

201-14949A

HIGH PRODUCTION VOLUME (HPV) CHALLENGE PROGRAM

TEST PLAN FOR  
ACETAMIDE, 2-CHLORO-N-(CHLOROMETHYL)-N-(2,6-DIETHYLPHENYL)-  
(CMA)  
(CAS NO.: 40164-69-0)

PREPARED BY:  
Monsanto Company

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## **OVERVIEW**

Monsanto Company hereby submits for review and public comment the test plan for 2-chloro-N-(chloromethyl)-N-(2,6-diethylphenyl)acetamide (CMA) (CAS No. 40164-69-0) included by the High Production Volume (HPV) Challenge Program in conjunction with the United States Environmental Protection Agency (US EPA) and the chemical industry.

Monsanto Company is a major producer of agricultural pesticides regulated and registered in the United States by the US EPA in accordance with provisions of the Federal Insecticide Fungicide and Rodenticide Act (FIFRA). Other countries also have similar regulations and an evaluation process in effect that must be completed before any pesticide product may be approved for a specific application.

CMA is only made as a process intermediate for the production of the final chemical product that is used as a pesticidal active ingredient. Alachlor, one of the active ingredients in a class of herbicide products related to acetanilide chemistry, is one of the final products that can be produced from CMA. In the final step of the manufacturing process of the alachlor technical material, for example, CMA can be converted to alachlor by a simple reaction with methanol. Products containing alachlor as the active ingredient, in accordance with provisions of FIFRA for the United States and similar laws in other countries, are thoroughly studied and characterized in risk assessment evaluations addressing toxicological endpoints identified by the SIDS endpoints.

In conjunction with existing data for CMA, together with the existing data available for the acetanilide herbicide alachlor (a structural analog), it is felt that in total, this data is adequate to address the goals and objectives of the HPV Challenge Program without the need to conduct any new or additional testing.

## **JUSTIFICATION FOR THE USE OF SURROGATE AND ADDITIONAL DATA WITH ALACHLOR**

HPV Challenge participants were directed in a letter from the US EPA dated October 14, 1999 to maximize the use of existing data together with the existing data of scientifically appropriate related chemicals in order to minimize additional animal testing. Structure-activity relationships, or SAR, could be used to reduce testing in at least three different ways. Among the suggested possibilities, SAR principles could be applied to a single chemical that is closely related to one or more better characterized chemicals ("analog").<sup>1</sup> Monsanto Company therefore intends to satisfy the goals of the HPV Challenge Program for CMA by providing existing data to address each SIDS endpoint where either adequate data already exists for CMA itself, or adequate existing data is provided by alachlor (an acceptable structural surrogate).

The chemical structures of CMA and alachlor [*2-chloro-N-(2,6-diethylphenyl)-N-methoxymethylacetamide*] are the same except that CMA has the chloromethyl moiety bonded to the acetanilide nitrogen and alachlor has a methoxymethyl group at that position. In other words, the chemical structures would be identical except that alachlor has CH<sub>3</sub>O- replacing and substituting for the labile Cl- of CMA. A simple reaction of CMA with methanol (CH<sub>3</sub>OH) will produce alachlor. (See the structure for CMA provided in the substance information section of the Robust Summaries, attached).

Alachlor and pesticide products containing alachlor as the active ingredient have been thoroughly studied and characterized in numerous environmental fate, toxicology and ecotoxicology studies. Herbicide products containing alachlor are registered in the United States by the US EPA for carefully selected applications after extensive evaluations so it is logical to incorporate the extensive information already available about the toxicology and ecotoxicology of alachlor as a well-characterized chemical "analog" for CMA because they are so closely related in chemical structure and because CMA is readily converted to alachlor.

## HPV Summary for CMA

The exclusive use of CMA as the final process intermediate in the manufacture of a pesticide active ingredient, minimizes its potential exposure to both workers and the environment. Worker exposure during manufacturing operations is monitored and has been shown to be easily minimized through engineering controls, or when necessary, through employment of personal protective equipment. The greatest potential for human exposure occurs during infrequent shipping operations between the single manufacturing location in the United States to another manufacturing facility located elsewhere. Monsanto Company believes that it can be concluded with reasonable certainty that the small potential for exposure to CMA during transport for the purpose of having it totally converted to another product in a controlled manufacturing facility will not result in harm to humans or the environment.

In total, these data are believed to be adequate to fulfill the requirements of the HPV Challenge Program without the need to conduct any new or additional tests.

**TEST PLAN SUMMARY**

2-Chloro-N-(chloromethyl)-N-(2,6-diethylphenyl)acetamide (CMA) CAS Registry Number: 40164-69-0	Data Available	Data Acceptable (Y/N)	Testing Required (Y/N)
<b>PHYSICAL/CHEMICAL PROPERTIES</b>			
Melting Point	38 – 39.5 C	Y	N
Boiling Point	~200 C, decomposes >~110 C	Y	N
Vapor Pressure	<3 mmHg @ 25 C	Y	N
Partition Coefficient*	Alachlor K <sub>ow</sub> : 1223	Y	N
Water Solubility	Unstable in water	Y	N
<b>ENVIRONMENTAL FATE</b>			
Photolysis*	Alachlor solution t <sub>1/2</sub> : 239 days	Y	N
Stability in Water (Hydrolysis)	Hydrolyzes rapidly	Y	N
Biodegradation*	Alachlor mean DT <sub>50</sub> : 17 days	Y	N
Transport between Environmental Compartments*	Alachlor Koc values indicate medium or moderate mobility in soils	Y	N
<b>ECOTOXICITY**</b>			
Acute Toxicity to Fish	Rainbow trout 96-hour LC <sub>50</sub> : 15 mg/L; slightly toxic	Y	N
	Bluegill sunfish 96-hour LC <sub>50</sub> : 13 mg/L; slightly toxic	Y	N
Acute Toxicity to Aquatic Invertebrates	<i>Daphnia magna</i> 48-hour EC <sub>50</sub> : 23 mg/L; slightly toxic	Y	N
Toxicity to Aquatic Plants*	Alachlor freshwater algae ( <i>Selenastrum</i> ) 96-hour EC <sub>50</sub> (cell density): 0.0029 mg/L; recovery observed after transfer to fresh media	Y	N
<b>MAMMALIAN TOXICITY**</b>			
Acute Toxicity	Oral, rat LD <sub>50</sub> : 1,650 mg/kg; slightly toxic	Y	N
	Dermal, rabbit LD <sub>50</sub> : 5,400 mg/kg; practically nontoxic	Y	N
	Eye irritation, rabbit: moderately irritating	Y	N
	Skin irritation, rabbit 4-hour exposure: severely irritating	Y	N
Repeated Dose Toxicity	Inhalation, 2-week rat: ≥0.007 mg/L resulted in clinical signs of toxicity	Y	N
Genetic Toxicity	Cell culture DNA repair assay: not genotoxic	Y	N
	Microbial and yeast assays: not mutagenic	Y	N
Reproductive/Developmental Toxicity	Oral, rat teratology: no effect at dose levels up to 300 mg/kg/day	Y	N

\* This endpoint is either completed or supported through the use of data with alachlor as a surrogate model compound, the active ingredient in herbicide products registered by the US EPA.

\*\* Toxicity classification is based on US EPA guidance.

## **SIDS DATA SUMMARY**

**General Information:** CMA is a substance used exclusively as a chemical intermediate to manufacture an active ingredient in common herbicide products based on the known acetanilide family of chemistry. The potential for any significant human exposure is primarily limited to a relatively small number of workers at a single manufacturing facility within the United States. Worker exposure is controlled, as needed, by engineering or through the use of personal protection equipment. Monitoring data of potential worker exposures has shown that most worker exposures have been below the limit of detection for the assay.

**Physical/Chemical Properties:** Data to assess the various physical/chemical properties (melting point, boiling point, vapor pressure, partition coefficient, and water solubility) of CMA were obtained from direct experimental measurements and company reports. CMA readily reacts with water, so water solubility and partition coefficient information with alachlor are provided for comparison purposes. Both CMA and alachlor have similar melting points and behave similarly by decomposing upon heating to temperatures higher than about 110 C. The thermal and storage stability of CMA is equal to or even better than alachlor, and combined with the observation that alachlor may tend to crystallize out of solution more readily than CMA under certain conditions, it is sometimes more feasible to ship CMA than alachlor to another manufacturing location.

**Environmental Fate:** Data to assess the environmental fate properties (photolysis, hydrolysis, biodegradation, and transport between environmental compartments) of CMA were obtained from direct experimental measurements and company reports. Primarily because CMA hydrolyzes rapidly in water and is used only as a chemical process intermediate, it will not be present in the natural environment as an intact chemical structure, and only chemical reaction or biodegradation products will be produced. In order to assess the characteristics in the environment of such products, study results for photodegradation, biodegradation, and soil adsorption/desorption are presented with <sup>14</sup>C-radiolabeled alachlor as the test material. Biodegradation of alachlor by microbial organisms is the main method of degradation in the environment with a half-life in most soils of about 2-3 weeks. Alachlor is adsorbed by soil colloids and has been classified to have medium or moderate mobility in soils. Photodegradation and volatilization of alachlor are not significant factors in its environmental fate.

**Ecotoxicity:** Data to assess the ecotoxicity potential (fish, *Daphnia*, and algae) of CMA were obtained from company reports for studies conducted according to regulatory guidelines. CMA was the test material for acute toxicity studies conducted with rainbow trout (96-hour LC<sub>50</sub>: 15 mg/L), bluegill sunfish (96-hour LC<sub>50</sub>: 13 mg/L), and *Daphnia* (48-hour EC<sub>50</sub>: 23 mg/L), all resulting in CMA being classified as "slightly toxic" to these species according to US EPA guidance, while an acute toxicity study with freshwater algae (*Selenastrum*, alachlor 96-hour EC<sub>50</sub>: 0.0029 mg/L, recovery observed after removal to fresh water) was performed with alachlor as the test material.

**Mammalian Toxicity:** Data to assess the mammalian toxicity potential (acute, repeated dose, genetic, reproductive/developmental) of CMA were obtained from company reports on completed studies with CMA used as the test material in every case. The LD<sub>50</sub> for acute oral exposure in the rat was 1,650 mg/kg, corresponding to US EPA pesticide category III, slightly toxic. CMA is considered to be practically nontoxic via dermal exposure in the rabbit (LD<sub>50</sub>: 5,400 mg/kg). CMA was found to be moderately irritating to eyes, but severely irritating to skin. Repeated inhalation exposure for two weeks resulted in clinical signs of toxicity at concentrations greater than or equal to 0.007 mg/L. Results from a cell culture DNA repair assay and from a microbial mutagenic assay indicate that CMA is not genotoxic and not mutagenic. No significant adverse effects were noted in a rat teratology study of CMA with oral exposure up to 300 mg/kg/day.

In conclusion, all the Screening Information Data Set (SIDS) endpoints have been addressed in meeting the objectives of the HPV Challenge Program for CMA without the need to conduct any new

or additional testing. The robust summaries are provided with this test plan. Where appropriate, some endpoints have been completed or supplemented by a logical comparison to alachlor as a model compound. The summarized data support the assessment that CMA, especially in its exclusive role as a chemical intermediate for manufacturing use, poses minimal risk of harm to workers, or to the general population and the environment.

#### **EVALUATION OF DATA FOR QUALITY AND ACCEPTABILITY**

The existing data for CMA was reviewed for quality and acceptability according to the general guidance provided by the US EPA for meeting the SIDS requirements for each endpoint.<sup>1, 2</sup> Additional data existing for alachlor, as a closely related chemical analog for CMA, were reviewed and are provided to supplement or reinforce the data given for some of the environmental fate and toxicological endpoints. Alachlor experimental data taken from Monsanto Company reports has been accepted and used by the US EPA under guidelines established for the registration of pesticide products. The approach described by Klimisch *et al.* (1997) specifies four categories for classifying adequacy of data applied to the ecotoxicology and human health endpoint studies.<sup>3</sup>

1. Reliable without Restriction: GLP procedures followed, accepted testing guideline followed.
2. Reliable with Restrictions: Documented procedures, but vary slightly from testing guidelines.
3. Not Reliable: Unknown or unacceptable testing methods, test organisms, or route of exposure.
4. Not Assignable: Insufficient detail to assign a rating.

#### **REFERENCES**

1. US EPA (1999). "Determining the Adequacy of Existing Data" OPPT, EPA.
2. US EPA (1998). "Guidance for Meeting the SIDS Requirements (The SIDS Guide)" OPPT, EPA.
3. Klimisch, H.-J., Andreae, M., and Tillman, U. (1997). "A Systematic Approach for Evaluating the Quality of Experimental Toxicological and Ecotoxicological Data" Regul. Toxicol. Pharmacol. **25**: 1-5.