

A 01

CODING FORMS FOR SRC INDEXING

Microfiche No.	OTS0559808		
New Doc ID	88000000001	Old Doc ID	8EHQ-1099-14561
Date Produced	09/24/99	Date Received	10/05/99
		TSCA Section	8E
Submitting Organization	BAYER CORP		
Contractor	BAYER AG		
Document Title	INITIAL SUBMISSION: TSCA HLTH & SFTY STUDY CVR SHEET W/CONTINUATION SHEET SUMMARIZING DERMAL PENETRATION STUDY IN RATS (PRELIMINARY RESULTS) WITH SXX 0665, DATED 092499		
Chemical Category	2-(1-CHLOROCYCLOPROPYL)-1-(2-CHLORPHENYL)-3-(1,2,4-TRIAZOL-*		

A 03

8E HQ-1099-14561

TSCA HEALTH & SAFETY STUDY COVER SHEET

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 (i.e. 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) 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
 Cert# P 917006932
 99-2-68

2.3 FOR EPA USE ONLY

3.0 CHEMICAL/TEST SUBSTANCE IDENTITY - Contains CBI
 CAS#: 120983-64-4 Reported Chemical Name (specify nomenclature if other than CAS name):
 2-(1-Chlorocyclopropyl)-1-(2-chlorophenyl) - 3-(1,2,4-triazol-1-yl)propan-2-ol
 Purity _____ %
 - Single Ingredient
 - Commercial/Tech Grade
 - Mixture
 Trade Name: SXX 0665 Common Name: _____

4.0 REPORT/STUDY TITLE - Contains CBI
 Dermal Penetration Study in Rats (preliminary results)
 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 VEHICLE OF
 TYPE: _____ ORGANISM (HE, EE only): RATS EXPOSURE (HE only): _____ EXPOSURE (HE only): _____
 Other: _____ Other: _____ Other: _____

6.0 REPORT/STUDY INFORMATION - Contains CBI - Study is GLP
 Laboratory: Bayer AG - Institut für Metabolismus etc. Mönchengladbach Report/Study Date: 7/29/99
 Source of Data/Study Sponsor (if different than submitter): Bayer AG Number of pages: 2
 continuation sheet attached

7.0 SUBMITTER INFORMATION - Contains CBI
 Submitter: Donald W. Lamb, Ph.D. Title: V. P., Prod. Safety & Reg. Affirs. Phone: 412-777-7431
 Company Name: Bayer Corporation Company Address: 100 Bayer Road
 Pittsburgh, PA 15205-9741 Submitter Address (if different): _____
 Technical Contact: Donald W. Lamb, Ph.D. Phone: (412)777-7431
 continuation sheet attached

8.0 ADDITIONAL/OPTIONAL STUDY COMMENTS - Contains CBI
 Preliminary results only, final report to be sent if issued.
 SXX 0665 is a metabolite of toxicological concern for a compound (JAU 6476) which is under development as a fungicide.
 continuation sheet attached

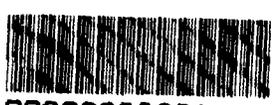
RECEIVED
EPA
99 OCT 5 AM 11:15



RECEIVED
EPA
99 OCT 20 AM 10:05

Submitter Signature: Donald W. Lamb Date: 9/24/99

Page 1 of 3



8800000001

27135

Contain NO CBI

A 04

As these results show there is a small to high portion of SXX 0665 entering the body. That portion is increasing quickly, when diluting the formulation with water.

For risk assessment the absorbable portion has to be added to the absorbed portion, unless we prove by a special study that this portion is not entering the systemic distribution.

For the special situation with SXX 0665 formed as metabolite of JAU 6476, a dermal penetration study of SXX 0665 should be conducted in the JAU 6476 EC formulation recipe, since dermal penetration is depending on the type of formulation

Erhard Weber

- Ø J. Applegate
- Dr. Reinhard Fritz
- Dr. Ditzens
- Dr. Maasfeld
- Dr. Ecker
- Dr. H. Weber
- Dr. Schade-Lehn

Contain NO CBI

RECEIVED

A 05

9.0 CONTINUATION SHEET
Submitter Tracking Number/Internal ID

P917006932
99-2-68

CONTINUED FROM COVER SHEET SECTION # 2.1

TSCA 8(e) Evaluation:

SXX 0665 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, JAU 6476 is presently under development, and it has been shown that JAU 6476 breaks down to SXX 0665, 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 JAU 6476 is applied). However, as JAU 6476 has fungicide properties, and the development of JAU 6476 as a fungicide is not based on the conversion of JAU 6476 to SXX 0665, JAU 6476 is not considered to be a delivery system for applying SXX 0665 to plants/seeds. Therefore, although SXX 0665 does have fungicide activity and may be of toxicological concern for evaluating risk assessment and in determining RFD values for JAU 6476, SXX 0665 is strictly a metabolite of JAU 6476 and is not a compound which is being developed for commercial use. Thus, SXX 0665 is not regulated by TSCA 8(e) Adverse Effects Regulations. However, as SXX 0665 is a metabolite of toxicological concern for a compound (i.e., JAU 6476) which is under development as a fungicide, all studies are being evaluated for reporting requirements.

The evaluation for the reporting of this study was based on the comparison of the μg equivalents of SXX 0665 potentially absorbed following dermal exposure to SXX 0665 and the results from acute toxicity and teratogenicity studies with SXX 0665. The dermal LD50 > 5000 mg/kg; the oral LD50 > 2500 mg/kg (6/23/99 = 99-2-46); the NOEL for teratogenicity (administered via gavage) was 1 mg/kg/day for rats (6/23/99 = 99-2-47 and 99-2-45); the NOEL for teratogenicity (administered via dermal application) was 30 mg/kg/day for rats. As the acute toxicity was low, this study would not indicate a potential problem based on the acute toxicity. However, if a 1000 fold safety factor is applied to the NOELs for teratogenicity, doses of 1 $\mu\text{g}/\text{kg}/\text{day}$ and 30 $\mu\text{g}/\text{kg}/\text{day}$ are obtained for the oral and dermal teratogenicity studies with SXX 0665, respectively. When the absorbed dose of SXX 0665 equivalents from the dermal absorption study is compared to the teratology NOELs with a 1000 fold safety factor, the dose of SXX 0665 exceeds the values for the teratology studies. Thus, it is concluded that this study be reported.

To put things into perspective in regards to the potential toxicity of JAU 6476, it should be noted that the above evaluation is based on the assumption that all of the JAU 6476 which gets on the skin during the mixing/application of JAU 6476 is converted to SXX 0665 (Note: It has been shown that a 25% emulsifiable formulation of JAU 6476 does not breakdown to SXX 0665 before or after dilution). Although the actual percentage of JAU 6476 which converts to SXX 0665 on the skin of humans is not known, based on a dermal absorption study with JAU 6476 250 EC with rats (9/17/99 = 99-2-67), only 9.6 percent of the applied dose to a rat was found to be converted to SXX 0665. Thus, the assumption that there is a 100% conversion of JAU 6476 to SXX 0665 on the skin of humans, which is what was assumed for the above evaluation with SXX 0665, is a very conservative estimate.

Contain NO CBI

A 06

P917.006932
99-2-68

Abstract

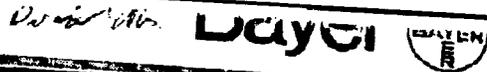
A dermal penetration study was conducted in the rat with SXX 0665 WG/WP.

Ten Hour Exposure

Dose	5 mg/rat 5 mg/cm ²	0.5 mg/rat 0.05 mg/cm ²	0.05 mg/rat 0.005 mg/cm ²
Percent at application site after wash	41	38	26
Amount in/at the application site [µg]	2050	190	13
Percent systemically absorbed	2	12	35
Amount systemically absorbed [µg]	100	60	18
Percent absorbed (incl. skin at the application site)	43	50	61
Amount absorbed (incl. skin at the application site) [µg]	2150	250	31
% total recovery	93	95	96

Contain NO CBI

A 07 Internal Note



Dr. Erhard Weber

Bayer AG
 Pflanzenschutz Entwicklung
 Institut für Metabolismus und
 Rückstandsanalytik
 Altraj-Nobel-Str.50
 D-40789 Monheim
 Tel. Durchwahl: (02173) 38- 3845
 Fax-Durchwahl: (02173) 38- 4014
 E-Mail: erhard.weber.ew@bayer-ag.de

SXX 0665 dermal penetration.doc

Monheim, 29.07.1999

SXX 0665 dermal penetration study rat (preliminary results)

A dermal penetration study in the rat with SXX 0665 WG/WP was conducted in the Institute of Metabolism Research and Residue Analysis in Monheim in 1993.

The study was started in May 1993 and the experimental part finished in July 1993.

Since the development of SXX 0665 was stopped in August 1993 the study was aborted and no report prepared.

Evaluating the raw data of this study the following preliminary results have been calculated:

10 hours of exposure			
Dose	5 mg/rat 0.5 mg/cm ²	0.5 mg/rat 0.05 mg/cm ²	0.05 mg/rat 0.005 mg/cm ²
Concentration	40 mg WG/ml = 20 mg SXX 0665/ml	4 mg WG/ml = 2 mg SXX 0665/ml	0.4 mg WG/ml = 0.2 mg SXX 0665/ml concentration in spray
% not absorbed	50	45	35
% absorbable = % at application site after wash	41	38	26
% absorbed = % entering the body	2	12	35
% total recovery	93	95	96

The Data Reporting is according to EPA OPPTS 870.7600:

Determination of the quantity and the percent absorbed for each animal and for the group (mean). The quantity absorbed is that portion of the dose which enters the systemic compartment of the organism. The quantity in/on the skin is localized in the epidermis (mainly the stratum corneum) and is not available for systemic distribution and toxicity until it enters the vascular dermis. This determination is based on the following distribution of the administered dose:

(A) Not absorbed—quantity in skin wash, and on the protective cover.

(B) Absorbable—quantity in/on the washed skin.

(C) Absorbed—quantity in the urine, cage wash, feces, expired air (if present), blood, organs (if collected), and the remaining carcass.

Contain NO CB