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

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

May 23, 2002

MEMORANDUM

SUBJECT: Metolachlor (PC Code 108801) and S-Metolachlor (PC Code 108800): HED's Response to Comments Submitted During 30-Day Registrant Comment Period. DP Barcode D282607.

FROM: Christina Jarvis, Risk Assessor
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THROUGH: Alan Nielsen, Branch Senior Scientist
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TO: Anne Overstreet, Chemical Review Manager
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INTRODUCTION:

The Health Effects Division (HED) acknowledges the comments received from Syngenta Crop Protection during the 30-day registrant comment period for metolachlor (Greg Watson memo, 04/29/2002). Syngenta was the only registrant who submitted comments on the preliminary tolerance reassessment eligibility decision document for metolachlor and s-metolachlor. Attached are HED's responses to the comments submitted by Syngenta. For clarity purposes, the comments have been grouped according to the specific discipline to which they refer (i.e., residue chemistry, dietary exposure, risk assessment, toxicology). HED's responses to the toxicology comments raised by Syngenta are attached to the back of this document.

Where applicable, Syngenta's comments have been incorporated into HED's revised disciplinary chapters. Spelling errors, typographical errors, and/or other minor editorial comments made by Syngenta are not specifically addressed in this response-to-comments document, but have been considered in the revised disciplinary chapters. The Agency also notes that Syngenta has stated their intention to generate and submit new data, as well as label amendments, for various crops outlined in the TRED. While these comments have not been specifically addressed in this response-to-comments document, any incoming studies and/or label amendments will be reviewed once they have been properly submitted to the Agency.

Input has been provided by Virginia Dobozy (toxicology), Rich Griffin (residential exposure), Sherrie Kinard (residue chemistry and dietary exposure), Ken Dockter (product chemistry), and Christina Jarvis (risk assessment and characterization).

I. PRODUCT CHEMISTRY

1. Syngenta's Comment:

The TRED did not review a previously submitted one year storage stability study (MRID 44183001, 1996) completed in commercial packaging. Syngenta will also be submitting a CGA-77102 spectra report to respond to the request for additional UV spectra data for s-metolachlor.

HED's Response:

MRID 44183001 (1996) has been reviewed by the Agency. HED's Product Chemistry chapter (D274330, 2/6/02) is revised by K. Dockter memos dated 4/19/02 (D281758) and 5/23/02 (D283040). The conclusions stated in these memos are as follows:

- UV/Visible absorption data are given. GLN 830.7050 is now satisfied.
- One percent of the technical (s-metolachlor) was lost when stored in simulated commercial packaging for one year. GLN 830.6317 is now satisfied.

II. RESIDUE CHEMISTRY:

1. Syngenta's Comment:

Syngenta requests the inclusion of all pending tolerances sponsored by Syngenta and IR-4, including sunflower and sugar beets (Syngenta) and asparagus, carrots, Swiss chard, grass grown for seed, all peppers, horseradish, and rhubarb (IR-4). Syngenta also requests clarification on the intention of the Agency to establish permanent tolerances for tomatoes, spinach, and grass forage and hay.

HED's Response:

The Agency has previously agreed to include sunflower, sugar beets, tomatoes, spinach, and grass grown for seed in the tolerance reassessment. The residue chemistry data for sunflower and sugar beets are currently under review, and a decision on permanent tolerances for these commodities cannot be made until an occupational assessment has been conducted. Residue chemistry data support permanent tolerances for tomatoes, spinach, and grass grown for seed. However, a permanent tolerance may not be granted until a full occupational assessment has been conducted. Since this is a tolerance reassessment document and not a reregistration eligibility decision document, an occupational assessment will not be done as part of this document. Asparagus, carrots, Swiss chard, all peppers, horseradish, and rhubarb are pending tolerances that will be reviewed by the Agency's Registration Division at a future date and will not be included in the tolerance reassessment eligibility decision document.

2. Syngenta's Comment:

Syngenta requests a tolerance for s-metolachlor for the Subgroup 1C, Tuberous and Corm Vegetables, based on the fact that the representative crop for this subgroup is potato and the TRED process has confirmed the potato tolerance meets the requirements of FQPA.

HED's Response:

Residue chemistry data support a crop group tolerance for Subgroup 1C, Tuberous and Corm Vegetables; however, a crop group tolerance may not be granted until a full occupational assessment has been conducted. Since this is a tolerance reassessment document and not a reregistration eligibility decision document, an occupational assessment will not be done as part of this document.

3. Syngenta's Comment:

Syngenta notes that s-metolachlor is applied at an application rate that is ~35% less than that historically used for metolachlor, and that many times throughout the TRED document the EPA confuses this application rate reduction (i.e., the application rate reduction of s-metolachlor is attributed to metolachlor).

HED's Response:

HED will clarify that s-metolachlor is applied at an application rate approximately 35% less than that used for metolachlor, or state that the s-metolachlor application rate is approximately 63% of the metolachlor application rate.

4. Syngenta's Comment:

Syngenta requests that the Agency lower the metolachlor tolerances to levels that can serve as a

compliance tool (i.e., at those levels appropriate for s-metolachlor) to prevent misuse of the currently registered end-use products that contain metolachlor.

HED's Response:

Available data do not support lowering most metolachlor tolerances at this time. The tolerances for metolachlor are set based on the maximum application rates listed on the labels.

5. Syngenta's Comment:

Syngenta believes that the creation of a subsection within the same 40 CFR citation for metolachlor and s-metolachlor will create confusion within the regulatory enforcement and production communities, especially in many instances where there is a difference in the crops allowed for s-metolachlor use and metolachlor use. Given the potential for confusion and the further development of s-metolachlor into several minor crops, Syngenta urges the Agency to create a separate section in the 40 CFR to support the use of s-metolachlor.

HED's Response:

The Agency does not feel it is necessary to further separate the metolachlor/s-metolachlor tolerances at this time. Tolerances for metolachlor and s-metolachlor will be divided into sub-sections of 40 CFR as described in the residue chemistry chapter (tolerances for metolachlor will be listed under §180.368(a)(1) through (d)(1), and tolerances for *S*-metolachlor will be listed under §180.368(a)(2) through (d)(2)).

6. Syngenta's Comment:

Data and a tolerance for corn, sorghum, and soybean aspirated grain fractions should not be required for s-metolachlor because the applications are made prior to fruiting or flowering or pre-emergence only. In addition, no detectable residues of s-metolachlor (or metolachlor) are present in field corn grain at exaggerated use rates, so it is highly unlikely that residues would occur in grain dust.

HED's Response:

Waiver requests for corn, sorghum, and soybean aspirated grain fractions will be reviewed by the Agency, should Syngenta wish to submit them.

7. Syngenta's Comment:

A March 22, 2002 Federal Register notice cancelled the existing tolerances for metolachlor for stone fruits and almonds; all uses for these crops should be removed from the TRED and all

metolachlor and s-metolachlor labeling where a tolerance is needed to support this use.

HED's Response:

HED will remove stone fruits from the dietary risk assessment and remove references to stone fruits from the disciplinary chapters; however, there is a crop group tolerance that exists for tree nuts. Almonds are part of the tree nut crop group and therefore will remain in the assessment.

8. Syngenta's Comment:

Sunflower and sugar beet residue data were generated with s-metolachlor; therefore, this data cannot be translated to support tolerances for metolachlor.

HED's Response:

HED agrees that sugar beets and sunflower tolerances are for s-metolachlor only.

III. DIETARY EXPOSURE ASSESSMENT

1. Syngenta's Comment:

Syngenta has conducted refined acute and chronic dietary risk assessments using field trial residues, market basket residues, percent crop treated data, processing data, and secondary residues calculated from livestock diets and metabolism studies. Syngenta's refined assessments resulted in a more realistic exposure evaluation than the Agency's tolerance-based estimate.

HED's Response:

HED's acute and chronic dietary risk estimates are well below the Agency's level of concern (<100% aPAD/cPAD). A more refined dietary risk assessment is not warranted at this time.

2. Syngenta's Comment:

Alfalfa and radishes (both crops grown for seed) are not included in the Agency's s-metolachlor assessment.

HED's Response:

The Agency notes that alfalfa and radishes (when grown for seed) are not considered to be food/feed items and do not have tolerances. Therefore, they were not included in the dietary assessment.

IV. NON-DIETARY EXPOSURE ASSESSMENT

1. Syngenta's Comment:

Syngenta has cancelled all metolachlor turf end-use products; no other registrant has received a registration for an end-use product containing metolachlor for use on turf.

HED's Response:

A search of REFS on 5/9/2002 shows that EPA Reg. No. 100-691, an emulsifiable concentrate formulation containing metolachlor as the active ingredient and labeled for use on turf, has been cancelled. EPA Reg. No. 100-950, an emulsifiable concentrate formulation containing s-metolachlor as the active ingredient and labeled for use on turf, is still active. Since the post-application risk estimates for metolachlor presented in the residential exposure assessment were not of concern (i.e., MOEs >100), and since there is still an active s-metolachlor registration with a turf use, the residential risk assessment will not be revised any further at this time. However, the revised TRED document will note the cancellation of EPA Reg. No. 100-691, and that use will not be included in the revised aggregate risk estimates.

V. TOXICOLOGY

Review and Response

Many of Syngenta's comments are repeated multiple places in the April 29, 2002 document. This review has divided their comments into General Issues and Editorial Comments. The comments (in italics) will be discussed and responded to only once. The citation (page, paragraph) included for the editorial comments is the first time the comment appears in the document. If additional information on an issue is provided later in the document, it will appear and be addressed with the first comment.

General Issues

1) Metabolism Issues

There are essentially two metabolism issues: 1) whether the metabolism of metolachlor and s-metolachlor are comparable; and 2) whether the water metabolites ESA and OA should be included in the risk assessment.

Issue 1

The August 14, 2001 MARC concluded that there are some deficiencies in the metabolism databases for metolachlor and s-metolachlor that prohibit a definitive conclusion about the comparable metabolism of the two chemicals. First, the study (MRID 44491402) in which there were side-by-side metabolic assays was conducted with only a single oral dose (0.5 mg/kg). Therefore, there are no data on high dose or repeated low-dose metabolism under the same study conditions. Second, a metabolic pathway was proposed for metolachlor (MRID 43164201) but not s-metolachlor. Third, most of the metabolites of both metolachlor and s-metolachlor have not been identified.

Based on the available data, the MARC made several observations about the comparable metabolism of metolachlor and s-metolachlor. Both are extensively absorbed and metabolized following oral administration. Elimination is via the urine and feces. There are some minor sex differences in the elimination patterns. In two metolachlor studies (MRIDs 40114401 and 43164201), at the single and low repeated doses of 1.5 mg/kg, females excreted more radio labeled chemical in the urine than in the feces, whereas males excreted more in the feces. The relative amounts of the administered dose in the urine and feces were similar at the single oral high dose (300 mg/kg). In a study with s-metolachlor (MRID 44491401), more radioactive chemical was excreted in the feces than urine for both males and females.

Tissue residues were highest in red blood cells for metolachlor (MRID 40114401); whole blood was highest for s-metolachlor (MRID 44491401). The MARC noted that maximum blood levels of s-metolachlor were reached at 24 hours and maintained throughout the end of the study (144 hours). Depletion was also delayed in other well-perfused organs, including the heart, lungs,

spleen, brain and bone. After 144 hours, 3-4% of the administered dose for both sexes at either 0.5 or 100 mg/kg was retained in all combined tissues (including whole blood). In the study with metolachlor, tissues of low- (1.5 mg/kg) and repeated low-dose rats contained approximately 2.5% of the ^{14}C dose at 7 days; approximately 3% and 4% were present in tissues of the high dose males and females, respectively. The MARC concluded that this was a high percentage of chemical to be retained and signified possible bioaccumulation.

Although the metabolic profiles of the two chemicals were qualitatively similar, there were quantitative differences. In MRID 44491402, both sexes administered the racemic mixture (metolachlor) eliminated more of several urinary metabolic fractions than did rats of any group treated with the s-enantiomer. There were also quantitative differences in fecal metabolites. The DER for this study notes that specific fecal fractions (e.g., F_{10}, F_{12}, F_{13}) were 3-7 fold higher in the case of the s-enantiomer compared to the racemic formulation when the relative amount of s-enantiomer (assuming 100% pure) only doubled relative to its 50% concentration in the racemic mixture.

The MARC concluded that, given the lack of certain data, such as proposed metabolic pathway for s-metolachlor and identification of metabolites for both chemicals, and uncertainties about findings in some studies, such as quantitative differences in metabolites, it was not possible to determine if the metabolism of the racemic mixture and s-metolachlor are comparable.

Syngenta suggests that the available general metabolism data allow EPA to conclude that the metabolism of metolachlor and s-metolachlor are similar. Qualitative differences are the goal of comparative metabolism studies; to attempt to utilize the data to make quantitative comparisons steps outside the goals of the study. Any time a comparison is made between a racemic mixture versus one antipode of the mixture, significant differences in reaction rates are expected when optically active enzymes are involved. A review of the literature on the metabolism of racemic and chiral xenobiotics demonstrates that it is common for reaction rates in metabolism to proceed at differential rates, while the metabolite profile remains equivalent. The registrant argues that the metabolism study (MRID 43164201) showed the metabolite patterns to be very similar between sexes, dose levels (1.5 and 300 mg/kg) and route of administration. This study reported the identification of 26 new rat metabolites of metolachlor. When added to the 13 previously reported structures, the disposition of metolachlor in the rat is well understood as documented by a comprehensive metabolic pathway.

In a comparative study (MRID44491402) with ^{14}C-S-Metolachlor and ^{14}C-Metolachlor, excreta samples from rats dosed at 0.5 mg/kg showed identical metabolite patterns for the two chemicals. In addition, samples from another study (MRID 44491401) were also examined. These samples represented dose groups B1 (0.5 mg/kg), U1 (0.5 mg/kg with pretreatment), D1 (100 mg/kg), G1 (0.5 mg/kg bile cannulated) and G2 (100 mg/kg bile cannulated). The metabolite patterns in excreta were identical for rats administered s-metolachlor irrespective of sex and dose level. However, small quantitative differences were apparent in some metabolite fractions.

As the disposition and metabolite pattern in urine and feces were the same for metolachlor and s-metolachlor, it is concluded that, apart from stereochemical aspects, the metabolite pathways in the rat are identical for the chemicals. A metabolic pathway is included in the response.

HED Response: HED acknowledges Syngenta's position on the comparable metabolism of metolachlor and s-metolachlor. However, since there is extremely low risk posed by metolachlor/s-metolachlor, further reconsideration/review of this issue is not warranted at this time.

Issue 2

The MARC concluded that the water metabolites CGA 354743 and CGA 51202 were less toxic orally than the parents due to reduced absorption of at least one of the metabolites, CGA 354743 (ESA). Only 17% of CGA 354743 was absorbed after oral administration in a metabolism study (MRIDs 44931716 and 44931717), whereas absorption was 69.8-93.2% for metolachlor (MRID 43164201) and 85% for s-metolachlor (MRID 44491401). The MARC determined that CGA 354743 and CGA 51202 should be included in the water risk assessment since they were found in greater abundance than the parent in water monitoring studies. In addition, the parent metolachlor has been classified as a Group C carcinogen. Without long-term studies in rats and mice with the metabolites, there are no data to substantiate that the metabolites are not carcinogenic. Potential long-term toxicity concerns are raised by the aniline moiety still being present in the metabolites.

The registrant argues that there is an extensive database on ESA and OA metabolites of s-metolachlor which demonstrates that they do not have the same level of toxicity as the parent. A bile cannulation study with ESA showed that this compound is not absorbed and therefore is of no relevance in the risk assessment; no variance in amount or length of exposure will alter this fact. The MARC recommendation on the approach to the risk assessment appears to be based on the levels of ESA and OA found or predicted to be in water. This decision appears to be in direct conflict with the Toxicology Chapter which states that "no toxicity was observed with these metabolites even at the limit dose (e.g., ≥1000 mg/kg)." The registrant acknowledges that when no data are available on the toxicity of metabolites, the EPA default assumption is one of toxicity equivalency to parent. However, given the available data, the registrant urges EPA to remove ESA and OA from the s-metolachlor risk assessment and generate a separate risk assessment for these metabolites utilizing the available, appropriate endpoints. At a minimum,

- *acute and intermediate endpoints utilized in the TRED should be different for ESA and OA since these data are available and have been deemed acceptable by EPA;*

- *chronic exposure should be adapted by a scaling factor to account for the differential toxicity demonstrated between s-metolachlor and ESA and OA metabolites;*

- *2nd tier assessments should be performed if needed to refine the assessments and more realistically assess the risk associated with the degradates.*

The registrant fears that the Office of Water and individual states may utilize the risk assessment for the parent to establish regulatory enforcement levels that are not appropriate for these metabolites.

Concerning the issue of dealkylation, the registrant states that the 1994 metabolism study with metolachlor showed that only two of the 36 metabolites identified were mono-dealkylated. Metolachlor is very resistant to dealkylation and since the available metabolism and toxicology data demonstrate a comparable profile and chiral orientation should not affect propensity for dealkyation, the same resistance is true for s-metolachlor. Further, both ESA and OA contain both alkyl side chains that are important in the resistance of dealkyation; therefore, like metolachlor and s-metolachlor, they would be resistant to dealkyation in mammalian systems.

Syngenta does not agree with EPA's conclusion that, since toxicity was not demonstrated with ESA and OA, the degree of difference in toxicity between parent(s) and degradates can not be established. Some assessment can be made based on the NOAELs established for the degradates (≥1000 mg/kg/day) and the parent compounds (approximately 24 mg/kg/day) in the subchronic toxicity studies in rats and the fact that the LOAEL for parent (≈240 mg/kg/day) is a NOAEL for the degradates.

HED Response: HED acknowledges Syngenta's concern over the inclusion of the ESA/OA metabolites in the risk assessment. However, since there is extremely low risk posed by metolachlor/s-metolachlor, further reconsideration/review of this issue is not warranted at this time.

2) Inhalation Study Issue

A 28-day inhalation study is required for s-metolachlor based on concern for toxicity by the inhalation route following applications on multiple days in a commercial setting.

Syngenta contends that route-to-route extrapolation from oral toxicity studies provides an appropriate basis for assessing risk associated with s-metolachlor and therefore, a 28-day inhalation study is not needed. There is no indication in any of the available toxicity studies of increased susceptibility of the lung to toxicity or accumulation of s-metolachlor. Metabolism and kinetics studies indicate that assessment of toxicity after oral exposure represents a good surrogate for inhalation exposure since a high percentage (at least 85%) of the administered dose is absorbed after oral exposure. Exposure via inhalation to dose levels equivalent to oral exposure is unlikely to result in higher systemic exposure. Furthermore, the potential for exposure during normal use practices to s-metolachlor in a form that would be inhalable or respirable is low. S-metolachlor is applied only in outdoor settings and the vapor pressure is relatively low. The registrant intends to submit a formal request for a waiver for the 28-day inhalation study. The registrant further argues that data gaps identified for s-metolachlor must also be applied to the metolachlor registration held by other registrants.

HED Response: When the HIARC determined that a 28-day inhalation study was required for s-metolachlor, it was with the understanding that metolachlor would no longer be marketed. Since

that meeting, a metolachlor registration has been granted to at least one other company. The tolerance reassessment requirements under FQPA for s-metolachlor should also be applied to metolachlor.

3) Acute Toxicity Studies

The acute toxicity studies included in Table 2 of the Toxicology Chapter were extracted from the April 1995 RED for metolachlor.

Syngenta states that the company submitted a newer battery of acute toxicity studies in 1994 and these should be included. The MRID numbers are 43492001 through 43492006.

HED Response: These studies are presently under review.

4) Clinical Sign in Prenatal Developmental Toxicity Study in the Rat with S-Metolachlor (MRID 43928925)

In the DER for this study, it states that the observation of pushing head through bedding for about one hour following dosing may be an indication of neurotoxicity.

Syngenta requests that EPA provide them with some literature citation or other evidence which might support this interpretation. The observation was made immediately following dosing and lasted only about 1 hour. Based on the laboratory's experience, this kind of behavior is seen as a response either to the taste of residual dosing solution that might be on the gavage needle, to salivation or to some local gastric irritation. At a minimum, Syngenta requests that EPA acknowledge this alternative interpretation as a possibility.

HED Response: DERs are prepared for individual studies by reviewers who are often not acquainted with the complete database on a chemical. When the HIARC considers all the toxicology studies, a weight-of-the-evidence evaluation is made of the neurotoxicity potential of a chemical, as required by FQPA. The HIARC was not concerned about the neurotoxicity of metolachlor/s-metolachlor, as evidenced by not requiring neurotoxicity studies.

5) Response to Specific Questions on MRID 4491402 (Metabolism Study with S-metolachlor)

The DER included five questions/comments, which are provided below with Syngenta's response in italics.

a) Specify the stereo isomeric purity of CGA-24705 and CGA-77102.

CGA-24705 is a racemate, therefore the enantiomer ratio is 1:1. CGA-77102 is the S-enantiomer. The enantiomer ratio (S:R) is >999:1 for the [Phenyl-U-^{14}C]-CGA-77102 and ca. 8:2 for the nonradiolabeled CGA-77102, respectively.

b) As discussed above (II-A), it is not clear why, following several months of storage, some of the urine specimens but not others seem to yield variable metabolite profiles that

are suggestive of decomposition. Therefore, this reviewer questions the validity of the CGA-24705 and CGA-77102 metabolite profile results even though the author of the study report discounted any effects due to the length and conditions of the specimen's storage. The Registrant needs to reassess the adequacy of the storage conditions and comment on the validity of the metabolite profile results in light of the storage-related variability.

Animal 95436 was dosed at 100 mg/kg with unlabeled CGA-77102 for 14 days followed by a single pulse of phenyl U[14]C-CGA-77102. The pretreatment may have induced higher enzyme levels in this animal, which could account for the higher conversion of polar conjugates Fr2 and Fr4 to corresponding aglycones Fr17 and Fr18 during storage. However, there is degradation during storage in several animal groups but qualitatively the patterns are the same. Therefore, it is a quantitative and not a qualitative change (no new metabolites) and it is concluded that the study is not compromised by the length and conditions of storage.

c) Explain why some metabolite fractions (e.g., F10, F12, and F13) were 3 - 7 fold higher in the case of the S-enantiomer (CGA-77102) compared to the racemic formulation (CGA-24705) when the relative amount of the S-enantiomer (assuming 100% pure) was, at the most, twice its concentration in the racemate mixture. On the other hand, some urinary metabolite fractions (e.g., U1, U2, and U3) were nearly 2 - 4 fold higher following administration of CGA-24705 than CGA-77102. Does this mean that these urinary metabolites are preferentially generated from the R-enantiomer and how is this observation related to the stereo isomeric composition of the two Metolachlor preparations?

Syngenta thinks that the general metabolism data allow EPA to conclude that the metabolism of metolachlor and s-metolachlor are similar. The goal of the comparative metabolism studies was to demonstrate qualitative differences; to attempt to utilize the data for quantitative comparisons steps outside the goals of the study. The groups which should be compared are B1 and B2 where metolachlor and s-metolachlor were administered orally at 0.5 mg/kg.

Any time a comparison is made between a racemic mixture versus one antipode of the mixture, significant differences in reaction rates are expected when optically active enzymes are involved. A review of the literature on the metabolism of racemic and chiral xenobiotics demonstrates that it is common for reaction rates in metabolism to proceed at differential rates, while the metabolite profile remains equivalent.

When evaluating these reactions, both the stereo isomer ratio (i.e., 80:20 for CGA-77102 and 50:50 for CGA-24705) and the reaction rate should be considered. Certain reaction rates can be 100 times faster with the R isomer and vice versa with the S isomer. Therefore, one cannot predict product ratios based solely on the starting isomer present at dosing.

The fractions mentioned in the EPA review are minor, with other fractions making up the majority of the residue. Also, some variation is due to the limits of the method. In some cases, no distinct spots were detected, only areas of radioactivity. Reliable quantitation of such a complex pattern where all spots are not separated at baseline is difficult and prone to variation. In summary, Syngenta thinks that the general metabolism of s-metolachlor and metolachlor are equivalent.

d) Explain why different dose levels (0.5 and 100 mg/kg) were selected for the pharmacokinetics (MRID 44491401) and metabolite pattern studies (MRID 44491402) of the S-enantiomer while higher doses (1.5 and 300 mg/kg) were used in the previous studies with the racemate mixture (CGA-24705).

In the original chronic rat studies with metolachlor, the high dose level was 3000 ppm which equates to 300 mg/kg in young animals. Some body weight effects were seen at this dose. Therefore, the high dose for the rat metabolism study was set at 300 mg/kg. The low dose was 1.5 mg/kg, the no effect level. In the new metabolism studies with s-metolachlor, the high dose was 100 mg/kg and the low dose was 0.5 mg/kg. The 100 mg/kg dose was based on EPA guidance to Ciba Geigy in the early 1990's.

e) The scientist(s) within HED who are responsible for performing the risk assessment on S-Metolachlor might need to follow up on the issue raised by T. McMahon (HED document no. 010990 dated May 23, 1994) regarding the formation of methylethylaniline and its possible contribution to the carcinogenicity of Metolachlor. The Registrant might have to comment on the possible formation and the level of methylethylaniline from S-Metolachlor (CGA-77102) in comparison to that from R/S-Metolachlor (CGA-24705).

In vivo rat metabolism studies have shown metolachlor to be very resistant to N-dealkylation. Even though s-metolachlor may undergo certain stereospecific metabolic transformations more rapidly than metolachlor, the resistance to undergo N-dealkylation or resistance to form methylaniline will not change. Independent of stereochemistry, the absence of animal formation, minimal reactivity at the chiral center and steric hindrance prevent dealkylation of metolachlor.

HED Response: Syngenta should submit these responses separately to upgrade the study classification. The study conduct and results, in light of the above information provided by the registrant, need a reevaluation, which is beyond the scope of the 30-day comment period.

Editorial Comments - Toxicology Chapter

Citation in Document	Syngenta's Comment	HED's Response
Page 3, Section 1.0, 3rd paragraph, 3rd sentence	The words "in female rats" should be deleted since the sentence reflects a discussion of the mouse carcinogenicity study	The revision has been made.
Page 4, 2nd paragraph, 2nd sentence (refers to MRID 43928923)	The mg/kg/day dose levels should be modified to reflect the ppm dose level equivalents based on the correction for analytically determined test item concentration in the diet.	The respective mg/kg/day dose levels should have been 1.9, 18.5, 187.9 and 624.7 for males and 2.3, 24.0, 237.8 and 763.9 for females. However, since this study was not used for endpoint selection, there are no effects on the risk assessment.
Page 10, Data Table for Metolachlor	The comment concerns whether Guideline 870.3150 has been satisfied for metolachlor.	MRID 00032174 should be acceptable/guideline in the table under 9.1.2 of the Appendix.
Page 12, 90-day oral toxicity study in the rat with s-metolachlor (MRID 43928923), 2nd paragraph	There is a suggestion that sentence be added to beginning of paragraph stating that there were no treatment-related deaths or clinical signs.	This revision is unnecessary. If not stated, it is assumed that there was no effect on these parameters.
Page 14, 90day oral toxicity study in the dog with s-metolachlor (MRID 43928922)	The study summary indicates that the study is acceptable but does not meet study guideline requirements and a new study must be conducted. However, the study is not identified as a data gap.	The study was classified as acceptable/nonguideline. There were dosing irregularities and lack of toxicity. As this study was not identified as a data gap by the HIARC, a new study is not required.
Page 15, Prenatal Developmental Toxicity Study in the rat with metolachlor (MRID 00151941), 2nd paragraph	The four treatment-related deaths occurred on GD 12, 13 and 15, not on GD 7, 8 and 10.	The deaths occurred on GD 12, 13 and 15. Although this study was used for risk assessment (acute reference dose), the endpoint was clinical signs, which were observed one day after treatment (HIARC report dated October 3, 2001).
Page 16, Prenatal Developmental Toxicity Study in the rat with metolachlor (MRID 43928925), 2nd paragraph	Sentence should state "...increase in clinical signs seen in all 500 and 1000 mg/kg/day animals...". The word "in" should replace the word "as".	This revision has been made.
Page 17, Prenatal Developmental Toxicity Study in the rabbit with s-metolachlor (MRID 43928924), 1st paragraph	The word receiving appearing after NJ should start with a lower case 'r' rather than a capital 'R'.	This revision has been made.

Page 17, Prenatal Developmental Toxicity Study in the rabbit with s-metolachlor (MRID 43928924), 2nd paragraph	There are several incomplete sentences in this paragraph.	The paragraph has been corrected.
Page 18, Reproduction and Fertility Effects in the rat (MRID 0080897), 1st paragraph	The batch number (FL-800362) and the purity (95.4%) of the chemical should be included.	At the time the Executive Summary was prepared, batch numbers were not routinely included.
Page 18, Reproduction and Fertility Effects in the rat with metolachlor (MRID 0080897), 3rd paragraph, 2nd sentence	The dose level (1000 ppm) at which body weight effects are being described should be included for clarity.	This revision has been made.
Page 19, Chronic Toxicity in the dog (MRID 40980701), 1st paragraph	The batch (FL-861768) and purity (97%) of the test material should be included.	At the time the Executive Summary was prepared, batch numbers were not routinely included.
Page 20, Combined Chronic Toxicity/Carcinogenicity Study in rats with metolachlor (MRID 00129377), 1st paragraph	The batch (FL-800362) and purity (95.3%) of the test material should be included.	At the time the Executive Summary was prepared, batch numbers were not routinely included.
Page 21, Carcinogenicity Study in mice with metolachlor (MRID 00117597)	The batch (FL-791174) and purity (95%) of the test material should be included.	At the time the Executive Summary was prepared, batch numbers were not routinely included.
Page 22, DNA damage/repair (MRID 00142828)	The dose levels should be 0.25, 1.25, 6.25 and 31.25 nl/ml.	This revision has been made.
Page 24, Section 4.8 Neurotoxicity, last sentence	The sentence should clarify that the convulsions were observed in the prenatal developmental toxicity study in rats with metolachlor.	This revision has been made.
Page 34, Section 7.2 Subchronic Toxicity, 2nd sentence	It should clarify that the 5000 ppm of s-metolachlor is discussed.	This revision has been made.
Page 35, 90-day Oral Toxicity in the rat with CGA 354743 (MRID 44931710), 1st paragraph	The mg/kg/day dose levels should be replaced with the mg/kg/day equivalents based on the correction for analytically determined test item concentration in the diet.	The respective mg/kg/day doses for CGA-354743 should have been 26.6, 90.6, 461 and 1638 for males and 30.1, 103, 560 and 1786 for females. The mg/kg/day dose for CGA 77102 should have been 454 for males and 597 for females. However, since this study was not used for endpoint selection, there are no effects on the risk assessment.
Page 35, 90-day Oral Toxicity in the rat with CGA 354743 (MRID 44931710), 4th paragraph	After the first mg/kg/day dose equivalent for the 20,000 ppm concentration, it should be specified that this is for males.	This revision has been made.
Page 44, Section 8.0 References	The acute toxicity studies for metolachlor conducted in 1994 should be included.	The studies are under review.
Page 45, MRID 00129377	The author name "Tisdelm" should be "Tisdel".	This revision has been made.

Page 54, Section 9.1 Toxicity Profile Summary Tables, carcinogenicity study in mice	A comment should be added following the dose levels to indicate that the mg/kg/day equivalents are based on 1 ppm in food equal to 0.150 mg/kg/day. Also, the NOAEL for this study should be 1000 ppm, not 100 ppm.	This revision has been made.