradation pattern of metolachlor can be described using either a linear first-order or integrated form of the first-order model. In either case, the aerobic soil metabolism half-life for metolachlor can range from 7.33 to 66 days.

The Agency pointed out there appears to be a discrepancy in the reported aerobic soil metabolism half-lives (MRID 43928936 and MRID 41309801A and B). The registrant believes the discrepancy in the reported half-lives is due to the half-life estimation method. In the original studies, half-lives were estimated using a linear regression model ($\ln(C0/C)=-k*t$). In the bridging studies, two first-order half-lives were estimated using a biphasic model with two distinct degradation curves.

The Agency reevaluated the data analysis for first-order half-life estimation in the aerobic soil metabolism studies (MRID 43928936 and MRID 41309801A and B) (Table 2). The data were fit using the first-order model (ln (C/Co)=-kt) and the integrated form of the first-order degradation model ($C=Coe^{-kt}$)(SigmaStat Regression Wizard). In theory, the first order degradation model fitting procedures should yield similar results when the data exhibit a first-order degradation pattern. The data indicate, however, that metolachlor degradation in soil does not appear to be a strict first-order degradation process because there are large differences between the linear and non-linear half-lives. The non-linear half-life estimates suggest a more rapid degradation rate than the linear half-life estimates. The reported first-order aerobic soil metabolism degradation half-lives for metolachlor range from 7.33 to 66 days depending on the half-life estimation method (Table 2). This range of half-lives is consistent with soil persistence data ($t_{1/2}$= 15 to 70 days) presented in the Extension Toxicology Network (EXTONET) (http://ace.orst.edu/info/extoxnet/pips/ metolach.htm).

EPA Comment:

b. There is a discrepancy in these bridging aerobic soil metabolism data and the bridging soil photolysis data. For the 0 to 21 day data, the bridging soil photolysis data reported a half-life of 78.8 and 95.1 days for metolachlor and CGA-77102. The aerobic soil metabolism data reported a half-life of 8 days for the 0 to 21 days data.

Novartis Response to EPA Comment "b":

As previously discussed on pages 6 and 7 of this report, the aerobic soil metabolism study (MRID# 43928936)[4] and bridging soil photolysis study (MRID# 43928935)[2] are similar in several ways: soil collection from the same area, dose rate (1.3 ppm), temperature range maintained at 25 ± 1°C and extraction schemes. However, the differences in half-lives (aerobic soil metabolism half-life for metolachlor and CGA-77102 = approx. 8 days, irradiated soil photolysis half-lives for metolachlor and CGA-77102 = 78.8 days and 95.1 days, respectively; dark control half-lives for metolachlor and CGA-77102 in the soil photolysis study = 40.9 days and 50.2 days, respectively) are attributed to the following differences: method of dosing, lack of soil binding (organic matter content), and study duration.

The major route of degradation for the parent compound (metolachlor or CGA-77102) was microbial degradation. In the aerobic soil metabolism study, the test substances were dosed and homogenized (roller mixed) throughout the moist, viable soil. This exposed the test substances to the majority of the microbial population present in the soil, producing shorter and similar half-lives (~8 days) for metolachlor and CGA-77102. In the soil photolysis study, the test substances were topically applied (by syringe) to the surface of the soil sample layers. This reduced the microbial population that was exposed to the test substances, and therefore, produced longer, similar half-lives (78.8 and 95.1 days, metolachlor and CGA-77102, respectively). The longer half-lives in the irradiated photolysis samples compared to the dark controls and the aerobic metabolism samples, indicates, that what little photolytic degradation may occur, is minor compared to microbial degradation.

Homogenization (roller mixing) of the test substances in the aerobic soil metabolism study exposed the test substances to a higher amount of organic matter present in the soil. For the soil photolysis study, samples were topically dosed, which concentrated the test substance on to the thin layer of soil surface (approximately 2 cm). Under conditions of irradiation (12 hour light cycle), there is partial drying of the soil surface. This reduces the amount of test substance which is solubilized. Loss of solubilized test material reduces both interaction with organic components of the soil and degradation by soil microbes. The rate of degradation is further slowed considerably during the 12 hour light cycle. During the 12 hour dark cycle, two things can occur: rehydration of the soil surface (by water sealed in the test vessels) and resolubilization of the test substance. This can cause possible further degradation.

Over time, the binding of the test substance to the soil limited the rate of aerobic soil metabolism (six month study duration) causing a secondary degradation rate (metolachlor and CGA-77102, half-lives = 30.6 days and 28.8 days, respectively) (Figure 1) and therefore, a biphasic half-life in the degradation profile. For the soil photolysis study, the binding of the test substances to the soil was less significant. Due to the minimal binding of the test substance to the soil and the short, required length of the study (thirty days), biphasic half-lives were not observed in the soil photolysis study.

EFED Rejoinder to Novartis' Response to Comment "b":

The Agency pointed out there appears to be a discrepancy between the half-lives of metolachlor in the photodegradation on soil studies (MRID 43928935) and aerobic soil metabolism studies (MRID 43928936). The registrant believes the aerobic soil metabolism studies yielded shorter half-lives because of soil mixing, better control of soil moisture, and the biphasic degradation pattern of metolachlor.

The Agency believes the reported half-lives for metolachlor and S-metolachlor in photodegradation on soil and aerobic soil metabolism studies are consistent with "normal" variation reported in the open literature. The reported first-order aerobic soil metabolism degradation half-lives for metolachlor range from 7.33 to 37.87 days depending on the half-life estimation method (Table 2). The photodegradation on soil half-lives in the dark controls range from 39.7 to 50.96 days depending on the half-life estimation method.(Table 1). This range of half-lives is consistent with soil persistence data ($t_{1/2}$= 15 to 70 days) presented in the Extension Toxicology Network (EXTONET) (http://ace.orst.edu/info/extoxnet/pips/metolach.htm

c. Biphasic half-lives were not reported in previous metolachlor data.

Novartis Response to EPA Comment "c":

Novartis response to comment "a" compares the data from the previous study (MRID# 41309801A and B,1989)[5] to the bridging study (MRID# 43928936,1995[4]) using a more advanced two compartment model (Origin) for the half-life calculations. By today's standards and advanced computations, the data from 1989 also produced biphasic half-life calculations. Figure 1 compares the data from the 1989 study and the 1995 study displaying similar curves. The primary half-lives of metolachlor for 1989 and the 1995 studies are 7.4 and 6.9 days, respectively. Also similar are the metolachlor secondary half-lives of 30.1 days (1989) and 30.6 days (1995).

EFED Rejoinder to Novartis' Response to Comment "c":

The Agency indicated that biphasic half-lives were not reported in the original aerobic soil metabolism study (MRID 41309801A and B).

The Agency reevaluated the data analysis for first-order half-life estimation in the aerobic soil metabolism studies (MRID 43928936 and MRID 41309801A and B) (Table 2). The data were fit using the linear first-order model ($\ln(C/Co)=-kt$) and the integrated form of the first-order degradation model ($C=Coe^{-kt}$)(SigmaStat Regression Wizard). In theory, the model fitting procedures should yield similar results when the data exhibit a first-order degradation pattern. The data indicate that metolachlor degradation does not appear to be a strict first-order degradation process because there are large differences between the linear and non-linear half-lives. The non-linear half-life estimates suggest a more rapid degradation rate than the linear half-life estimates. The reported first-order aerobic soil metabolism degradation half-lives for metolachlor range from 7.33 to 66 days depending on the half-life estimation method (Table 2). This range of half-lives is consistent with soil persistence data ($t_{1/2}$= 15 to 70 days) presented in the Extension Toxicology Network (EXTONET) (http://ace.orst.edu/info/extoxnet/pips/ metolach.htm).

The Agency believes the aerobic soil metabolism (MRID 43928936) should be upgraded to acceptable bridging data for linking the racemic metolachlor and S-metolachlor. These data illustrate that metolachlor and S-enriched metolachlor are expected to be moderately persistent in soil.

Anaerobic Soil Metabolism (162-2, MRID# 41309810A and B[5])
Aerobic and Anaerobic Aquatic Metabolism (162-3 and 162-4, MRID# 41185701[6])
EPA comments (page 9 of 10, footnote number 7)

EPA Comment:

These data requirements were considered fulfilled under the previous metolachlor data review. However, based on the new CGA-77102 and metolachlor bridging data, these data requirements can not be considered fulfilled at this time. Supporting data are needed to determine if there are anaerobic soil and aquatic and aerobic aquatic biphasic half-lives, as well. If additional data indicate that metolachlor anaerobic metabolism and/or aerobic aquatic metabolism is not biphasic, these data can be used to fulfill the respective data requirements."

Novartis Response to EPA Comment:

Under aerobic aquatic conditions (MRID# 41185701[6]), metolachlor can be predicted to have biphasic half-lives of 39 (primary) and 24 (secondary) days. The half-life is estimated, since data is available only through 30 days (Figure 2).

Half-life determinations for the anaerobic soil (MRID# 41309810A and B[5]) and anaerobic aquatic (MRID# 41185701[6]) studies were re-evaluated (Figures 3 and 4). For both studies, half-live calculations produced similar linear, non-biphasic curves [80.9 days (anaerobic soil metabolism) versus 78.2 days (anaerobic aquatic)]. It can be concluded that under anaerobic conditions, degradation of metolachlor and CGA-77102 is minor.

EFED Rejoinder to Novartis' Response to Comment:

The Agency indicated that biphasic half-lives were not reported in the aerobic and anaerobic aquatic and anaerobic soil metabolism studies (MRID 41309810A and B; MRID 41185701). The registrant believes the degradation of metolachlor in an anaerobic aquatic metabolism and anaerobic soil metabolism studies were adequately described using the first-order linear degradation model.

The Agency reevaluated the data analysis for first-order half-life estimation in the aerobic aquatic and anaerobic soil metabolism studies (MRID 41185701; MRID 41309810A and B). (Table 3). The data were fit using the linear first-order model (ln (C/Co)=-kt) and the integrated form of the first-order degradation model ($C=Coe^{-kt}$)(SigmaStat Regression Wizard). In theory, the model fitting procedures should yield similar results when the data exhibit a first-order degradation pattern. The data suggest that metolachlor degradation in anaerobic soil and an anaerobic aquatic environments is adequately described using a first-order linear or nonlinear degradation model because there are no large differences between the linear and non-linear half-lives. One exception may be noted in the anaerobic aquatic metabolism study where the nonlinear half-lives were shorter than the linear half-lives.

The Agency believes the anaerobic aquatic and anaerobic soil metabolism studies (MRID 41185701; MRID 41309810A and B) should be upgraded to acceptable data for the racemic metolachlor. These data illustrate that metolachlor is expected to be moderately persistent in oxic and anoxic aquatic environments.

Table 3. Anaerobic and Aerobic Aquatic Metabolism

Study	MRID	Metolachlor	Test Conditions	Linear Half-life (days)			Non-Linear Half-life (days)			Transformation Products
				H20	Sed	Sum	H20	Sed	Sum	
Aerobic Aquatic Metabolism	41185701	racemic	South Dakota sediment/water 1-D TLC/2-TLC/HPLC/GC oxic	18	54	47	12	117	52	50720 51202 37735 41638 37913 40172
Anaerobic Aquatic Metabolism	41185701	racemic	South Dakota sediment/water 1-D TLC/2-TLC/HPLC/GC anoxic	46	94	78	10		4.6	50720 51202 37735 41638 37913 40919 40172
Anaerobic Soil Metabolism	41309810	racemic	Iowa soil 1-D TLC/2-TLC/HPLC/GC oxic/anoxic			81			75	50720 51202 40919 40172 41638

Photodegradation in Water (161-2, MRID# 40430202[7])
EPA comments (page 9 of 10, footnote number 9)

<u>EPA Comment</u>:

Based on previous soil photolysis data and these bridging data, the status of the aqueous photolysis data is considered supplemental and the data requirement not fulfilled at this time. After additional data addressing the discrepancies in the previous metolachlor data and in these bridging data, the status of this data requirement will be reevaluated.

Novartis Response to EPA Comment:

The soil photolysis irradiated half-lives in the bridging study for metolachlor and CGA-77102 were 78.8 days and 95.1 days, respectively (MRID# 43928935[2]). The previously submitted aqueous photolysis study (MRID 40430202[7]) also produced a similar irradiated half-life (70 days). These studies demonstrate that metolachlor and CGA-77102 have linear, non-biphasic half-life profiles in both soil and aqueous photolysis studies (Figure 5). It can be concluded that under photolytic conditions, degradation of metolachlor and CGA-77102 strongly correlate to each other. Photolysis can be considered a minor pathway for degradation.

EFED Rejoinder to Novartis' Response to Comment:

The Agency believes the reported half-lives for metolachlor and S-metolachlor in photodegradation on soil and photodegradation in water studies are consistent. The reported first-order half-lives in photodegradation on soil studies range from 8.99 to 94.95 days depending on the half-life estimation method (Table 2). The large variation in reported half-lives appear to be dependent on the experimental conditions. The photodegradation in water half-life was 70 days. Open literature data suggests that metolachlor is expected to photodegrade slowly in water [Extension Toxicology Network (EXTONET) (http://ace.orst.edu/info/extoxnet/pips/ metolach.htm)]. These data suggest that photodegradation in soil or water is not expected to be a major degradation pathway for metolachlor.

The Agency believes the photodegradation in water study (MRID 40430202) should be upgraded to acceptable data for racemic metolachlor. These data illustrate that metolachlor is not expected to photodegrade rapidly in water.

Field Dissipation (164-1)

EPA comments (page 9 of 10, footnotes 1, 4 and 5)

EPA Comment:

These data requirements are supported by previous submitted metolachlor environmental fate data.

Additional field dissipation data are needed to support registration of metolachlor and CGA-77102. Previous Data Evaluation Records for the above field dissipation MRIDS should be reexamined prior to submitting the additional data for the field dissipation data requirement. It should be noted that field data should reflect the different application methods, treatment sites, and maximum application rates. It should also be noted that previous field data did not calculate biphasic half-lives.

Turf field dissipation data are needed to support turf uses. It is presently understood that an application for turf uses may be submitted in the future.

Novartis Response to the EPA Comments:

As a result of the 1987 Registration Standard for Metolachlor, Novartis conducted field dissipation studies from 1987-89, which were reviewed by the Agency. The studies were ruled as upgradable, but by the time the reviews were received, the study samples were five years old, without supporting storage stability information.

In the same time period (1989), Ciba (now Novartis) conducted a small-scale retrospective groundwater study in four highly vulnerable, high use rate, limited geographical areas of the United States. This study was ultimately rejected by the Agency, but did show that metolachlor was detected in vulnerable groundwater, albeit not at levels which exceeded the Health Advisory. In 1992, the Pesticides in Ground Water Data Base indicated low-level contamination of groundwater in 20 states, with three incidences of ground water levels which exceeded the health advisory. All three incidences (one each in WI, NY and MO) were attributable to point source problems (WI, NY) or extreme vulnerability (MO).

When all of these data were considered together, the Metolachlor RED, issued in 1995, indicated that there was a concern for groundwater contamination by metolachlor; that sufficient data were available to make an overall environmental assessment of metolachlor; and that additional data would not be expected to change the overall assessment. Rather than submit additional field dissipation data, the Agency and Novartis have agreed that Novartis data from the two small-scale prospective groundwater studies, required by the 1995 Data Call In which involve both metolachlor and CGA-77102, will be used to assess field dissipation. This was confirmed in an EFGWB review dated 2/16/95, which stated in No. 3 of the **Recommendations**: Increased monitoring of soil water and ground water will better meet the needs of the study than an on-site field dissipation study. EFGWB's Chemistry Review section concurs that there is no need for another field dissipation study for metolachlor.

Regarding the need for a turf field dissipation study - Novartis is still in the process of deciding whether or not it will register CGA-77102 on turf. The Agency comment is noted.

EFED Rejoinder to Novartis' Response to Comment:

The Agency agrees with the registrant that submission of small-scale prospective ground water monitoring studies can supplant the need for additional field dissipation studies on row crops. Field dissipation studies on turf are reserved pending registration of metolachlor use on turf.

EPA comment (page 9 of 10, footnote 6)

EPA Comment:

Based on possible annual applications, these data requirements are needed to make a more complete environmental assessment.

Novartis Response to the EPA Comment:

As a member of the Spray Drift Task Force, Novartis is relying on Task Force studies for these data requirements.

EFED Rejoinder to Novartis' Response to Comment:

The Agency acknowledges the registrant's reliance on the Spray Drift Task Force data.

REGISTRANT'S OVERALL CONCLUSIONS

Under aerobic conditions, the major route of degradation for metolachlor and CGA-77102 was microbial degradation. It can be concluded that under aerobic, nonsterile conditions, metolachlor and CGA-77102 degrade biphasically (primary half-life: 6.9-7.4 days (metolachlor), 6.9 days (CGA-77102); secondary half-life: 30.1-30.6 days (metolachlor), 28.8 days (CGA-77102)) when homogenized (roller mixing) with soil. Under aerobic aquatic conditions, metolachlor can be predicted to have biphasic half-lives of 39 days (primary) and 24 days (secondary).

Degradation of metolachlor and CGA-77102 under photolytic and anaerobic conditions was minor. The longer half-life for the bridging soil photolysis study can be attributed to the method of dosing (topical), organic matter content of the soil, and lack of exposure to much of the microbial population in the soil. For photolysis, data indicates metolachlor and CGA-77102 have linear (non-biphasic) half-lives (78.8 and 95.1 days for metolachlor and CGA-77102, respectively). The aqueous photolysis half-life (linear, non-biphasic, 70 days) is similar to the bridging soil photolysis study. Half-life determinations under anaerobic conditions are similar and linear (non-biphasic) [78.2 days (anaerobic aquatic) versus 80.9 days (anaerobic soil metabolism)].

EFED Rejoinder to Novartis' Overall Conclusions:

The Agency believes the bridging studies for metolachlor and S-metolachlor should be upgraded to fulfill the photodegradation in water (161-2), photodegradation on soil (163-1), aerobic soil metabolism (162-1), anaerobic soil metabolism (162-2), anaerobic aquatic metabolism (162-3), and aerobic aquatic metabolism (162-4) data requirements.
The basic experimental approach was to compare half-lives as well as the type and quantities of transformation products between metolachlor and S-metolachlor. Althought this approach is reasonable, it is complicated because the experimental conditions were not similar among

the various environmental fate studies. The Agency notes that future studies on metolachlor and S-metolachlor should report the enantiomeric ratio during the study. These data are expected to directly assess preferential degradation, sorption, or bioconcentration of the R- and S- enantiomer of metolachlor.

A major problem with linking the original environmental fate studies for metolachlor and the more recent bridging studies for metolachlor and S-metolachlor is the description of the degradation pattern for metolachlor and S-metolachlor. There is a claim that metolachlor degradation in soil is biphasic because it does not fit a linear first-order degradation model (ln(C/Co)=-kt). The Agency believes the reported first-order half-lives (described using either the linear model [ln(C/Co=-kt or $C=Coe^{-kt}$) for metolachlor and S-metolachlor in the photodegradation on soil and aerobic soil metabolism studies are consistent with "normal" variation of metolachlor persistence in soil as reported in the open literature. The reported first-order aerobic soil metabolism degradation half-lives for metolachlor range from 7.33 to 37.87 days. The photodegradation on soil half-lives in the dark controls range from 39.7 to 50.96 days. These ranges of half-lives regardless of the first-order half-life estimation method are consistent with metolachlor soil persistence data ($t_{1/2}$= 15 to 70 days) presented in the Extension Toxicology Network (EXTONET) (http://ace.orst.edu /info/extoxnet/pips/ metolach.htm). This type of variation in reported half-lives complicates comparing half-lives among specific environmental studies which have been conducted under different environmental conditions. However, there is a consistent interpretation that metolachlor and S-metolachlor are expected to be moderately persistent in soil and aquatic environments.

The Agency believes that metolachlor appears to be stable in photolysis on soil or in water. Also, the Agency agrees with the registrant that submission of prospective ground water monitoring studies can supplant the need for additional field dissipation studies on row crops. Field dissipation studies on turf are reserved pending metolachlor registration on turf.

EPA'S COMMENTS/RESPONSES - NOVARTIS RESPONSES [*The Koc comparison in_Equivalency of Pesticides Metolachlor and S-Metolachlor with Respect to Ground Water Contamination (Docket Number OPP-36190A, 4/21/20000)]*

Novartis Comment

The registrant (Novartis) believes that S-metolachlor has a higher soil sorption affinity than metolachlor. This conclusion is based on analysis of batch equilibrium data from US and foreign soils (Burkehard, 1978; Ellgehausen, 1997; Spare, 1995; and Ecochemistry CGA-77102 Status Report, 1994). The registrant's assessment of non-paired batch equilibrium data indicates that S-metolachlor has significantly higher (P<0.0010) Koc coefficient (mean 219.556) when compared to racemic metolachlor (mean 69.288) (Ellgehausen H, 1997 and Spare, 1995). Further analysis of non-GLP paired batch equilibrium data indicate that a non-significant difference (P=0.203) between the Koc coefficient for metolachlor (249.250) and S-metolachlor (265.875)(Ecochemistry CGA-77102 Status Report, 1994). The registrant contends the higher Koc coefficients for S-metolachlor are expected to minimize the leaching potential of CGA-77102.

EFED Rejoinder

The Agency believes that there is no difference in soil sorption affinity between metolachlor and S-metoachlor. Although the comparison of non-paired batch equilibrium data indicate there is a significant difference in Koc coefficients for metolachlor (mean Koc=69.288) and S-metolachlor (mean Koc= 219.556), the difference can be attributed to higher average soil organic content (SOC) content in the test soils used in the S-metolachlor sorption studies rather than an actual increase in the sorption affinity of S-metolachlor. Similar Koc coefficients for metolachlor (mean Koc=249.250) and S-metolachlor (mean Koc=265.875) were observed in paired batch equilibrium studies. These data suggest that metolachlor and S-metolachlor are expected to be highly mobile to mobile in soil and water environments.

The data clearly show that soil sorption of metolachlor and S-metolachlor is highly dependent on the SOC content. Based on linear regression analysis, there is a significant relationship between Kd and SOC (Yo=-0.0254; slope=2.273; adjusted R^2=0.93) for the combined metolachlor and S-metolachlor sorption data. These data indicate that 97% of the variability in soil:water partitioning for metolachlor and S-metolachlor is related to SOC. Similar regression equations were observed for individual analysis of the sorption data for metolachlor and S-metolachlor. Therefore, the Koc model (as described by the slope of the Kd and SOC relationship) is an appropriate soil partitioning model for metholachlor and S-metolachlor. Below are the regression equations for the batch equilibrium data for metolachlor and S-metolachlor

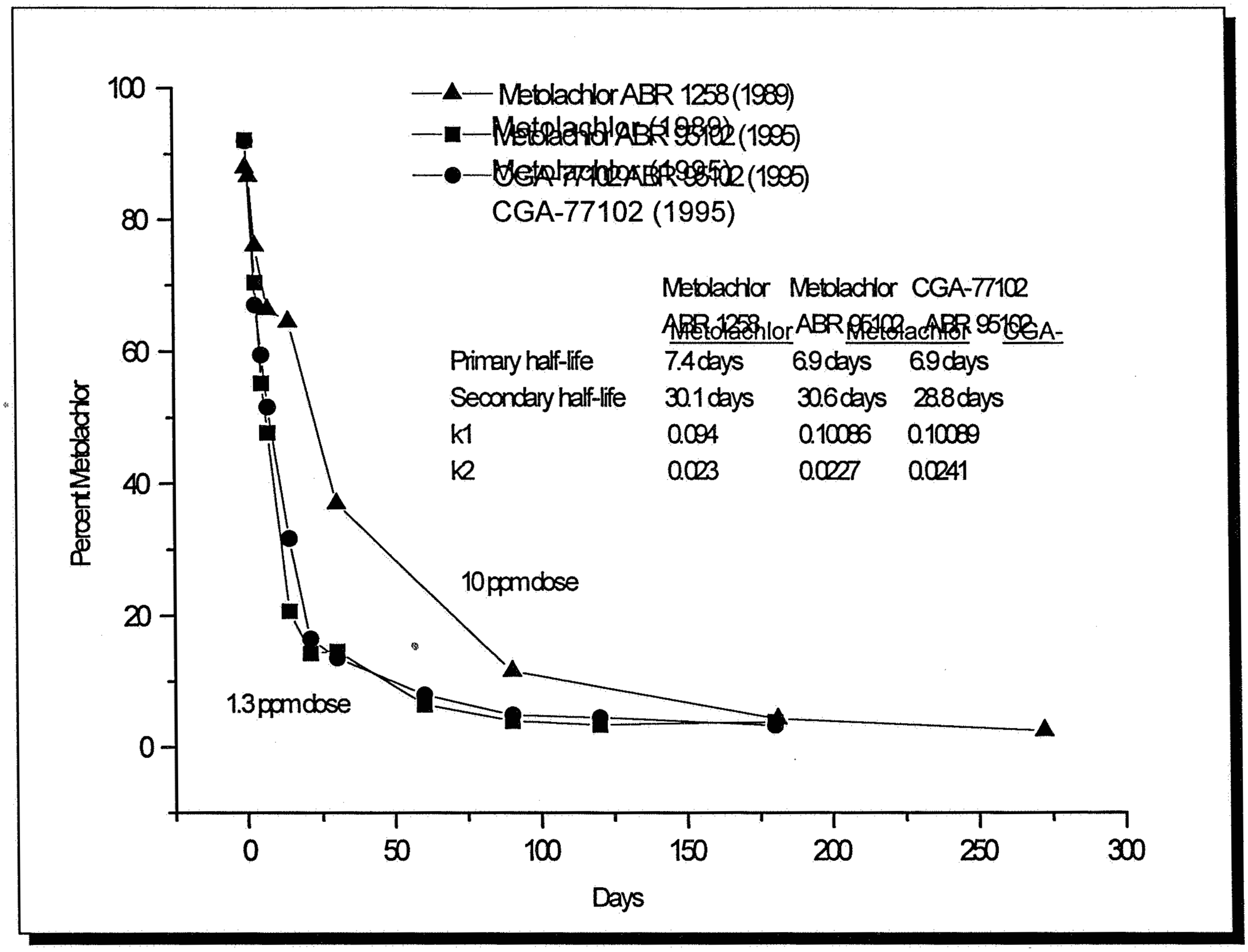
Mixture	Study ID	R^2	Intercept	Slope
Racemic	Burkhard	0.85	-2.0013	3.2993
Racemic	Spare	0.94	-0.0003	0.7114
Racemic	Status Report	0.50	-0.0530	2.9618
S-Metolachlor	Ellgenhauser	0.99	0.1859	2.2599
S-Metolachlor	Spare	0.48	-0.5513	2.6959
S-Metolachlor	Status Report	0.49	0.1147	2.6844

The registrant observed a significant difference in Koc coefficients for metolachlor (mean Koc=69.646) and S-metolachlor (mean Koc= 219.559) in the non-paired batch equilibrium studies. This observation appears to be associated with the use of soil partitioning coefficients as point estimates rather than an average estimate across many soils with different organic matter contents. The use of Koc coefficients as point estimates does not allow for normalization of the soil:water coefficient (Kd) and SOC which results in higher. sorption coefficients in soils with a higher organic carbon content. This result is expected because SOC is the main variable controlling sorption of metolachlor and S-metolachlor as indicated by the extremely high coefficient of determination (R^2) between Kd and SOC. The impact of SOC can be observed in the registrant submitted non-paired batch equilibrium studies for S-metolachlor and racemic metolachlor (Burkehard, 1978; Ellgehausen, 1997; Spare, 1995). The SOC in the test soils are not similar; the SOC ranged from 0.5 to 3.3% (average=1.7875%; SD=1.128%) and 0.17 to 19.8% (average=3.4666%; SD=6.2718%) for the test soils used on racemic metolachlor and S-metolachlor, respectively. In contrast, the paired batch equilibrium studies using the same soils did not yield a significant differences (P=0.23). Additionally, the Koc model (as described by the slope of Kd and SOC relationship) clearly shows the variability of the slopes for racemic metolachlor (0.7114 to 3.2993) bracket the S-metolachlor (2.25 to 2.695). These data suggest the difference in point estimate Koc coefficients between racemic metolachlor and S-metolachlor appears to be dependent on the higher average SOC content in the test soils used in the S-metolachlor sorption studies rather than an actual increase in the sorption affinity of S-metolachlor.

TABLE I: COMPARISON OF THE SOIL CHARACTERISTICS FROM THE PREVIOUS (MRID# 40430203) AND BRIDGING (MRID# 43928935) SOIL PHOTOLYSIS STUDIES

Soil Characteristic	Bridging Study Ciba-Geigy ABR-95128 (MRID 43928935)	Previous Study Agrisearch Project 1262 (MRID 40430203)
% Sand	75	53.2
% Silt	16	37.6
% Clay	9	9.2
Texture	Sandy Loam	Sandy Loam
pH	7.5	5.9
Cation Exchange (meq/100g)	10.3	13.6
% Organic Matter	**2.9**	**5.0**
% Moisture at 1/3 Bar	13.4	23.9
Bulk Density (g/cc)	1.09	1.24

FIGURE 1: COMPARISON OF METOLACHLOR AND CGA-77102 FROM AEROBIC SOIL METABOLISM STUDIES PERFORMED IN 1989 (MRID# 41309801 A AND B) AND 1995 (MRID# 43928936)



	Metolachlor ABR 1258	Metolachlor ABR 95102	CGA-77102 ABR 95102
Primary half-life	7.4 days	6.9 days	6.9 days
Secondary half-life	30.1 days	30.6 days	28.8 days
k1	0.094	0.10086	0.10089
k2	0.023	0.0227	0.0241

FIGURE 2: HALF-LIFE DETERMINATION: AEROBIC AQUATIC METABOLISM OF METOLACHLOR (MRID# 41185701)

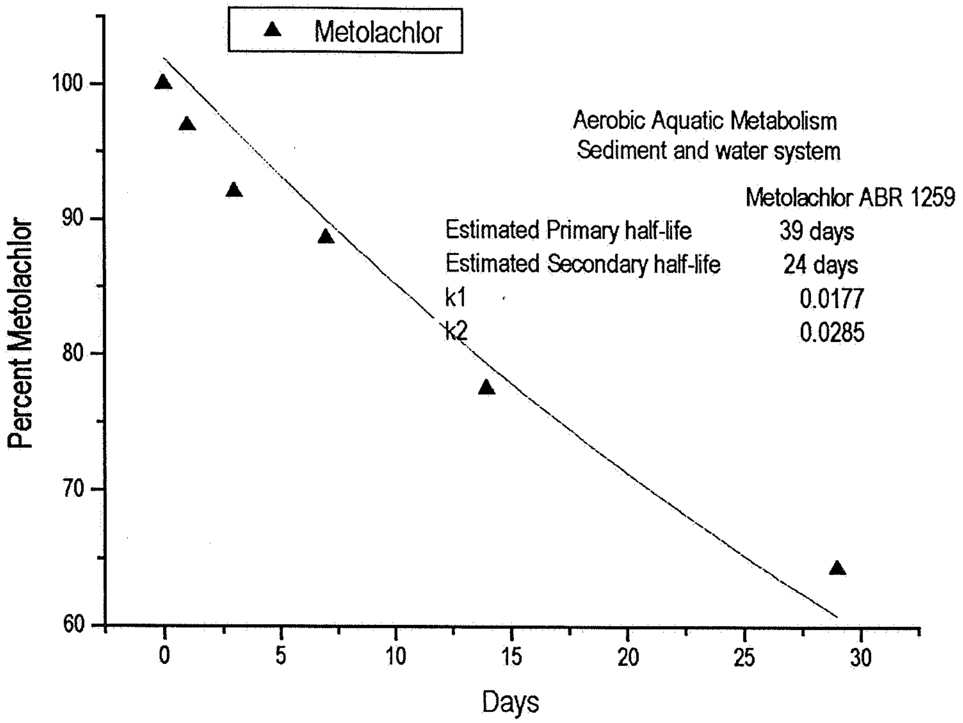


FIGURE 3: HALF-LIFE DETERMINATION: ANAEROBIC SOIL METABOLISM (MRID# 41309801 B)

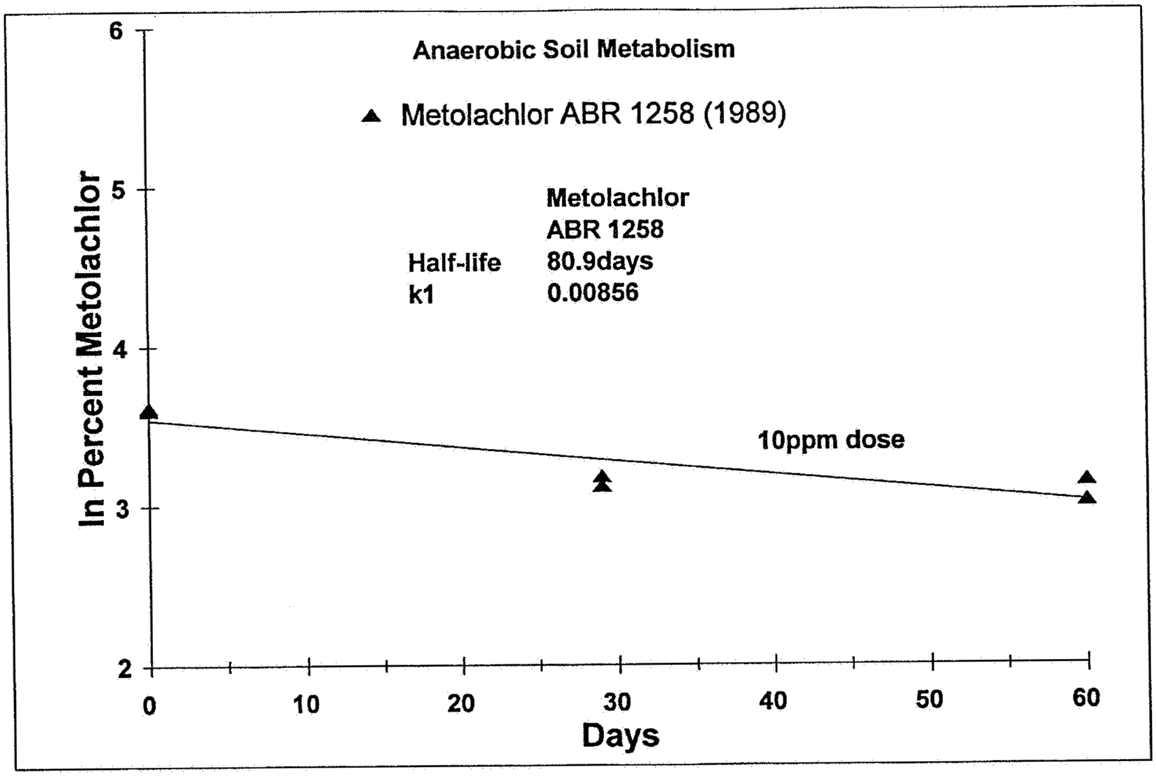


FIGURE 4: HALF-LIFE DETERMINATION: ANAEROBIC AQUATIC METABOLISM (MRID# 41185701)

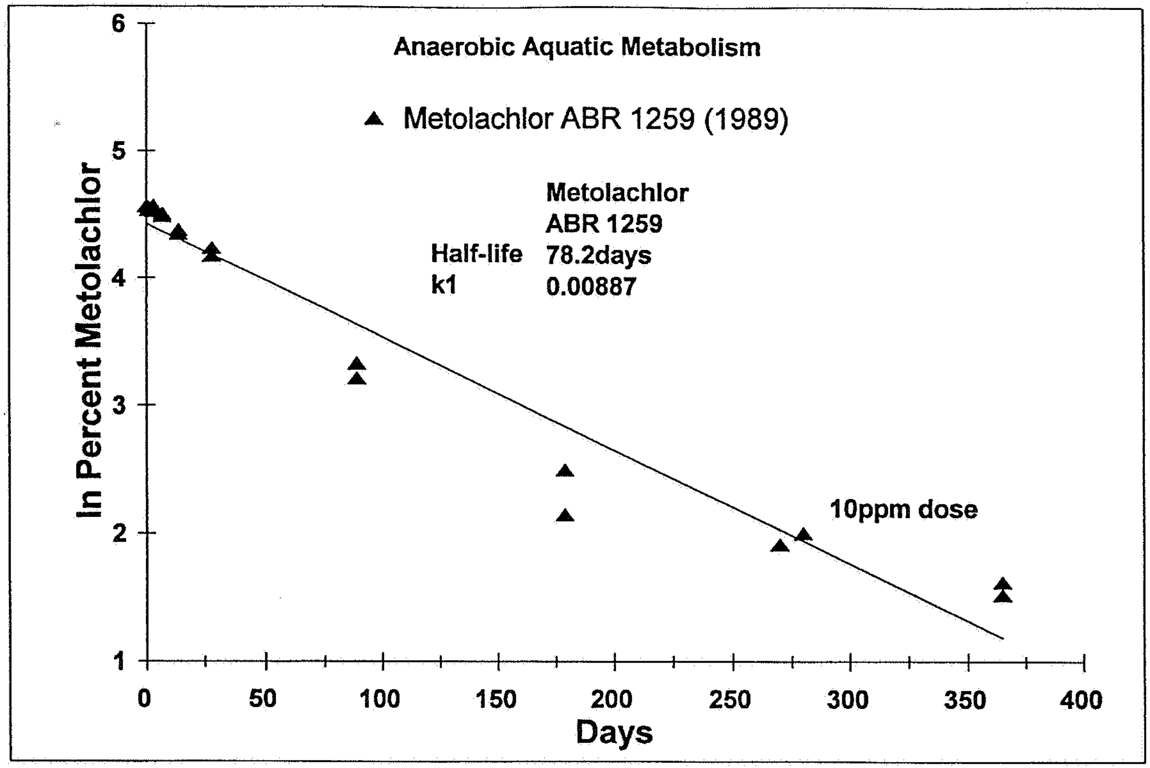
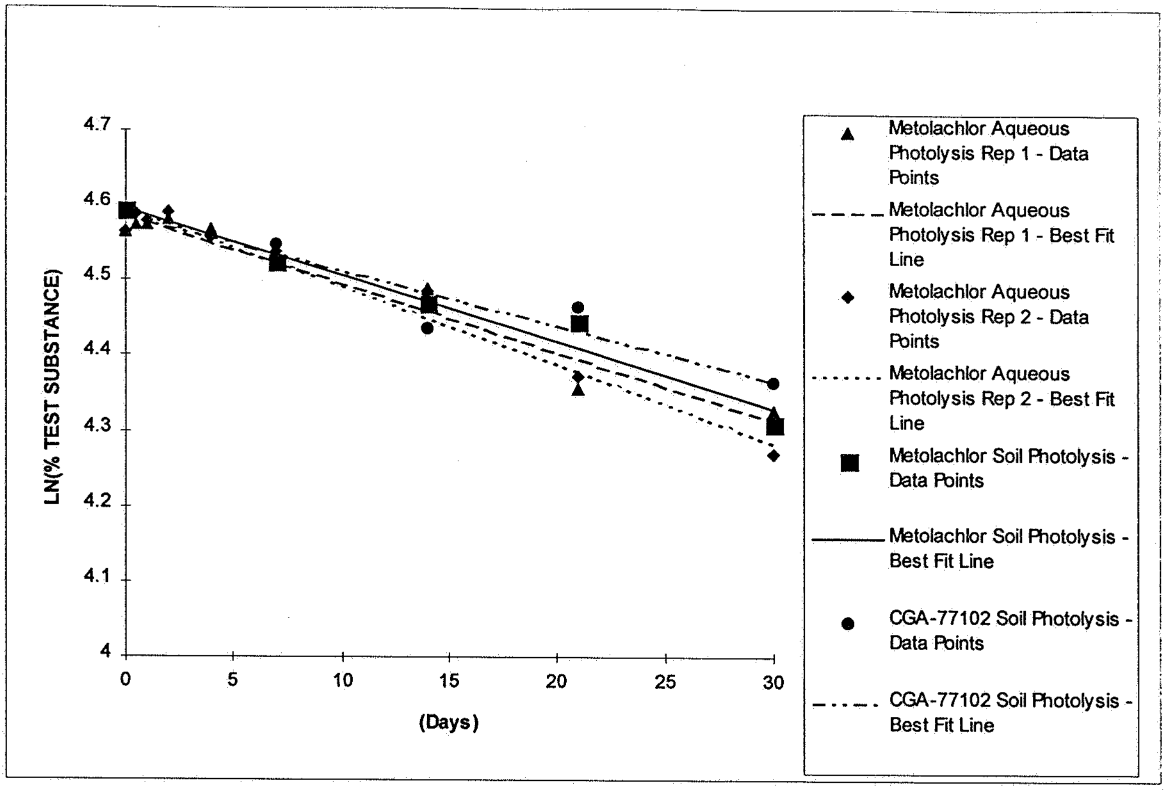


FIGURE 5: COMPARISON OF METOLACHLOR AND CGA-77102 PHOTOLYSIS (MRID# 43928935 SOIL, MRID# 40430202 AQUEOUS) HALF-LIVES



	Metolachlor			CGA-77102
	Aqueous Photolysis		Soil Photolysis	Soil Photolysis
	Rep 1	Rep 2		
k =	-0.0091	-0.0104	-0.0088	-0.0073
Half-Life =	76.5 days	66.7 days	78.8 days	95.1days

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