TSCA HEALTH & SAFETY STUDY COVER SHEET

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1.0 SUBMISSION TYPE

☐ 8(d) **XX 8(e)** ☐ FYI ☐ 4 ☐ OTHER: Specify_____

- Initial Submission XX - Follow-up Submission ☐ Final Report Submission

Previous EPA Submission Number or Title if update or follow-up: Docket Number, if any: #

☐ continuation sheet attached

2.1 SUMMARY/ABSTRACT ATTACHED
(may be required for 8(e): optional for §4, 8(d) & FYI)

X- YES ☐ NO

2.2 SUBMITTER TRACKING NUMBER OR INTERNAL ID
7106 4575 1292 0337 7937
01-2-35

2.3 FOR EPA USE ONLY

3.0 CHEMICAL/TEST SUBSTANCE IDENTITY

Reported Chemical Name (specify nomenclature if other than CAS name):

CAS#

Purity ___%

X- Single Ingredient

☐ Commercial/Tech Grade

☐ Mixture *Trade Name:* _ *Common Name:* AMS 20249

	CAS Number	*NAME*	*% WEIGHT*
Other chemical(s) present in tested mixture			

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4.0 REPORT/STUDY TITLE

Review of A Two-Generation Dietary Reproduction Study in Rats – Report# 109835

COMPANY SANITIZED

☐ continuation sheet attached

5.1 STUDY/TSCATS INDEXING TERMS

[CHECK ONE]

HEALTH EFFECTS (HE): X ENVIRONMENTAL EFFECTS (EE):_____ ENVIRONMENTAL FATE (EF):_____

5.2 STUDY/TSCATS INDEXING TERMS (see instructions for 4 digit codes)

STUDY TYPE: RPRO SUBJECT ORGANISM (HE, EE only) RATS ROUTE OF EXPOSURE (HE only):__ VEHICLE OF EXPOSURE (HE only)_

*Other:*_____ *Other:*_____ *Other:*_____

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6.0 REPORT/STUDY INFORMATION ☐ Study is GLP

Laboratory Bayer Toxicology Report/Study Date 12/18/2001

Source of Data/Study Sponsor (if different than submitter) _____ Number of pages _-

☐ continuation sheet attached

7.0 SUBMITTER INFORMATION

Janet M. Mostowy, Ph.D.
VP, Product Safety & Regulatory Affairs Phone: 412-777-3490
Bayer Corporation - 100 Bayer Road, Pittsburgh, PA. 15205

Submitter Address (if different): _____

Technical Contact: ___Same as above_____ Phone: ( )_____

☐ continuation sheet attached

8.0 ADDITIONAL/OPTIONAL STUDY COMMENTS

This compound is

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Submitter Signature: _____ **Date:** 12/19/2001

8902 00000 50 $1

Continuation of 2.1

AMS 20249 is a compound which was under development as a potential fungicide, but development of this compound was ceased due to the toxicity profile of the compound. A related fungicide, AMS 21619 is presently under development, and it has been shown that AMS 21619 breaks down to AMS 20249, upon drying, after application to plants/seeds, and upon administration to test animals. (Note: The extent of breakdown varies considerably based on the plant/seed to which AMS 21619 is applied). However, as AMS 21619 has fungicide properties, and the development of AMS 21619 as a fungicide is not based on the conversion of AMS 21619 to AMS 20249, AMS 21619 is not considered to be a delivery system for applying AMS 20249 to plants/seeds. Therefore, although AMS 20249 does have fungicide activity and may be of toxicological concern for evaluating risk assessment and in determining RFD values for AMS 21619, AMS 20249 is strictly a metabolite of AMS 21619 and is not a compound which is being developed for commercial use. Thus, AMS 20249 is not regulated by TSCA 8(e) Adverse Effects Regulations. However, as AMS 20249 is a metabolite of toxicological concern for a compound (i.e., AMS 21619) which is under development as a fungicide, and this study contains data that triggers reporting (i.e., dystocia [possibly secondary to liver toxicity], a decrease in the day 4 viability index, an increase in the cannibalization of pups, a reduction in pup viability on lactation days 0-4, and a possible developmental effect [i.e., cleft palate]), thus the reporting.

Summary

Technical grade AMS 20249 was administered via the diet to CD Sprague-Dawley rats for two generations (one mating per generation) to test for potential reproductive effects. The test compound was administered at nominal dose levels of 0, 40, 160, and 640 ppm (actual doses were 0, 40.6, 161, and 653 ppm). The P and F1 parents were comprised of 30 rats/sex/group. The P and F1 parents received AMS 20249 in the diet throughout the entire study, beginning at six weeks of age for the P parents and at weaning for the F1 parents. Prior to breeding, the animals received treated feed for a ten-week period. P parents were mated to produce F1a litters and F1 parents (randomly selected F1a pups) were mated to produce F2a litters.

During the study, adult animals were evaluated for the effect of the test compound on body weight, food consumption, clinical signs, estrous cycling, mating, fertility, gestation length, and litter size. The offspring were evaluated for compound-related effects on sex ratio, pup viability, body weight gain, and clinical signs. Gross necropsy evaluations were performed on all adults and pups. Histopathologic evaluation of reproductive organs, the pituitary, liver, and gross lesions was performed on all P and F1 adults.

The following summarizes the findings from a two-generation dietary reproduction study with AMS 20249 in Sprague-Dawley rats.

1. There was an increase in early deaths in P and F1 females in the high-dose group. All of the early deaths were associated with dystocia.

2. The only compound-related clinical sign was an increase in the cannibalization of F1a and F2a pups in the high-dose group.

3. There was no compound-related effect on body weight or food consumption for females (premating) or males (throughout the entire study).

4. There was no compound-related effect on gestation or lactation body weights.

5. There was no compound-related effect on gestation food consumption. However, there was a compound-related decrease in lactation food consumption in the high-dose group for both the F1a and F2a breedings.

6. There was no compound-related effect on estrous cycling.

8. There was no compound-related effect on the mating index, fertility index, or the time to insemination.

Continuation of 2.1

8. There was no compound-related effect on the gestation length.

9. There was an increase in dystocia in the high-dose group for P and F1 dams, which may have been due to compound-related effects on the liver.

10. There was no compound-related effect on the gestation index, birth index, or the number of implantation sites.

11. There was no compound-related effect on pup gender, litter size, live birth index, or birth weight.

12. There was a compound-related reduction in the F1a and F2a pup weights in the high-dose group on lactation days 7, 14, and 21.

13. There was a compound-related decrease in the day 4 viability index for the F1a and F2a pups in the high-dose group, which was not due to cannibalization. However, there was no reduction in the day 7, 14, and 21 viability indices.

14. Liver weights were statistically significantly increased in the high-dose group P males and the high-dose group F1 males and females.

15. Multifocal vacuolization of hepatocytes was observed histologically in the mid- and high-dose group P and F1 males and in the high-dose group P and F1 females. Necrosis was also observed in the high-dose group P and F1 females.

16. In the F1a generation, there were three pups (in two litters) in the high-dose group which had cleft palate. Based on the low background incidence of cleft palate in the rat, this finding cannot be excluded as being compound-related.

In conclusion, AMS 20249 demonstrated parental toxicity (i.e., hepatic effects) at doses of 160 and 640 ppm and reproductive effects at 640 ppm: 640 ppm -- dystocia [possibly secondary to liver toxicity], a decrease in the day 4 viability index, an increase in the cannibalization of pups, a decrease in pup body weight on lactation days 7, 14, and 21, a reduction in pup viability on lactation days 0-4, a possible developmental effect (i.e., cleft palate). No parental effects were observed in the 40 ppm dose group and no reproductive effects were observed in the 160 ppm dose group. Therefore, the no-observed--effect-level (NOEL) for overall toxicity and reproductive effects was 40 ppm and 160 ppm, respectively.