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OFFICE OF
PESTICIDES AND
TOXIC
SUBSTANCES

MEMORANDUM

SUBJECT: Review of Documents Related to the Equivalency of Racemic Metolachlor (Metolachlor) and S-Metolachlor for Environmental Fate and Ecotoxicity

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THRU: Dana Spatz, Acting Chief
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This memorandum provides clarification, reanalysis, and review of data on the equivalency of metolachlor and s-metolachlor with regard to environmental fate and ecotoxicity. Attached are completed reviews of documents to assess equivalency of metolachlor and s-metolachlor.

EFED concludes, based on Subdivision N laboratory data, there are sufficient bridging data to compare the environmental behavior of metolachlor to s-metolachlor. Metolachlor and s-metolachlor half-lives and degradation products in aerobic soil are similar. Additionally, the formation and degradation patterns of mobile degradation products, metolachlor ESA and metolachlor OA, were similar for metolachlor and s-metolachlor. The soil sorption affinity of metolachlor and s-metolachlor, expressed as K_f, K_d, or K_{oc}, are not significantly different. This conclusion is based on a comparison of laboratory data without enantioselective chemical analysis. Therefore, the stereochemistry of degradation products is unknown.

Extensive ground and surface water monitoring data for metolachlor in the United States indicates metolachlor and its degradation products (metolachlor OA and metolachlor ESA) are detected in ground and surface waters. The degradation products are generally detected at higher concentration than metolachlor in ground water. The registrant's assessment on the

impact of switching from metolachlor to S-metolachlor on environmental loading is inconclusive because numerous variables (such as agricultural practices, climate, pesticide usage, etc) were not considered in the analysis. Registrant- sponsored monitoring data in Switzerland indicate the switch from metolachlor to S-metolachlor led to changes in enantiomeric ratios of metolachlor in surface water. This replacement , however, did not result in lower metolachlor concentrations. Additionally, preliminary retrospective field data from the Office of Research and Development (ORD)/National Exposure Research Laboratory (NERL) indicate preferential occurrence of s-metolachlor in deep soil samples and ground water at sites with historic metolachlor applications. This observation while still very preliminary may be attributed to preferential degradation of R enantiomers in anaerobic environments. Although there are extensive ground and surface water monitoring data of metolachlor in the United States, the available data are not sufficient to allow enantioselective differentiation of metolachlor. This type of information is needed to evaluate the direct impact of switching from metolachlor to s-metolachlor on water quality.

Available ground and surface water models such as GENEEC, SCI-GROW, PRZM-EXAMS predict that lower application rates of s-metolachlor will result in lower environmental concentrations when compared to metolachlor. Similar registrant modeling results were predicted for S-metolachlor concentrations in groundwater at GA and MN test sites. The significance of the modeling results is difficult to assess because the modeling was conducted using inadequate calibration techniques. Additionally, the Pesticide Root Zone Model (PRZM), which is based on linear processes, will predict lower concentrations with lower application rates regardless of the calibration technique.

The ecotoxicity data are supportive of bridging toxicity profiles of metolachlor and s-metolachlor. Although the ecotoxicity studies were not conducted using identical test conditions and procedures, the ecological effects of metolachlor and s-metolachlor are similar except for the risk to non-target plants. The very low avian toxicity for metolachlor suggest minimal expected differences between metolachlor and s-metolachlor. Also, there are adequate data to provide informed comparisons on toxicity for fish, plants, and invertebrates. The only difference in risk is associated with the slightly greater risk of s-metolachlor to non-target plants.

The uncertainties in this assessment are associated with the lack of enantioselective ground and surface water monitoring data to confirm the impact of s-metolachlor and metolachlor and their degradation products on water quality. Preliminary field data from ORD/ NERL indicate enantioselective occurrence of S-metolachlor in deep soil and groundwater samples at three sites with historic metolachlor applications. Additionally, enantioselective degradation of the metolachlor in surface soils was detected at some field sites. In order to address these uncertainities, environmental fate laboratory data are needed to clarify the equivalency of anaerobic aquatic/soil degradation for metolachlor and s-metolachlor. Also, any future ground and surface water monitoring for metolachlor and its degradation products should employ some enantioselective analysis techniques to confirm the potential loading and exposure of metolachlor stereoisomers and their degradation products.

Reevaluation of Existing Data on Equivalency of Metolachlor and S-Metolachlor for Environmental Fate

1.) *Review of the Stereochemistry of Metolachlor*

Metolachlor has four stable stereoisomers because there are two chiral centers. These stereoisomers exist as diastereomers (non-mirror images), enantiomers (mirror images), and atropisomers (conformation isomers). Enantiomers have the same chemical and physical properties (except for the direction they rotate plane polarized light), but can react differently with other chiral systems in the environment (e.g., soil metabolism rates and products could be different). This also can explain why one enantiomer may be more active than the other. Unlike enantiomers, diastereomers and atropisomers have different physical properties (i.e., solubility, melting point, density, etc.) and similar (not identical) chemical properties.

2.) *Comparison of Metolachlor OA and Metolachlor ESA Degradate Formation and Decline Patterns for Racemic and S-Metolachlor*

A reevaluation of the photodegradation on soil (MRID 43928935) and aerobic soil metabolism (MRID 43928936) studies indicate the isomer ratio of applied metolachlor (100% S isomer or racemic metalachlor) did not impact the formation or degradation rate of metolachlor ESA and metolachlor OA.

Table 1 summarizes the data from the aerobic soil metabolism study for both the racemic and enriched isomer versions of parent metolachlor (and s-metolachlor) as well as the corresponding degradates, ethanesulfonic acid (ESA) and oxanillic acid (OA). The data show that the degradation profile of metolachlor ESA and OA are similar for metolachlor and s-metolachlor.

Table 1. Comparison of Racemic and s-isomer Metolachlor Formation and Decline Data for Parent, CGA-354743 (ESA), and CGA-51202 (OA) from Aerobic Soil Metabolism Study MRID 43928936 using Two Dimensional TLC Data.

Time (days)	Percent Applied of Racemic Parent	Percent Applied of s-isomer Parent	Percent Applied of Racemic CGA-354743 (ESA)	Percent Applied of s-isomer CGA-354743 (ESA)	Percent Applied of Racemic CGA-51202 (OA)	Percent Applied of s-isomer CGA-51202 (OA)
0	91.4	92.0	0	0	0	0.3
3	68.2	67.0	3.1	3.5	4.8	3.5
5	54.5	59.6	5.2	4.3	6.3	4.3
7	45.3	51.6	6.1	6.2	8.3	6.2
14	20.7	31.7	7.1	7.1	8.4	7.1
21	13.8	16.5	7.7	8.9	10.3	8.9
30	13.7	13.6	8.6	9.6	9.0	9.6
60	6.1	8.0	10.7	12.4	8.8	12.4
90	3.9	4.9	7.3	7.9	6.0	7.9
120	4.3	4.5	6.7	7.8	4.7	7.8
180	3.0	3.3	5.8	6.7	2.7	6.7

Table 2 summarizes the data for both the racemic and enriched isomer versions of parent Metolachlor (and s-metolachlor) as well as the corresponding oxanillic acid (OA) from the "Photodegradation of ^{14}C-Metolachlor and ^{14}C-CGA-77102 on Soil" (MRID 43928935). The degradate ESA was not detected in the Soil Photolysis study. The data show similar formation and decline patterns suggesting that neither the racemic nor the enriched isomer will form the OA degradate in greater amounts through photolysis on soil.

Table 2. Comparison of Racemic and s-isomer Metolachlor Formation and Decline Data for Parent and CGA-51202 (OA) from Photodegradation on Soil Study MRID 43928935 using TLC Data.

Time (days)	Percent Applied of Racemic Parent	Percent Applied of s-isomer Parent	Percent Applied of Racemic CGA-51202 (OA)	Percent Applied of s-isomer CGA-51202 (OA)
0	98.72	98.71	0.25	0.0
7	92.29	94.56	0.10	0.0
14	87.27	84.55	0.93	0.52
21	85.20	86.96	0.15	0.23
30	47.43	78.64	0.91	0.73

3) ***Review and Clarification of Batch Equilibrium Studies:***

The Agency reevaluated the mobility assessment to provide 1) a formal review of all batch equilibrium data, 2) a statistical analysis for comparing sorption coefficients of S-metolachlor and metolachlor, and 3) reasons for relative differences in sorption coefficients for metolachlor and S-metolachlor.

The Agency reviewed the batch equilibrium data for S-metolachlor and metolachlor used for comparing equivalency in mobility (Table 1). The paired batch equilibrium data (Soil Behavior of Maize Chloroacetanilides, June 10, 1994 and Ecochemistry CGA-77102 Status Report July, 5 1994) were not reviewed because there was no documentation regarding the experimental design, material and methods, and discussion of results. The non-guideline batch equilibrium studies provide ancillary data on the soil:water partitioning of metolachlor and S-metolachlor. The review of the batch equilibrium data indicate a miscalculation for Koc values reported in Burkhart, 1978. Recalculation of the data yielded Koc values ~ 3 fold higher than reported in the registrant's data submission. These calculation errors were verified with the registrant (Warner Phelps, Syngenta, 10/10/01).

Table 1: Review Summary of Submitted Batch Equilibrium Data for S-metolachlor and racemic metolachlor

Study	Status	Quality of Data	Subdivision N Deficiency
Racemic			
Burkhart, 1978 MRID 00078291	Ancillary	Moderate	Analysis is not chemical specific; residue specific methods referenced were not described; tabular raw data were not provided
Spare, 1987 MRID 40496404	Acceptable 2/25/93	High	None
Soil Behavior of Maize Chloroacetanilides, June 10, 1994	Not Acceptable	Low	Paired soil study; simple partitioning coefficient at 1 ppm; no estimate of Freundlich coefficient
S-Metolachlor			
Ellgehausen, H. 1997	Supplemental	Moderate	Foreign soils
Spare, 1995 MRID 43928937	Acceptable 4/23/97	High	No enantiometric ratios reported
Ecochemistry CGA-77102 Status Report July, 5 1994	Not Acceptable	Low	Paired soil study; simple partitioning coefficient at 1 ppm; no estimate of Freundlich coefficient

The registrant (Syngenta) provided statistical analysis of batch equilibrium data for metolachlor and S-metolachlor. Their analysis indicate s-metolachlor had statistically higher organic carbon sorption coefficients (K_{oc}) than metolachlor in non-paired batch equilibrium studies. Conversely, there were no statistical differences in Koc values for s-metolachlor and metolachlor in paired batch equilibrium studies. The Agency notes the statistical comparison of non-paired data was conducted on uncorrected data. The Agency's review indicated the K_{oc} coefficients for metolachlor and S-metolachlor are similar. This conclusion was reached through a non-statistical comparison of slopes between Kd and percent soil OC. The Agency hypothesized earlier that the higher K_{oc} partitioning coefficients for S-metolachlor in non-paired studies was due to a higher range of organic carbon content in test soils. This is an erroneous statement because organic carbon partitioning coefficients (Koc) are normalized for organic carbon content. The exact reason for differences in partitioning coefficients in non- paired batch equilibrium studies is difficult to assess at this time.

Additional statistical analysis of the batch equilibrium data were conducted to assess potential mobilities of S-metolachlor and racemic metolachlor. The data were analyzed using the following comparisons: 1) paired batch equilibrium data, 2) non-paired data from Subdivision N guideline batch equilibrium studies, and 3) all nonpaired batch equilibrium data. The paired batch equilibrium data were assessed separately because the test methods were not

similar to the other studies, and the quality of the data are not known. The analysis indicates there are no statistical difference ($P>0.05$) in Freundlich adsorption coefficients (Kf) or organic carbon partitioning coefficients (Koc) for the metolachlor and S-metolachlor. This conclusion was consistent among the different data comparisons. It is important to recognize differences in average Koc values were pronounced in non-paired studies [135 (racemic) vs 219 (S-enriched)]. However, the small sample size (n= 8 to 9 samples) coupled with the high standard deviations (85 to 94) led to nonsignificant differences in the Koc values. A significant difference in Koc may or may not occur with more observations.

5) Contact experts on chiral environmental chemistry or environmental chemistry of metolachlor in ORD (Dr. Wayne Garrison,ORD/Athens), USDA (Drs. Laura McConnel and Walter Schmidt), USGS (Drs. Dana Kolpin and William Foreman)

Dr. Wayne Garrison has conducted preliminary research showing enantioselective occurrence of S-metolachlor in deep soil samples and ground water at field sites with historical racemic metolachlor use. These data suggest anaerobic degradation of metolachlor is enantioselective. Similar enantiometric ratios of metolachlor were observed in surface soils and runoff waters when compared to the enantiomeric ratios in applied racemic metolachlor. However, more recent field data indicate enantioselective occurrence of S-metolachlor in surface soils. These data suggest enantioselective degradation of metolachlor may not be constant across different soil types.

6) Review Literature on Environmental Behavior and Stereochemistry of Metolachlor

Buser, H. R., T. Poiger, et al. (2000). "Changed enantiomer composition of metolachlor in surface water following the introduction of the enantiomerically enriched product to the market." Environ. Sci. Technol. 34(13): 2690-2696

The study provides data on the impact of the use of S-metolachlor in the watersheds of two Swiss lakes on enantiomer/isomer composition of metolachlor in surface water. The monitoring was conducted from early 1998 to 1999, a period of time S-metolachlor was starting to replace racemic metolachlor. The data indicate the ratios of S enantiomer of metolachlor was increasing relative to the R enantiomer in surface water. The authors attribute this observation to the replacement of racemic metolachlor with S-metolachlor.

Müller, M. D. and H. R. Buser (1995). "Environmental behavior of acetamide pesticide stereoisomers. 2. Stereo- and enantioselective degradation in sewage sludge and soil." Environ. Sci. Technol. 29(8): 2031-2037

The authors concluded metolachlor has low to moderate enantioselective degradation in anaerobic sewage sludge and aerobic soil.

DATA EVALUATION RECORD

I. Study Type: Batch Equilibrium

II. Citation:

Burkhard,N.1978. Adsorption and Desorption of Metolachlor (Dual) in Various Soil Types. Submitted by Ciba-Geigy Limited. Performed by Biochemistry, Department R&D Plant Protection, Agrochemicals Division, Ciba-Geigy Limited, Basil,Switzerland. MRID 00078291.

III. Reviewer:

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V. Conclusions:

The study provides ancillary data on metolachlor residue partitioning in mineral soils. Deficiencies in the study are: 1.) the ionic strength of equilibration solutions was not controlled; 2.) Non-specific residue analysis was presented and used for calculation of Freundlich adsorption coefficients, 4.) Raw data of equilibrium concentration (Ce) and soil sorption (X/M) were not presented; and 5.) Foreign soils were used in the study. Although the data submission lacks detailed descriptions of the residue specific analysis and raw data, the data indicate metolachlor has a low sorption affinity for soil.

Estimated Freundlich coefficients for metolachlor, based on liquid scintillation counting, were 10 (1/n=.85) for Vetros soil, 3.18 (1/n=.85) for Les Evouettes soil, 1.54 (1/n= 0.84) for Collombey soil, and 1.69 (1/n=0.85) for Lakeland soil. Reversible sorption of metolachlor is unlikely because the desorption coefficients for Les Evouettes silty loam are slightly higher than the adsorption coefficients

VI. Materials and Methods:

The study was conducted on slightly-acid to alkaline Swiss soils and a US soil (Table 1). Soil physical properties of test soils ranged pH 6.3 to 7.8, $CaCO_3$ 0 to 15%, OM% 1.2 to 5.6, and CEC 3.7 to 29.4 meq/100 g soil. Isotopic dilution of analytical grade metolachlor with radiolabeled metolachlor (SA= 20.8 μCi) was used to make standard metolachlor solutions. Ten to fifty grams of soil were mixed with 100 ml water containing radiolabeled metolachlor concentrations of 1, 2.5, 5.0, and 10 μg/ml. Solutions were mixed for 24 hours, filter extracted, and then analyzed using liquid scintillation and gas liquid chromatography Desorption studies were conducted on filtered soils from adsorption studies. Washed soil cakes were place into 100 ml of water and then mechanically shaken for 1 and 3 days at 20°C. After shaking, soil solutions were filter extracted and then analyzed by liquid scintillation. The extent of adsorption and desorption was determined by difference in concentrations from pre-equilibration and post-equilibration solutions. Freundlich (non-linear sorption model) coefficients were estimated using a linearized Freundlich equation where the y intercept = -log Kf and slope=1/n.

VII. Study Author's Comments:

The registrant stated the batch equilibrium data demonstrate "that metolachlor is not very strongly adsorbed to soil particles". Estimated Freundlich coefficients, based on liquid scintillation counting, were 10 (1/n=.85) for Vetros soil, 3.18 (1/n=.85) for Les Evouettes soil, 1.54 (1/n= 0.84) for Collombey soil, and 1.69 (1/n=0.85) for Lakeland soil (Table 2). Similar adsorption coefficients were reported for liquid gas chromatography analysis. (Reviewer Note: The data submission does not provide raw data to confirm residue specific Freundlich coefficients.) Desorption data for the Les Evouettes silty loam soil demonstrated that desorption occurred at slower rate than absorption (Fig 2). Also, reversible sorption of metolachlor is unlikely because the desorption coefficients are slightly higher than the adsorption coefficients.

VIII. Reviewer's Comments

1.) Equilibration were conducted in water rather than 0.01 M CaCl2 solution. As per Subdivision N guidelines, a 0.01 M $CaCl_2$ solution is required to control ionic strength of the equilibration solution. Schwarzenbach, et al., 1993 states that changes of typical levels of dissolved salts is not expected cause major changes in estimating the organic matter partitioning coefficients (K_{om}). Because the metolachlor exhibited low sorption affinity to the test soils, it is unlikely the use of 0.01 M $CaCl_2$ solution will alter study results and hence interpretation of metolachlor mobility.

2.) There was no detailed description of specific residue methods such as liquid gas chromatography (LGC) in the study submission. The lack of residue specific data limits the ability to confirm the presence of metolachlor in batch equilibrium studies.

3.) Foreign soils were used in the study. The registrant failed to cross-reference the foreign soils to comparable US soils.

DATA EVALUATION RECORD

I. Study Type: Batch Equilibrium

II. Citation:

Ellgehausen, H. 1995. Adsorption/Desorption of CGA 77102 in Various Soil Types. Submitted by Novartis Crop Protection AG,. Performed by Environmental Safety/ Ecochemistry, Basil,Switzerland. No MRID.

III. Reviewer:

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V. Conclusions:

The study provide supplemental data on the sorption of S-metolachlor to soil. The data are deemed as supplemental because foreign soils were not compared to U.S. soils.

Freundlich adsorption coefficients were 1.4 (1/n=0.90) for the Collombey loamy sand, 1.0 (1/n=.88) for the Speyer standard soil sand, 4.6 (1/n=0.97) for the Gartenacker silt loam, 11.5(1/n=1.00) for Vetroz silt loam, and 44.8 (0.92) for the Illarsaz humic silt loam. Freundlich desorption coefficients were 2.0 (1/n=0.92) for the Collombey soil, 1.7 (1/n=0.94) for the Speyer standard soil, 8.2(1/n=1.04) for the Gartenacker soil, 15.2 (1/n=1.02) for Vetroz soil, and 55.8 (1/n=0.93) for the Illarsaz soil.

VI. Materials and Methods:

Five foreign soils were evaluated in the batch equilibrium study. Physicochemical properties and origins of the test soils are shown in Table 1.

Preliminary Study

A preliminary study was conducted to assess the time required for reaching steady-state (equilibrium) conditions. Five grams of each test soil was placed into a centrifuge tube, suspended in 25 ml of 0.01 M CaCl2, and pre-equilibrated for approximately 2 days (weekend) at room temperature. After pre-equilibration, each soil slurry was centrifuged and supernatant

removed. The wet soil pellets were further suspended in 25 or 100 ml of stock solution containing 2 ug/ml of radiolabeled metolachlor and then shaken (equilibrated) for 0, 1, 2, 4,6, 8, and 24 hours. Soil solution ratios ranged from 5 to 20. After each equilibrium period, duplicate 100 µL aliqout samples for each soil were removed for chemical analysis using LSC. At the termination of the study, radiolabeled residues in the 24 hour sample were determined using HPLC.

Definitive Adsorption/Desorption Study

In the definitive study, ten grams of each soil was placed into each of twelve 150ml centrifuge tubes, suspended in pesticide free aqueous phase (assume 0.01M CaCl2) , and equilibrated for 24 hours. After the 24 hour pre-incubation, the supernatant was removed from each test system and then radiolabeled metolachlor stock solution plus 0.01M CaCl2 were added to obtain a final metolachlor concentrations of ~ 0.1 to 2.0 ug/ml. Soil solution ratios ranged from 2 to 20 depending on the soil type (Table 2).

The soil test systems were shaken at ~200 rpm at 20^{0}C for 24 hours in the dark. After equilibration, the soil suspensions were centrifuged at 2500 rpm for 5 minute and aliquots for chemical analysis by LSC. The remaining supernatant was removed and the wet soil pellet was weighed. Pesticide free 0.01M $CaCl_2$ was added to each soil pellet at volumes equal to those used in the adsorption experiment. After addition of the 0.01M $CaCl_2$ solution, the soil test systems were shaken for 24 hours at 20^{0}C in the dark. After the first desorption equilibration, the test systems were centrifuged and 2 aliquots of clear supernatant (1 ml) were taken for chemical analysis by LSC. The desorption process was sequentially repeated using a similar process.

After the desorption experiment, the radioactivity in each soil pellet was determined using combustion-LSC. Additionally, radioactivity adsorbed on the centrifuge walls was extracted using an acetone wash. The radioactivity in the acetone rinsate was determined by LSC.

After the adsorption step, soils in samples 1 and 2 were removed and extracted 3X with acetone/water. The radioactivity in the soil extracts was determined by LSC and thereafter combined for chemical analysis. Non-extractable radioactivity (remaining after a acetone/water extraction) in soil was determined by combustion-LSC.

The combined soil extracts were concentrated at 350C using vacuum rotary evaporator. The concentrated soil extracts were analyzed using HPLC. The HPLC system was equipped with a C18 column with a gradient solvent system of water/ acetone; UV/VIS and radioactive detectors were used for detection of residues.

Freundlich (non-linear sorption model) coefficients were estimated using a linearized Freundlich equation where the y intercept = -log Kf and slope = 1/n.

VII. Study Author's Comments:

Steady-state ("equilibrium") conditions were reached within 24 hours of equilibration (Figure 1). The percent adsorption, at a concentration of 2 ug/ml, ranged from 11.97% for Speyer soil to 55.07% for the Illarsaz soil. Therefore, the study was conducted using a 24 hour equilibration time.

Freundlich adsorption coefficients were 1.4 (1/n=0.90) for the Collombey loamy sand, 1.0 (1/n=.88) for the Speyer standard soil sand, 4.6 (1/n=0.97) for the Gartenacker silt loam, 11.5(1/n=1.00) for Vetroz silt loam, and 44.8 (0.92) for the Illarsaz humic silt loam. Freundlich desorption coefficients were 2.0 (1/n=0.92) for the Collombey soil, 1.7 (1/n=0.94) for the Speyer standard soil, 8.2(1/n=1.04) for the Gartenacker soil, 15.2 (1/n=1.02) for Vetroz soil, and 55.8 (1/n=0.93) for the Illarsaz soil.

VIII. Reviewer's Comments

1.) Foreign soils were used in the study. The registrant failed to cross-reference the foreign soils to comparable US soils.