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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

MEMORANDUM

15 JUL 1992

SUBJECT: Carcinogenicity Peer Review of SAN582H

FROM: Deborah L. McCall 6/3/92
Toxicology Branch II / Section III
Health Effects Division (H7509C)

and
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Health Effects Division (H7509C)

TO: Cynthia Giles-Parker
Product Manager #22
Registration Division (H7505C)

The Health Effects Division Carcinogenicity Peer Review Committee met on March 4, 1992 to discuss and evaluate the weight-of-the-evidence on SAN582H with particular reference to its carcinogenic potential. The Peer Review Committee agreed that SAN582H should be classified as Group C - possible human carcinogen and recommended that for the purpose of risk characterization the Reference Dose (RfD) approach should be used for quantification of human risk.

A. Individuals in Attendance:

1. Peer Review Committee: (Signatures indicate concurrence with the peer review unless otherwise stated.)

Karl Baetcke

Lucas Brennecke

William L. Burnam

George Ghali

Richard Hill

William Sette

Kerry Dearfield

Esther Rinde

2. Reviewers: (Non-committee members responsible for data presentation; signatures indicate technical accuracy of panel report.)

Deborah McCall[1] Deborah McCall

James Rowe James Rowe

Bernice Fisher Bernice Fisher

3. Peer Review Members in Absentia: (Committee members who were unable to attend the discussion; signatures indicate concurrence with the overall conclusions of the Committee.)

Penelope Fenner-Crisp Penelope A. Fenner-Crisp

Marcia Van Gemert Marcia Van Gemert

Reto Engler Reto Engler

Robert Beliles Robert P Beliles

Marion Copley Marion Copley

Julie Du

Jean Parker Jean Parker

Hugh Pettigrew Hugh Pettigrew

John Quest

Yin-Tak Woo Yin Tak Woo

4. Other Attendees:

Eve Andersen (Clement)
Sangeta Khatter (RD)

B. Material Reviewed:

The material available for review consisted of DER's, one-liners, and other data summaries prepared by Deborah McCall; tables and statistical analysis by Bernice Fisher. The material reviewed is attached to the file copy of this report. The data reviewed are based on studies submitted to the Agency by Sandoz Crop Protection Corp.

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[1] Also a member of the PRC for this chemical. Signature indicates concurrence with the peer review unless otherwise noted.

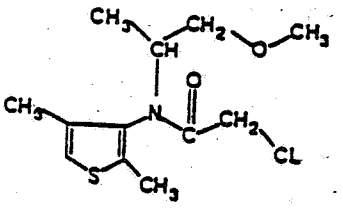
C. Background Information:

SAN582H [2-chloro-N-[(1-methyl-2-methoxy)ethyl]-N-(2,4-dimethylthien-3-yl)-acetamide] and its oxalamide metabolite, [N[(1-methyl-2-methoxy)ethyl]-N-(2,4-dimethylthien-3-yl)-oxalamide] have no permanent tolerances established. It is manufactured by Sandoz Crop Protection Corporation as a herbicide for use on corn and soybeans.

The registrant has submitted 27 studies in support of a temporary EUP (crop destruct in soybeans and a temporary tolerance in corn of 0.01 ppm).

The Caswell (or Tox Chem) Number of SAN582H is 195J. The PC code is 129051. The Chemical Abstracts Registry Number (CAS No.) is 87674-68-8.

The structure of SAN582H is



D. Evaluation of Carcinogenicity Evidence:

1. Rat Carcinogenicity Study

Reference: Ruckman, S.A., et al. 1990. (§ 83-1a & 83-2a) Combined Chronic Toxicity/ Carcinogenicity Study in Rats with SAN582H. Unpublished report prepared by Huntingdon Research Centre Ltd., submitted to the Agency by Sandoz Crop Protection Corporation. Report No. SDZ 335/891445, dated March 1, 1990. MRID No. 417068-08.

a. Experimental Design

SAN582H was administered by admixture with the diet in pellet form to male and female Sprague-Dawley rats (50 animals/sex/group) for 104 weeks at levels of 0, 100, 700, or 1500 ppm. Twenty additional animals/sex/group were designated for interim sacrifice at 52 weeks.

b. Discussion of Tumor Data

The male rats had a significantly increasing dose-related trend in combined benign and/or malignant liver tumor rates (Table 1). Pairwise comparisons were not statistically significant. The incidence of malignant liver cell tumors (4%) are just outside the historical control data range (0-3.6%). The number of animals with benign tumors was increased in the high-dose group, but pairwise statistical significance was not reached.

The female rats had a significantly increasing dose-related trend in the ovarian adenomas (Table 2). Statistical analysis of these results indicated no significant pairwise comparison. The incidence in the 1500 ppm group of 12% is approximately twice the average of the historical incidence of 5.5%.

Table 1. SAN 582H - Sprague-Dawley Male Rats, Hepatocellular Tumor Rates[+] and Exact Trend Test and Fisher's Exact Test Results (p values)

Tumors	Dose (ppm)			
	0	100	700	1500
Benign	0/49	0/45	1[a]/48	2/48
(%)	(0)	(0)	(2)	(4)
p=	0.063	1.000	0.495	0.242
Malignant	0/49	0/45	0/48	2[b]/48
(%)	(0)	(0)	(0)	(4)
p=	0.063	1.000	1.000	0.242
Both	0/49	0/45	1/48	4/48
(%)	(0)	(0)	(2)	(8)
p=	0.006**	1.000	0.495	0.056

[a] First Benign tumor observed at week 104, dose 700 ppm.
[b] First Malignant tumor observed at week 104, dose 1500 ppm.

Table 2. SAN 582H - Sprague-Dawley Female Rats, Ovarian Adenoma Tumor Rates[+] and Exact Trend Test and Fisher's Exact Test Results (p values)

Tumors	Dose (ppm)			
	0	100	700	1500
Adenomas	2/50	1/50	2/50	6[a]/49
(%)	(4)	(2)	(4)	(12)
p=	0.020*	0.500	0.691	0.128

[a] First adenoma observed at week 103, dose 1500 ppm.

[+] Number of tumor bearing animals/Number of animals examined, excluding those that died or were sacrificed before week 53.

Significance of trend denoted at Control. Significance of pair-wise comparison with control denoted at Dose level.

* $p<0.05$ ** $p<0.01$

c. Non-neoplastic Lesions and Other Observations

The incidence of altered eosinophilic hepatocytes in male rats was increased from 4% in control and 100 ppm-dosed rats to 12 and 20%, respectively, in 700 and 1500 ppm-dosed rats. A significant ($p=0.008$) positive trend was noted for this effect, as was a significant ($p=0.044$) pairwise comparison at 1500 ppm. Liver weights were increased at terminal sacrifice for the females, but not the males.

Other effects observed in male rats were an increase in the incidence of stomach epithelial hyperplasia, from 12% in control rats to 40% in rats at the 1500 ppm dose level ($p=0.008$, by pairwise comparison). A significant ($p=0.007$) positive trend was also found across dose levels for this alteration. Hyperplasia of the parathyroids increased from 10% in control male rats to 36% in the 1500 ppm-dose group, again showing a significant positive trend across dose levels and a significant pairwise comparison at 700 and 1500 ppm versus controls.

In female rats, bile duct hyperplasia incidence was increased in a dose-dependant manner, from 6% in controls to 40% in the 1500 ppm-dose group. Significant pairwise comparisons were found at the 700 or 1500 ppm dose levels compared to controls, as was a significant positive trend across doses ($p<0.001$). A significant positive trend was found for female rats with cystically dilated bile ducts ($p=0.036$), but no significant pairwise comparisons were found. Ovarian tubular hyperplasia was also increased in incidence, from 24% in the control rats to 28% and 44% in the 700 and 1500 ppm dose groups, respectively. A significant ($p=0.003$) positive trend was found across doses, as was a significant pairwise comparison at the 1500 ppm dose level when compared to controls ($p=0.012$).

The nasal turbinates were also examined, but there are no reports of increased incidences of neoplastic or non-neoplastic lesions in this area. Two cross sections were reviewed for each animal, these were taken from between the incisive papilla and first upper molar tooth.

A statistically significant decrease in food consumption in male and female rats of the 700 and 1500 ppm dose group was noted when compared to the controls for study weeks 1 and 13.

A statistical evaluation of mortality indicated significant decreasing mortality with dose increments in both male and female rats.

d. Adequacy of Dosing for Assessment of Carcinogenic Potential

The dosing was considered to be adequate for assessing the carcinogenic potential of SAN582H, based on body weight gain depressions of 16% in males and 30% in females seen at 1500 ppm. The dosing was not considered to be excessive.

2. Mouse Carcinogenicity Study

Reference: Hooks, W.N., et al. 1990. (§ 83-2) Potential tumorigenic effects in prolonged dietary administration to mice with SAN582H. Unpublished report prepared by Huntingdon Research Centre Ltd., submitted to the Agency by Sandoz Crop Protection Corporation. Report No. SDZ 346/90189, dated September 13, 1990. MRID No. 416624-15.

a. Experimental Design

SAN582H was administered in the diet for 94 weeks to groups of 104 CRL:CD-1 (ICR) BR mice at levels of 0, 30, 300, 1,500, and 3,000 ppm. Two satellite groups at doses levels of 0 and 3,000 ppm with 16 mice/group/sex were sacrificed after 65 weeks on treatment.

b. Discussion of Tumor Data

Interim or terminal neoplastic histopathology did not reveal any treatment-related effects on the incidence of benign or malignant tumors.

c. Non-neoplastic Lesions

A dose-related generalized hepatocyte enlargement (minimal) in treated animals of both sexes at interim and terminal sacrifice. Minimal hyperkeratosis at the limiting ridge of the stomach was observed in both sexes in the 3,000 ppm group at interim sacrifice, but this was attributed to irritation and was not seen at terminal sacrifice. A significant elevation of liver weights in both sexes was observed at interim sacrifice. Significantly elevated liver and kidney weights were observed for females in the 1,500 and 3,000 ppm dose groups at terminal sacrifice.

d. Adequacy of Dosing for Assessment of Carcinogenic Potential:

The tested doses were adequate for assessment of carcinogenic potential. The decrease in body weight gains during the first year of treatment was 28% in the males and 29% in the females.

E. Additional Toxicology Data on SAN582H:

1. Metabolism: SAN582H was extensively metabolized within 3 days of dosing. Less than 2.5% of the C14 dose was recovered as unchanged parent compound, and 22 metabolites were reported; 21 were found in the urine and feces which were identified. However, because 61 to 78% of the C14 dose was not identified or characterized the study is unacceptable.

2. Mutagenicity: SAN582H has been tested in several mutagenicity studies. The acceptable tests fulfill all 3 of the required categories: gene mutations, structural chromosomal aberrations, and other genotoxic effects (e.g. DNA damage and repair).

Salmonella assay: Negative with and without activation in Ames assay.

Acceptable. (MRID 415965-42).

Chromosomal aberration using CHO cells in vitro: Considered positive under the conditions of the assay with and without activation. Acceptable. (MRID 415965-43).

Mouse Micronucleus assay: Negative in an Unacceptable assay in vivo. This assay needed higher dosing (MRID 418227-03).

Unscheduled DNA synthesis with rat hepatocytes: Unequivocally positive in an Acceptable assay in vitro (MRID 415965-44), negative in an Acceptable assay in vitro (MRID 416624-16), and negative in an Unacceptable assay in vitro (MRID 418227-02).

BALB/3T3 Mouse mammalian cell transformation (in vitro): Negative in an Unacceptable assay. (MRID 418227-01).

Of the acceptable assays, SAN582H was negative in a Salmonella assay. However, there are two acceptable assays which exhibit positive mutagenic effects - one UDS in vitro was unequivocally positive where UDS activity occurred at levels well below cytotoxic levels and one Chromosomal aberration using CHO cells. In the "negative" acceptable UDS, there was suggestive activity. The overall UDS response is consistent with positive responses induced by analogs (e.g. Alachlor, Acetochlor) in this assay.

3. Developmental Toxicity

Developmental Toxicity in Rats by Oral route (MRID 416159-04). Rats were administered via gavage at 0, 50, 215, or 425 mg/kg/d during gestation days 6-15. Maternal toxicity was evidenced by excess salivation, increased liver weight, and reduced body weight gain and food consumption in the 215 and 425 mg/kg/d dose level. Developmental toxicity was evidenced by increased incidence of resorptions in the 425 mg/kg/d dose group. Maternal NOEL = 50 mg/kg/d and Developmental LOEL = 215 mg/kg/d.

Developmental Toxicity in Rabbits by Oral Route (MRID 417068-09). SAN582H was orally dosed to presumed pregnant rabbits at dose levels of 0, 37.5, 75, or 150 mg/kg/d during gestation days 6-18. Maternal toxicity was evidenced by decreased body weight, food consumption and abortion/premature delivery in the 75 and 150 mg/kg group. Developmental toxicity was evidenced by low incidence of abortion/premature delivery and hyoid alae angulated changes in the 150 mg/kg group. Maternal NOEL = 37.5 mg/kg/d, Developmental NOEL = 75 mg/kg/d.

Two Generation Reproduction in Rats (MRID 416159-05). Dose levels were: 0, 100, 500, or 2000 ppm (7, 36, or 150 mg/kg/d for males and 8, 40, or 160 mg/kg/d for females). Parental toxicity was evidenced by significant reductions in body weight and food consumption in males and significant increases in absolute and relative liver weights in both sexes of the 2000 ppm group. Significant reductions in pup weight during lactation were noted in 2000 ppm dose group. A combined Systemic/Reproductive NOEL = 500 ppm and LOEL = 2000 ppm.

4. Acute, Subchronic, and Chronic Toxicity Studies

Acute: The standard battery of 6 acute tests were performed for SAN582H. The acute oral LD50 in rats was 2139.8 mg/kg in males and 1296.8 mg/kg in females (combined 1569.8 mg/kg); acute dermal (4 h) LD50 in rabbits was > 2.0 g/kg; acute inhalation LC50 in rats was > 4990 mg/m3; SAN582H was minimally irritating to the eyes and skin of rabbits; and SAN582H was a slight sensitizer in guinea pigs.

Subchronic: 13-Week Oral Feeding Study in Rats (§82-1) (MRID No. 416159-01) - Sprague Dawley rats were fed diets containing SAN582H at concentrations of 0, 50, 150, 500, 1500, or 3000 ppm (Attachment 5). Compound-related reductions in body weight, increase in relative liver weight, centrilobular hepatocytic enlargement and an increase in total protein and cholesterol levels were observed at 1500 ppm or higher dose levels. The study was classified as Minimum. The Systemic Toxicity NOEL = 500 ppm and the LOEL = 1500 ppm.

13-Week Oral Feeding Study in Dogs (§82-1) (MRID No. 416159-02) - SAN582H was fed to groups of 4 ♂ & ♀ beagle dogs for 13 weeks at dietary levels of 0, 100, 750, or 2000 ppm. Periportal hepatocellular vacuolation was noted in the 2000 ppm dose group. Histological liver changes were noted in the 750 and 2000 ppm dose group. Body weight and body weight gains of the 750 ppm (females only) and the 2000 ppm (males only) were depressed throughout the study. The study was classified as Minimum. NOEL = 100 ppm and the LOEL = 750 ppm.

52-Week Oral Toxicity Study in Dogs (§83-1) (MRID No. 416159-03) - SAN582H was fed to groups of 4 ♂ & ♀ beagle dogs for 52 weeks at dietary levels of 0, 25, 250, or 1250 ppm. Periportal hepatocyte vacuolation was noted in the 1250 ppm dose group. Liver changes in the 1250 ppm dose group correlate with the increase in serum alkaline phosphatase, cholesterol levels, and the increase in liver-to-body weight ratio. The study was classified as Guideline. NOEL = 250 ppm and the LOEL = 1250 ppm.

5. Structure-Activity Correlations

SAN582H is structurally related (usually in only one branch of the moiety) to Acetochlor, Metolachlor, Propachlor, Alachlor, Allidochlor, and Butachlor, as illustrated in Figure 1.

Acetochlor has been classified as a Group B2, based upon the findings of increased incidence of malignant or combined malignant and benign tumors in multiple species, and positive mutagenic effects including a DNA damage repair (UDS) assay. Male Sprague-Dawley rats had increased incidences of nasal papillary tumors at doses of 1500 ppm and 5000 ppm in the diet, and papillary adenocarcinomas at 5000 ppm. Female rats had no increases in tumors.

Metolachlor, in a dietary administration study in rats, was found to cause a significantly elevated incidence of proliferative liver lesions in females (neoplastic nodules and carcinomas, combined) at 150 mg/kg. Metolachlor was classified as a Group C Carcinogen; this classification was recently confirmed at a meeting of the FIFRA Scientific Advisory Panel. The HED evaluation

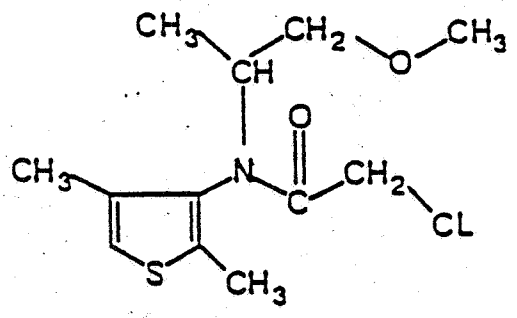
concluded that a low dose extrapolation model should be used for quantitative risk assessment.

Propachlor, in a two year chronic toxicity/carcinogenicity study in rats showed evidence of an increased incidence of thyroid neoplasia and ovarian tumors (benign and malignant granulosa/theca cell tumors and undifferentiated sarcomas). However, the study did not use high enough dose levels to adequately assess the carcinogenic potential of Propachlor, and no control data were provided. A carcinogenicity study in mice also used doses below those necessary to adequately assess the carcinogenicity potential. Propachlor was not mutagenic in a chromosome aberration assay, cytogenetic assay, gene mutation assay, or 2 UDS assays.

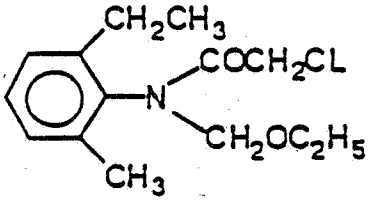
Alachlor is carcinogenic in 2 species (rats and mice). In a dietary administration study in rats, nasal turbinate tumors were found at 42 mg/kg, stomach tumors at 126 mg/kg in both sexes, and thyroid follicular adenomas at 146 mg/kg in males. In a dietary administration study in mice an increased incidence of lung tumors was observed at 260 mg/kg in females. Alachlor gave a positive mutagenic response in one Ames assay (negative in 4 others), and in a DNA damage/repair (UDS) assay. Negative findings were reported from other bacterial assays, in vitro cytogenetics, HGPRT assay and microsome plate incorporation. The Peer Review Committee has classified Alachlor as a B2 carcinogen and Alachlor has undergone Special Review (PD4 has been completed).

Butachlor is carcinogenic in rats. In a dietary administration study (interim report only, dated 1982), stomach tumors were induced at 3000 ppm (150 mg/kg) in females. Butachlor was found to be weakly mutagenic in one Ames assay, and negative in bacterial DNA repair tests. The Peer Review Committee has not evaluated this chemical.

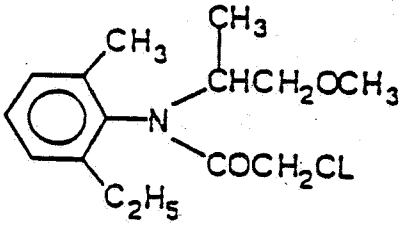
Figure 1. Structural Analogs of SAN582H



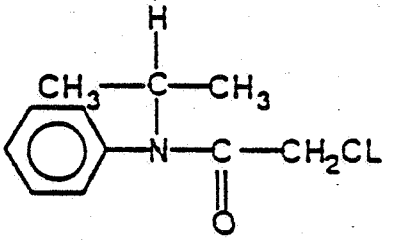
SAN 582H



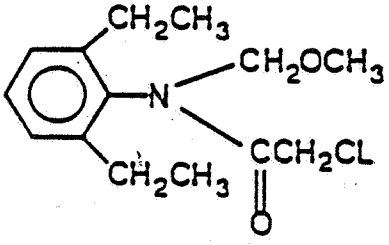
Acetochlor



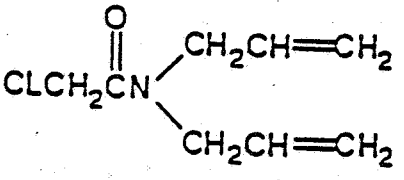
Metolachlor



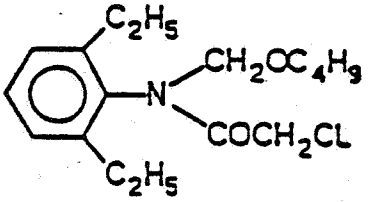
Propachlor



Alachlor



Allidochlor



Butachlor

F. Weight of Evidence Considerations:

The Committee considered the following facts regarding the toxicology data on SAN582H in a weight-of-the-evidence determination of carcinogenic potential:

1. SAN582H was associated with benign liver cell tumors in male rats treated with up to 1500 ppm in the food. There was a statistically significant increased dose-response trend, but no significant pair-wise increase. The incidences were slightly above historical control ranges. Females had a statistically increased trend in ovarian tubular adenomas, but no pair-wise increase. The doses were adequate for assessing carcinogenic potential. The first tumors appeared late-- 104 weeks for the males and 103 weeks for the females.

2. Non-neoplastic changes were also seen in the target organs in the chronic study. This included altered eosinophilic hepatocytes in the males, and ovarian tubular hyperplasia in the females. The subchronic studies also showed that the liver was the target organ.

3. SAN582H was not carcinogenic in a mouse study which used acceptable doses.

4. In the unscheduled DNA synthesis assay, SAN582H was unequivocally positive at levels below cytotoxic levels and it was weakly positive in a chromosomal aberration (CHO) assay. The UDS results were suggestive in a second assay and are consistent with activity by analogs. SAN582H was negative in a Salmonella assay. Based on these studies, there appears to be mutagenic activity that would contribute to the weight-of-evidence for carcinogenesis by SAN582H.

5. Structurally related compounds have shown both carcinogenic and mutagenic activity.

G. Classification of Carcinogenic Potential:

The Peer Review Committee considered the criteria contained in the EPA's "Guidelines for Carcinogen Risk Assessment" [FR51: 33992-34003, 1986] for classifying the weight of evidence for carcinogenicity.

The Peer Review Committee agreed that the classification for SAN582H should be Group C - possible human carcinogen and recommended that for the purpose of risk characterization the Reference Dose approach should be used for quantification of human risk (RfD).

This decision was based on a statistically significant increasing trend for benign liver cell tumors in male rats and a statistically significant increasing trend for ovarian tubular adenomas in female rats. This study was conducted using adequate doses for the determination of carcinogenic activity. SAN582H has shown positive results in genotoxicity tests, and is structurally related to other carcinogens. The PRC recommends that an additional UDS assay be performed in testicular tissue. The PRC also recommends that the slides of the nasal turbinates of the rats be reevaluated, since nasal tumors were seen in the rat bioassay of the structurally related Alachlor.

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