

CODING FORMS FOR SRC INDEXING

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Date Produced	12/10/01	Date Received	01/10/02
		TSCA Section	8E
Submitting Organization	BAYER CORP		
Contractor	BAYER TOXICOLOGY		
Document Title	SUPPORT: TSCA HLTH & SFTY STDY CVR SHT W' SUMMRY OF COMBINED STDY ON CHRONIC TOX & CARCINOGENICITY IN WISTAR RATS (DIETARY ADMIN FOR 2 YRS) OF AMS 21618 [], DTD 121001 (SANITIZED)		
Chemical Category	AMS 21618 (CONFIDENTIAL)		

TSCA HEALTH & SAFETY STUDY COVER SHEET
8EHQ-0102-14945
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1.0 SUBMISSION TYPE <input type="checkbox"/> 8(d) <input checked="" type="checkbox"/> XK 8(e) <input type="checkbox"/> FYI <input type="checkbox"/> 4 <input type="checkbox"/> OTHER: Specify _____ - Initial Submission <input checked="" type="checkbox"/> Follow-up Submission <input type="checkbox"/> Final Report Submission Previous EPA Submission Number or Title if update or follow-up: <u>8EHQ-01-14945</u> Docket Number, if any: # _____ <input type="checkbox"/> continuation sheet attached		
2.1 SUMMARY/ABSTRACT ATTACHED (may be required for 8(e): optional for §4, 8(d) & FYI) <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO	2.2 SUBMITTER TRACKING NUMBER OR INTERNAL ID 7106 4575 1292 0337 7944 01-2-33	2.3 FOR EPA USE ONLY
3.0 CHEMICAL/TEST SUBSTANCE IDENTITY <i>Reported Chemical Name (specify nomenclature if other than CAS name):</i> CAS# <u>N/A</u> Purity <u>___</u> % <input checked="" type="checkbox"/> Single Ingredient <input type="checkbox"/> Commercial/Tech Grade <input type="checkbox"/> Mixture <i>Trade Name:</i> _____ <i>Common Name:</i> <u>AMS 21618</u> <i>CAS Number:</i> _____ <i>NAME:</i> _____ <i>% WEIGHT:</i> _____ Other chemical(s) present in tested mixture: _____ <input type="checkbox"/> continuation sheet attached		
4.0 REPORT/STUDY TITLE <u>Combined Study on Chronic Toxicity & Carcinogenicity in Wistar Rats (Dietary Administration for 2 Years) Report # PH 31357</u> <input type="checkbox"/> continuation sheet attached		
5.1 STUDY/TSCATS INDEXING TERMS [CHECK ONE] HEALTH EFFECTS (HE): <input checked="" type="checkbox"/> ENVIRONMENTAL EFFECTS (EE): _____ ENVIRONMENTAL FATE (EF): _____		
5.2 STUDY/TSCATS INDEXING TERMS (see instructions for 4 digit codes) STUDY TYPE: <u>CTOX</u> SUBJECT ORGANISM (HE, EE only): <u>RATS</u> ROUTE OF EXPOSURE (HE only): _____ VEHICLE OF EXPOSURE (HE only): _____ <i>Other:</i> _____ <i>Other:</i> _____ <i>Other:</i> _____		
6.0 REPORT/STUDY INFORMATION <input type="checkbox"/> Study is GLP Laboratory: <u>Bayer AG Toxicology</u> Report/Study Date: <u>12/10/2001</u> Source of Data/Study Sponsor (if different than submitter): _____ Number of pages: - <input type="checkbox"/> continuation sheet attached		
7.0 SUBMITTER INFORMATION Janet M. Mostowy, Ph.D. VP, Product Safety & Regulatory Affairs Phone: 412-771-3490 Bayer Corporation - 100 Bayer Road, Pittsburgh, PA. 15205 Submitter Address (if different): _____ Technical Contact: <u>Same as above</u> Phone: () _____ <input type="checkbox"/> continuation sheet attached		
8.0 ADDITIONAL/OPTIONAL STUDY COMMENTS <u>This compound is</u> <input type="checkbox"/> continuation sheet attached		

Submitter Signature: [Signature] Date: 12/10/01

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9.0 CONTINUATION SHEET
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Continuation of 2.1

Preliminary results from this chronic rat study with AMS 21618 were reported to the EPA 8(e)HQ-01-14945 based on the findings of an increase in the incidence of adenocarcinomas in the uterus of animals dosed with 12500 ppm of AMS 21618. As the final report is now available, this report results are being submitted. Please note: upon final evaluation of this study the preliminary finding of an increase in adenocarcinomas in the 12500 ppm dose group was not considered to be compound-related.

Summary: AMS 21618 was administered orally via the diet to Wistar rats (50 males and 50 females per dose) at doses of 0, 40, 100, 1000, and 5000 ppm for males and 0, 100, 500, 2500, and 12500 ppm for females for a period of up to 753 days (108 weeks).

In addition, a group of 10 male and 10 female Wistar rats per dose group were treated likewise with AMS 21618 and sacrificed after a treatment period of about 1 year.

Averaged over the study period, the mean daily test compound intake was 2.1, 5.2, 53.0, and 271.9 mg/kg for males and was 6.9, 35.2, 181.3, 1083.2 mg/kg for females.

Clinical examinations revealed a higher incidence of vaginal bleeding for females in the 12500 ppm dose group as compared with the other groups. The functional observations and the determination of grip strength showed no signs or symptoms indicating evidence of a neurotoxic potential in rats exposed to AMS 21618.

There was no evidence of a compound-related effect on mortality.

There were no compound-related ophthalmological findings.

There was a compound-related decrease in body weight for males in the 5000 ppm dose group and for females in the 2500 and 12500 ppm dose groups.

There was a compound-related increase in the mean food intake for females in the 12500 ppm (13% per animal, 29% relative to body weight).

There was a compound-related decrease in water intake for females in the 12500 ppm dose group (21% per animal).

There was not compound-related hematological effects (including blood clotting).

During the interim sacrifice, absolute and relative liver weights were increased for females in the 12500 ppm dose group. During the final sacrifice, relative liver weights were increased for males in the 5000 ppm dose group and for females in the 12500 ppm dose group. Together with occasional differences of some parameters during clinical-chemistry examinations (i.e., significant decrease in activity of ALAT, significant decrease in triglyceride concentration, and significant decrease in bilirubin concentration) this might indicate a slight effect of AMS 21618 on liver metabolism when high-doses are administered over a long period of time. However, histopathological investigations gave no evidence of compound-related effects on the liver.

There was a slight decrease in the urinary excretion of: 1) phosphate for males in the 5000 ppm dose group and for females in the 2500 and 12500 ppm dose groups and 2) calcium for females in the 12500 ppm dose group. There was an increase in urine pH for females in the 2500 and 12500 ppm dose groups.

There was a statistically significant decrease of calcium concentration in bone ash and fresh bone of females in the 12500 ppm dose group, which were possibly compound-related.

During necropsy, cecal enlargement was seen in males in the 5000 ppm dose group. However, it can not be concluded that this is a compound-related effect.

Histopathological investigations revealed a statistically significant increase in the incidence of uterine adenocarcinomas for females in the 12500 ppm dose group (20%). However, considering the incidence of historical control values for adenocarcinomas (0-24%), it can not be concluded that this is a compound-related effect.

A slight increase in the incidence (12%) of focal uterine glandular hyperplasia was observed in females in 12500 ppm dose group. As this incidence is only slightly above historical control data, this finding is probably incidental.

There was a significant increase in the number of males and females in the high dose group (5000 ppm or 12500 ppm, respectively) with an increased number of mast cells in the mesenteric lymph node.

There were no other compound-related gross or histopathological findings in other organs and tissues for either sex.

In conclusion, the chronic administration of AMS 21618 to male and female rats was tolerated without adverse effects up to and including 1000 ppm (equal to 53.0 mg/kg) for males and up to and including 500 ppm (equal to 35.2 mg/kg) for females.