

CODING FORMS FOR SRC INDEXING

Microfiche No.		OTS0559839			
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Date Produced	10/08/99	Date Received	11/16/99	TSCA Section	8E
Submitting Organization		BAYER CORP			
Contractor		BAYER AG			
Document Title		INITIAL SUBMISSION: TECHNICAL GRADE MKH 3586, A COMBINED CHRONIC TOXICITY/ONCOGENICITY TESTING STUDY IN THE RAT, WITH TSCA HLTH & SFTY STUDY CVR SHT DATED 111099			
Chemical Category		1H-1,2,4-TRIAZOLE-1-CARBOXAMIDE, 4-AMINO-N-(1,1-DIMETHYLETH*			

**INITIAL
SUB-
MISSION**

TSCA HEALTH & SAFETY STUDY COVER SHEET

PR 20612

BEHQ-1199-1459

TSCA CBI STATUS:

CHECK IF THIS PAGE CONTAINS CONFIDENTIAL BUSINESS INFORMATION (CBI)

Clearly mark the confidential information with bracketing and check the box in the appropriate section (Contains CBI). Submit a sanitized cover sheet with CBI deleted. Mark the sanitized copy, "Public Display Copy" in the heading.

1.0 SUBMISSION TYPE - Contains CBI
 8(d) X - 8(e) FYI 4 OTHER: Specify _____
 Initial Submission 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 8(d) & FYI)
 YES NO

2.2 SUBMITTER TRACKING NUMBER OR INTERNAL ID
 P917-006-942
 99-274

2.3 FOR EPA USE ONLY
 99-016 PH12 97
 OPPT CBIC

3.0 CHEMICAL/TEST SUBSTANCE IDENTITY - Contains CBI
 Reported Chemical Name (specify nomenclature if other than CAS name):
 CAS# 129909-90-6
 1H-1,2,4-Triazole-1-carboxamide, 4-amino-N-(1,1-dimethylethyl)-4,5-dihydro-3-(1-methylethyl)-5-oxo-
 Purity 98 +%
 Single Ingredient
 Commercial/Tech Grade
 Mixture
 Trade Name: MKH 3586 Common Name: _____
 CAS Number: _____ NAME: _____ % WEIGHT: _____
 Other chemical(s) present in tested mixture: _____
 continuation sheet attached

4.0 REPORT/STUDY TITLE - Contains CBI
 Combined Chronic Toxicity/Oncogenicity Testing Study in the Rat, Report # 109260
 continuation sheet attached

5.1 STUDY/TSCATS INDEXING TERMS [CHECK ONE]
 HEALTH EFFECTS (HE): ENVIRONMENTAL EFFECTS (EE): _____ ENVIRONMENTAL FATE (EF): _____

5.2 STUDY/TSCATS INDEXING TERMS (see instructions for 4 digit codes)
 STUDY SUBJECT ROUTE OF EXPOSURE (HE only): _____ VEHICLE OF EXPOSURE (HE only): _____
 TYPE: _____ ORGANISM (HE, EE only): RATT EXPOSURE (HE only): _____
 Other: _____ Other: _____ Other: _____

6.0 REPORT/STUDY INFORMATION Contains CBI Study is OLP
 Laboratory: Agriculture Division Tox Lab Report/Study Date: 10/8/99
 Source of Data/Study Sponsor (if different than submitter): _____ Number of pages: 4,612
 continuation sheet attached

7.0 SUBMITTER INFORMATION Contains CBI
 Submitter: Donald W. Lamb, Ph.D.
 Title: Vice President, Product Safety & Reg. Affairs
 Phone: 412-777-7431
 Company: Bayer Corporation Address: 100 Bayer Road, Pgh, PA 15205-9741
 Technical Contact: Same as above Phone: () _____
 continuation sheet attached

8.0 ADDITIONAL/OPTIONAL STUDY COMMENTS Contains CBI
 Compound is an experimental herbicide
 continuation sheet attached



OPPT CBIC

99 DEC -2 AM 9:53

RECEIVED OPPT NCIC

Contains No CBI



Submitter Signature: Donald W Lamb

Date: 11/10/99

9.0 CONTINUATION SHEET

Submitter Tracking Number/Internal ID

P 917 006 8942
99-2-74

CONTINUED FROM COVER SHEET SECTION # 2.1

Although the finding of a slight increase in astrocytomas in the high-dose was not deemed to be compound-related, this is a rare type of tumor and thus the reporting.

Abstract

Test substance, objectives, and study design. 4-amino-N-(1,1-dimethylethyl)-4,5-dihydro-3-(1-methylethyl)-5-oxo-1H-1,2,4-triazole-1-carboxamide (MKH 3586) is a chemical with herbicidal properties that is currently undergoing regulatory testing to support its registration as an agricultural herbicide. The principal objectives of this 2-year combined chronic toxicity/oncogenicity testing bioassay, of which the rat is the preferred test species, were: (1) to establish, under conditions of prolonged and repeated exposure, a definitive chronic toxicological profile for the MKH 3586-exposed rat, thus permitting determination of a maximum dose, uncomplicated by geriatric changes, which produces no observed adverse effects through at least 1 year (NOEL) and (2) to characterize and possibly predict, based on the response in a rodent test species, the oncogenic potential of MKH 3586 in the human.

In this study, the technical grade of MKH 3586 was administered continuously in the feed to separate 1- and 2-yr sacrifice groups of the Fischer 344 rat (60-70 animals/dose/sex total) at nominal dietary concentrations of 0, 50, 500, or 1,250 males/1,000 females ppm relative to the percentage of purity of the test substance. All test diets (including control) were available for *ad libitum* consumption at all times; the homogeneity and stability of MKH 3586 as a dietary admixture was confirmed. Body weight and food consumption determinations were conducted weekly for approximately 8 months and once a month thereafter; detailed clinical examinations of each animal were conducted weekly throughout the study. Standard hematologic, clinical chemistry, and urinalysis endpoints were evaluated from blood (drawn via the orbital sinus) and urine collected at approximately 3, 6, 12, 18, and 24 months into the study. Ophthalmologic exams were conducted on all acclimatized animals prior to exposure, and then again on all surviving animals just prior to termination of the 1- and 2-yr segments of the study. All animals placed on study were subject to a postmortem examination, which included (1) documenting and saving all gross lesions, (2) weighing designated organs, and (3) collecting representative tissue specimens for histopathologic evaluation.

Results. The mean daily intake of the test substance (mg MKH 3586/kg body wt/day) over approximately 2 years at nominal dietary concentrations of 50, 500, or 1,250 males/1,000 females ppm, respectively, was 2.3, 25, and 67 for males and 2.7, 30, and 65 for females. Body weight gain (BWG) remained unaffected in both sexes at 50 ppm. An overall decline of 6% BWG was noted in 500-ppm females, while 8 and 12% declines in BWG were noted in 1,250/1,000-ppm males and females, respectively. Clinical chemistry considerations included increases in serum cholesterol in 500- and 1,250/1,000-ppm males and females, as well as increases in thyroxine, and triiodothyronine in 500- and 1,250-ppm males. No evidence of a MKH 3586-induced toxicity was observed in any other in-life parameter, including food consumption/utilization, survival, clinical observations, ophthalmology, hematology, and urinalysis. Organ weight changes attributable to exposure to the test substance included increased liver weight in 1-year 500- and 1,250/1,000-ppm males and females. Evaluation of organ/body wt. ratios suggest that other organ weight changes observed in this study were secondary to MKH 3586-induced decreases in body weight gain. Histopathological considerations included a decrease in the background incidence of vacuolation of the liver in 1-yr 1,250-ppm males and a non-statistical and non-compound-related increase in astrocytomas in the high-dose group males and females at the end of the study. No other histopathological evidence of a MKH 3586-induced toxicity was observed in this study.

Conclusions Through approximately 2 years of continuous and repeated dietary exposure to the test substance, the toxicological response of the rat was principally characterized by alterations in body weight gain as well as structural and/or functional alterations in liver-related endpoints. Based on the lack of an adverse compound-related effect in the liver at a dose of 50 ppm in males and females, a systemic chronic toxicity NOEL of 2.3 mg MKH 3586/kg body wt/day was established for the rat (specifically, 2.3 and 2.7 mg MKH 3586/kg body wt/day for male and female rats, respectively). The rat, like the mouse (Wahle, 1999), showed no evidence of a compound-induced neoplastic response in any tissue examined.