Reviewed by : Whang Phang, Ph.D. 7/23/87
Section III, Toxicology Branch (TS-769c)
Secondary Reviewer: Marcia van Gemert, Ph.D.
Section III, Toxicology Branch (TS-769c) 7/24/87

DATA EVALUATION REPORT

STUDY TYPE: Primary DNA Damage: Mitotic Gene Conversion (Saccharomyces cerevisiae) (2 studies)

MRID NO.: 116489 & 116491 TOX. CHEM. No.: 320

TEST MATERIAL: 2, 4-DP (purity not specified)

SPONSOR: Amchem Products, Inc., Ambler, PA

TESTING FACILITY: Pharmakon Laboratories, Scranton, PA

CITATION: Two studies:

1). Naismith, R.; Matthews, R.; Godek, E. (1979) Summary Data: Mitotic Gene Conversion-Saccharomyces cerevisiae: Study No. PH-304-AM-179-2,4-DP. (Unpublished study received Mar 26, 1979 under 264-231; prepared by Pharmakon Laboratories, submitted by Union Carbide agricultural Products Co., Inc., Research Triangle Park, NC; CDL: 237875-Q).

2). Naismith, R.; Matthews, R.; Godek, E. (1979) Summary Data: Mitotic Gene Conversion-Saccharomyces cerevisiae: Study No. PH-304-AM-19-DP. (Unpublished study received Mar 26, 1979 under 264-231; prepared by Pharmakon Laboratories, submitted by Union Carbide agricultural Products Co., Inc., Research Triangle Park, NC; CDL: 237875-S)

CONCLUSION: The two mitotic gene conversion studies carried out using strain D_7 of S. cerevisiae. The first study used a broad range of 2, 4-DP concentrations (from 0.001 to 10 mg/ml); the 2nd study tested the range of concentrations from 4 to 10 mg/ml. For each dose level, 30 replicates were carried out. These two studies had been reviewed (Holder; Tox. Doc. No. 001995; Attachment 1). Additional data taken from the submission are presented in Attachment 2 to supplement the extracted data presented in the Holder review.

The data indicate that 2,4-DP caused a statistically significant increase in the number of convertants at 6, 8, and 10 mg/ml treated yeast. These increases also showed a dose-related effect, which requires no metabolic activation.

A combination of these two studies provides adequate information for a mitotic gene conversion assay in yeast and is considered as an acceptable study.

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ATTACHMENT 1

001995

§5.0 Gene Conversion in Saccharomyces Cervisiae D_7 [two experiments]. (Section P of 264-231; EPA 237875)

This test measures the unilateral replacement of a defective locus in the tryptophan operon in sister chromatids. The locus is in trp 5 where two mutations exist: trp 5-12 and trp 5-27. This organism is try -. Mutation causing normal sequences to unilaterally replace the defective locus will restore wild type activity (trp $^+$). Thus, if the cells are challenged with test compound the number of convertants that occur on trp minus medium reflect the gene conversion events. This process is normally rare occuring only once per 10^5 cells/generation, but can be greatly increased by a mutagen.

Concentrations of 2,4 DP acid employed were 10, 1, 0.1, 0.001, 0.001 mg/ml. At the high dose there was 2.3 X 10^{-4} moles/37.5 X10 cell. NQO at 10^{-6} M was the positive control and phosphate buffer was negative control.

Results were:

Exp. # 1 (Range Finding)

Conc:	0	.001	.01	0.1	1.0	10	10^{-6}M NQO
Convertants per 10^5 cell	3.4	3.1	3.6	3.2	3.0	5.6	30.7
% survival	100	89	88	86	79	59	78

Another study with the same protocol but different doses was performed. Results were:

Conc:	0	4	6	8	10	12	10^{-6} NQO
convertants per 10^{-5} cells	0.7	0.9	1.3	3.5	3.6	0.62	4.4
Survival (%)	100	83	83	77	66	18	90

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In exp. #1 it is seen that 10 mg/ml produces a significant number of mitotic gene conversions (p=.001). Concentrations of $\leq$ 1 mg/ml were ineffective. In exp. #2 the range of response was more accurately defined with 4 mg/ml being marginal and 6, 8, and 10 mg/ml showing a definite dose response (p=.001). The 12 mg/ml concentration was toxic as shown by the precipitous drop in survival (18%). It should be noted that response to the same amount of NQO in both experiments was different (30.7 in exp. #1 and 4.4 in exp.# 2). This means that the cells in exp. #1 were more responsive than those cells in exp. #2. However, this does not alter the interpretation of the results.

5.1 Conclusions: 2,4 DP acid promotes gene conversions during mitosis at concentrations $\geq$ 4.0 mg/ml causing Saccharomyces Cervisiae to mutate trp - trp +. No metabolic activation studies were presented in these studies.

5.2 Claffification of Study : Valid, only for unactivated 2,4 DP

ATTACHMENT 2

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PHARMAKON LABORATORIES (DATA TAKEN From the Submission; MRID No. 116489)

Mutagenesis Section

Saccharomyces cerevisiae

Mitotic Gene Conversion

SUMMARY DATA

Client Amchem Products, Inc.

Material 2-(2,4, Dichlorophenoxy)-propionic acid

Description Tan powder

Date Received July 5, 1978

Date Performed January 8, 1979

Pharmakon Reference 211, pgs. 37-41

CONTROLS / TEST COMPOUND

Concentration	Phosphate Buffer			10% DMSO			NCO 10^{-6}M			10 mg/ml		
Survival (%)	100			92.6			78.1			59.1		
Convertants/Plate	7	7	8	9	13	7	98	72	80	25	11	6
	10	14	8	10	9	4	77	76	82	0	13	20
	6	8	11	14	6	9	58	74	82	17	11	10
	11	9	10	2	8	7	81	75	81	15	16	12
	14	11	5	5	9	7	103	74	70	10	12	[illegible]
	7	14	3	15	9	10	82	56	85	12	15	23
	6	8	8	8	9	7	84	73	70	8	13	18
	10	8	7	11	8	10	56	66	72	17	11	12
	5	2	5	5	17	14	66	74	80	24	20	18
	10	10	10	9	9	9	77	93	85	10	14	10
Total	252			269			2332			420		
Revertants/ 10^5	3.36			3.59			30.69			5.6		
P value	--			0.7049			11.5509***			4.9822***		

Concentration	1 mg/ml			0.1 mg/ml			0.01 mg/ml			0.001 mg/ml		
Survival (%)	78.9			85.8			88.1			88.9		
Convertants/Plate	6	13	9	5	14	11	9	8	9	13	8	4
	4	16	8	4	8	7	9	6	8	8	8	4
	6	5	10	5	7	6	10	8	7	2	5	13
	9	10	5	4	6	8	16	9	13	15	5	8
	7	9	9	9	3	10	6	9	11	5	11	6
	4	10	9	15	10	17	8	10	12	8	3	11
	6	6	2	6	5	10	6	5	5	7	7	8
	4	6	9	9	6	13	9	8	12	11	8	10
	4	6	9	7	9	7	8	10	6	6	3	6
	8	6	9	11	7	7	13	7	9	6	15	6
Total	223			242			266			230		
Revertants/ 10^5	2.97			3.23			3.55			3.07		
P value	1.2281			0.4276			0.6542			0.8847		

*** Denotes statistical significance at the .001 level.

Investigator Edmund S. Dodd Date January 8, 1979 Study Director Robert W. Naismith Date January 8, 1979

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ATTACHMENT 2 (continued)

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BEST DOCUMENT AVAILABLE

PHARMAKON LABORATORIES

(DATA TAKEN From Submission, MRID No. 116491)

Mutagenesis Section

Saccharomyces cerevisiae

Mitotic Gene Conversion

SUMMARY DATA

Client: Amchem Products, Inc.

Material: 2-(2,4-Dichlorophenoxy)-proionic Acid

Description: Tan Powder

Date Received: July 5, 1978

Date Performed: January 30, 1979

Pharmakon Reference: 211, pgs. 37-41, 43-44

	CONTROLS									TEST COMPOUND														
Concentration	Phosphate Buffer			10% DMSO			NQO 10-6M			12 mg/ml*			10 mg/ml			8 mg/ml			6 mg/ml			4 mg/ml		
Survival (%)	100			95.3			89.7			18.3			66.2			6.9			83.1			82.6		
Convertants/ Plate	4	5	4	2	3	2	15	14	9	2	2	2	6	4	11	9	8	6	4	1	2	5	2	1
	1	1	7	2	2	2	7	9	17	2	2	2	0	10	9	12	13	2	4	2	3	2	4	5
	2	1	3	3	0	1	10	6	13	2	2	0	9	10	18	6	6	10	4	2	3	2	3	3
	[illegible]	2	3	3	2	1	8	7	8	0	1	1	10	9	8	5	8	17	4	5	5	1	1	2
	1	0	0	1	3	0	12	15	13	0	2	0	6	8	11	5	7	10	2	3	4	2	3	3
	1	2	1	0	0	1	9	11	5	1	1	4	6	10	3	10	18	7	4	1	3	1	1	4
	0	2	1	1	2	2	5	11	12	4	2	1	8	7	3	13	7	6	4	4	2	1	1	5
	1	3	1	0	1	0	12	11	13	2	1	0	9	13	9	15	5	7	2	5	5	3	1	2
	2	1	0	1	1	3	16	10	11	2	4	1	16	9	5	6	9	10	3	4	7	1	1	1
	1	2	0	0	1	4	16	13	12	3	1	0	17	10	13	4	14	5	3	2	2	0	3	4
Total	54			44			330			47			268			260			99			68		
Convertants/ 10^5	0.72			.58			4.4			0.62			3.57			3.46			1.32			.91		
P value	-			0.9286			13.8721***			0.6447			9.0010***			8.8532***			3.8961***			1.1954		

* dose of 12 mg/ml considered to be toxic to yeast strain D-7

*** denotes statistical significance at .001 level

Investigator Edward S. Sodik Date Jan. 30, 1979 Study Director Robert W. Naismith Date Jan. 30, 1979

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