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CENTRAL RESEARCH AND DEVELOPMENT DEPARTMENT

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Document Control Office: (WH-557)
 Chemical Information Division
 Office of Toxic Substances
 U.S. Environmental Protection Agency
 401 M Street, S.W.
 Washington, DC 20460

Gentlemen:

We are submitting information on 1,4-dichlorobutene-2 (1,4-DCB) supplementing information which was previously submitted in accordance with the provisions of Section 8(e) of the Toxic Substances Control Act. Du Pont recently conducted a chronic inhalation study in which rats were exposed to 1,4-DCB vapor for approximately six hours per day, five days per week at concentrations of 0 ppm, 0.1 ppm, 0.3 ppm or 1.0 ppm. Rats were exposed for 19 months and surviving rats were held without exposure for an additional five months. Compound-related nasal tumors were observed in all groups exposed to 1,4-DCB. Statistically significant increases in the incidences of nasal tumors were observed in all exposure groups for benign tumors and in the 1.0 ppm group for malignant tumors. When the incidences of benign and malignant tumors were combined, statistically significant increases were observed in the 0.3 ppm and 1.0 ppm groups. No other compound-related tumors were observed. Tumor type and incidence of nasal tumors for each group are shown in Table I.

This study was conducted as a result of the findings from a previous study on 1,4-DCB conducted by Du Pont (see Table II) which indicated that there were statistically significant increases in the incidences of nasal tumors in rats exposed to 0.5 ppm or 5.0/2.5 ppm*. Following the preliminary findings of the initial inhalation study which were reported to the Administrator by letter dated October 7, 1977, communications were made to our employees and to other producers of 1,4-DCB. We also undertook a program to assure that workplace exposures would not exceed 0.05 ppm eight-hour and twelve-hour time-weighted average.

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An epidemiology study was also conducted that followed approximately 600 workers from 1956 through 1982 for cancer incidence, and 1957 through 1980 for mortality, and did not indicate that employees are at an increased risk of developing cancer.

In view of the findings in our second animal study, we are supplementing previous information reported to the Administrator. A final report is being prepared and will be submitted when completed.

We plan to advise our employees and other manufacturers of 1,4-DCB of our findings. We also are reviewing our current workplace exposure limit in view of these results.

We are sending a copy of this letter to OSHA, NIOSH and NCI.

Please contact me if you have any questions concerning this matter.

Sincerely,

Charles F. Reinhardt

Charles F. Reinhardt, M.D.

CFR:cmk
Enc.

- * Rats in the high concentration groups were exposed to 5.0 ppm for 30 weeks followed by 2.5 ppm for 23 weeks at which time exposures were terminated and the animals held for an additional 52 weeks.

CC: Dr. Vincent DeVita, Jr.
Director
National Cancer Institute

Dr. J. Donald Miller
Director
National Institute of Occupational
Safety and Health

Mr. Patrick R. Tyson
Acting Assistant Secretary
Occupational Safety and Health Administration

TABLE 1

NASAL TUMORS OBSERVED IN LONG-TERM TOXICOLOGY STUDY IN MICE WITH 1,4-DICHLOROBENZENE

Group: Dose (ppm): No. of nasal cavities examined:	12		24	
	1	0	1	0
	159	159	146	146
Benign tumors: Adenoma	0	3	12	30
Incidence of benign tumors:	0/159 (0%)	3/146 (2.12)%	12/146 (8.23)%	30/126 (23.81)%
Malignant tumors:				
Adenocarcinoma:	0	0	2	11
Carcinosarcoma:	0	0	0	3
Mixed carcinoma:	0	0	0	3
Sarcoma, unclassified:	1	0	0	0
Spindle cell sarcoma:	0	1	0	0
Rhabdomyosarcoma	0	0	0	1
Incidence of malignant tumors	1/159 (0.62)	1/146 (0.72)	2/146 (1.37)	16/126 (12.70)%
Total number of animals with nasal tumors	1	4	14	30
Incidence of animals with nasal tumors	1/159 (0.62)	4/146 (2.72)	16/146 (9.58)%	30/126 (23.81)%

* Significantly increased ($p < 0.05$) by method of Peto et al. (IARC monograph 1980)

TABLE II

NASAL TUMORS OBSERVED IN LONG-TERM RAT INHALATION STUDY (STUDY #1)Males

	Group:	I	III	V
	Dose (ppm):	0	0.5	5.0-2.5*
No. of nasal cavities examined:		128	130	130
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Benign Tumors: ^b		0	23	2
Incidence of benign tumors		0%	25.4%*	1.5%
Malignant Tumors: ^c		0	11	114
Incidence of malignant tumors		0%	8.5%*	87.7%*
Total number of animals with nasal tumors:		0	42	114
Incidence of animals with nasal tumors		0%	32.3%*	87.7%*

Females

	Group:	II	IV	VI
	Dose (ppm):	0	0.5	5.0-2.5*
No. of nasal cavities examined:		129	128	128
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Benign Tumors:		0	23	5
Incidence of benign tumors		0%	18.0%*	3.9%*
Malignant Tumors:		0	2	113
Incidence of malignant tumors		0%	1.6%	88.3%*
Total number of animals with nasal tumors		0	24	113
Incidence of animals with nasal tumors		0%	18.8%*	88.3%*

* Denotes tumor incidence significantly ($p < 0.05$) increased over control incidence by Fisher's Exact test.

^a Rats were exposed to 5 ppm for 30 weeks followed by 2.5 ppm for 23 weeks at which time exposures were terminated and the rats were held for an additional 52 weeks.

^b Types of benign tumors diagnosed included adenoma and hemangioma.

^c Types of malignant tumors diagnosed included adenocarcinoma/carcinoma, squamous cell carcinoma, mixed carcinoma, carcinosarcoma and rhabdomyosarcoma.