INDUSTRIAL HYGIENE FOUNDATION OF AMERICA, INC.

MELLON INSTITUTE, 4400 FIFTH AVENUE

PITTSBURGH 13, PA.

Report on

A COMPARISON OF THE SUBACUTE INHALATION TOXICITY OF ETHYLENE DICHLORIDE, TRICHLOROETHYLENE, AND A MIXTURE OF THE TWO

for

PITTSBURGH PLATE GLASS COMPANY

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by

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SL 082907

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INTRODUCTION

This report presents data and conclusions on the subacute inhalation toxicity of a mixture of trichloroethylene (67%) and ethylene dichloride (33%) containing a stabilizing system. The objective of the study was to determine if there is significant synergistic action, as revealed by behavioral, growth, mortality, and pathological data, on laboratory animals exposed to the vapors of the mixture. The effects were evaluated by comparing the response on a group of rats subjected to the vapors of the mixture during daily exposures with the effect on rats similarly exposed to trichloroethylene and ethylene dichloride vapors, alone.

Adams, Spencer, et al[1, 2] reported that rats exposed to 400 ppm of ethylene dichloride for three, daily, seven-hour exposures had a mortality of 60%, a rapid loss in body weight, a slight increase in liver and kidney weights, and upon histopathological examination revealed slight cloudy swelling of the liver with a few large fat vacuoles but no kidney damage. Rats exposed to 200 ppm of ethylene dichloride tolerated 151 exposures in 212 days and showed no evidence of adverse effects as judged by general appearance and behavior, growth, mortality, or histopathological examination. In exposures to trichloroethylene groups of rats tolerated 400 ppm for as many as 173 exposures in 243 days without evidence of adverse effects as judged by mortality or general appearance and behavior. Growth curves were slightly depressed, liver and kidney weights were increased, but no

significant changes were observed in any tissue upon histopathological examination. Rats exposed to 200 ppm of trichloroethylene tolerated as many as 151 exposures in 205 days without adverse effects as judged by general appearance and behavior, mortality, growth, organ weights, and histopathological examination of tissues.

On the basis of these studies it was decided to employ the effects on rats exposed to ethylene dichloride, the more toxic of the two solvents, as the point of reference in this study. Since at the 400 ppm concentration level the trichloroethylene rats exhibited a greater increase in liver and kidney weights than the ethylene dichloride but upon histopathological examination showed no lesions while the ethylene dichloride did, organ weights were considered irrelevant to this study. The effects considered of prime significance in this study are growth, mortality, and pathological. A concentration and length of daily exposure of ethylene dichloride was chosen so as to produce a response severe enough to cause some mortality by three weeks and sufficient data to terminate the study after approximately one month. The length of daily exposures were to be increased if effects were not adequate. The same volume of liquid as was evaporated to yield the ethylene dichloride concentration was used for trichloroethylene and the mixtures of ethylene dichloride and trichloroethylene so that the exposures were comparable on the basis of liquid vaporized. Each group of rats was thus exposed to the same liquid volume of its respective solvent for equal periods of time.

MATERIALS AND METHODS

A five gallon drum each of the Trichloroethylene-Ethylene Dichloride Mixture, Reference No. 61701-3-213-231, hereafter referred to as the mixture; of Trichloroethylene, Reference No. 61701-3-213-230, hereafter referred to as TCE; and of Ethylene Dichloride, Reference No. 61712-3-213-232, hereafter referred to as EDC was received for testing.

The apparatus consisted of three, seven-cubic-foot, stainless steel chambers, three vapor generating units, and analytical chemical equipment. Each chamber contained five animal cages, had a glass-windowed door for observation of the animals during exposure, and was constructed to maintain the animals twenty-four hours per day. Each vapor-generating unit was composed of a monodrum mechanism,[3] a single syringe feeder,[4] a glass Graham condenser, and glass and tygon tubing connections. The monodrum mechanism drove the single syringe feeder, which contained the solvent, at a calculated, constant rate, delivering the required amount of chemical into the condenser. Hot water was passed through the outer jacket of the condenser and as the solvent was dropped into its spiral, tubular center, it was evaporated, mixed with air, and drawn through the chamber. The calculated vapor concentrations were in good agreement with the results of analysis by combustion and determination of total halogen colorimetrically using mercuric chloranilate.[5]

Twenty-five male, albino rats were exposed to each compound. They were fed ad libitum on Purina Lab Chow except during the exposure when water and feed were withheld. The rats were weighed each morning before the exposure. Animals that died during the testing period and those sacrificed terminally were subjected to autopsy and the lungs, livers, and kidneys were dissected for histopathological preparation and examination.

The experimental conditions are presented in Table 1. As subnoted in the table, the length of exposure was increased during the study from five hours per day to eventually seven hours per day in order to produce more significant effects within the proposed one-month period. The EDC concentration, upon which the concentrations of the other solvents were based, was held constant during the study at 300 ppm, midway between the 200 ppm no effect level and the 400 ppm, 60% mortality level.

Table 1 -- Exposure Conditions

Solvent	Concentration			Length of Exposure		
				Daily	Actual Exposure	Overall Period
	ml./l.	mg./l.	ppm	(hrs)	(days)	(days)
EDC	0.000951	1.194	301	5-7*	24	32
TCE	0.0009502	1.392	260	5-7	24	32
Mixture	0.000952	(EDC 0.395	100	5-7	24	32
		(TCE 0.934	174			

* See text for explanation of variation.

RESULTS

The mortality data are presented in Table 2.

Table 2 -- Exposure Results

Solvent	Weight Data		Mortality Data			
	Original Average (gms.)	Final Average (gms.)	Extraneous No.	Extraneous %	Experimental No.	Experimental %
EDC	200	278	1	4	12	48
TCE	200	312	0	0	2	8
Mixture	200	307	1	4	0	0

The striking lethal effect of the EDC (48%) is shown in contrast to the lower mortality of TCE (8%) and the absence of experimental death for the mixture. The extraneous deaths occurred during the second week of exposure and were of probable bacterial origin showing signs of severe pneumonia and slight empyema. The experimental TCE deaths occurred during the third and final weeks of the test period. Five of the experimental EDC deaths occurred during the third week and seven during the final week. Table 2 also shows that the increase in weight of the TCE and mixture exposed rats significantly exceeds that of the EDC exposed rats. The difference in growth effect is graphically presented in Figure 1. The following points should be noted: The three curves were distinct following the third day of exposure but even after three weeks their difference was not of a high level

of significance. After increasing the exposure periods to seven hours there was a definite effect on growth. Concern over the possible killing of all of the EDC exposed rats brought about trials with different lengths of exposure periods during the third week. However, it was finally decided to continue the exposure length at seven hours during the remainder of the study. The sharp dips in the EDC growth curve (mean weight) are due to acute weight losses in a number of severely affected rats. The subsequent sharp rises in the curve are due to the removal of the animals from subsequent calculation of the mean weight after their deaths.

The kidneys and livers of five of the EDC fatalities were examined microscopically. All showed severe renal tubular necrosis, enough to account for the death of the animals. One animal showed, in addition, hepatic necrosis.

Ten of the surviving animals were also similarly examined. All three groups were represented and no significant or constant renal or hepatic lesions were found.

The lungs of the surviving animals, however, showed minor degrees of focal chronic interstitial pneumonitis, characterized by cellular proliferation and desquamation.

CONCLUSIONS

Rats exposed for the same period of time and to the same vaporized volume of a TCE (67%)-EDC(33%) mixture as those exposed to EDC and TCE alone, exhibited a lower mortality rate than either and a growth rate intermediate between the two. Volume for volume, the mixture was less toxic than EDC alone, and was similar in toxicity to TCE, the major constituent of the mixture.

Hence, the toxicity of the mixture was essentially that which would be expected from a simple summation of the toxicities of the constituents. These results are in general agreement with other studies[6, 7] of toxicities of mixtures of halogenated and other organic solvents.

REFERENCES

1. Adams, E. M., et al: Vapor Toxicity of Trichloroethylene Determined by Experiments on Laboratory Animals. A.M.A. Arch. Ind. Hyg. & Occ. Med. 4, 469, 1951.

2. Spencer, H. C., et al: Vapor Toxicity of Ethylene Dichloride Determined by Experiments on Laboratory Animals. A.M.A. Arch. Ind. Hyg. & Occ. Med. 4, 482, 1951.

3. Monodrum Apparatus manufactured by Gorrell & Gorrell, Westwood, N.J.

4. Single-Syringe-Feeder manufactured by Modern Metalcraft, Midland, Mich.

5. Method for the Determination of Chloride Using Mercuric Chloranilate. Fisher Scientific Company Technical Data Sheet.

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7. Pozzani, U.C., et al: The Toxicological Basis of Threshold Limit Values: 5. The Experimental Inhalation of Vapor Mixtures by Rats, with Notes Upon Relationship Between Single Dose Inhalation and Single Dose Oral Data. Am. Ind. Hyg. Assoc. J. 20, 364, 1959.

Figure 1 -- Growth Effects

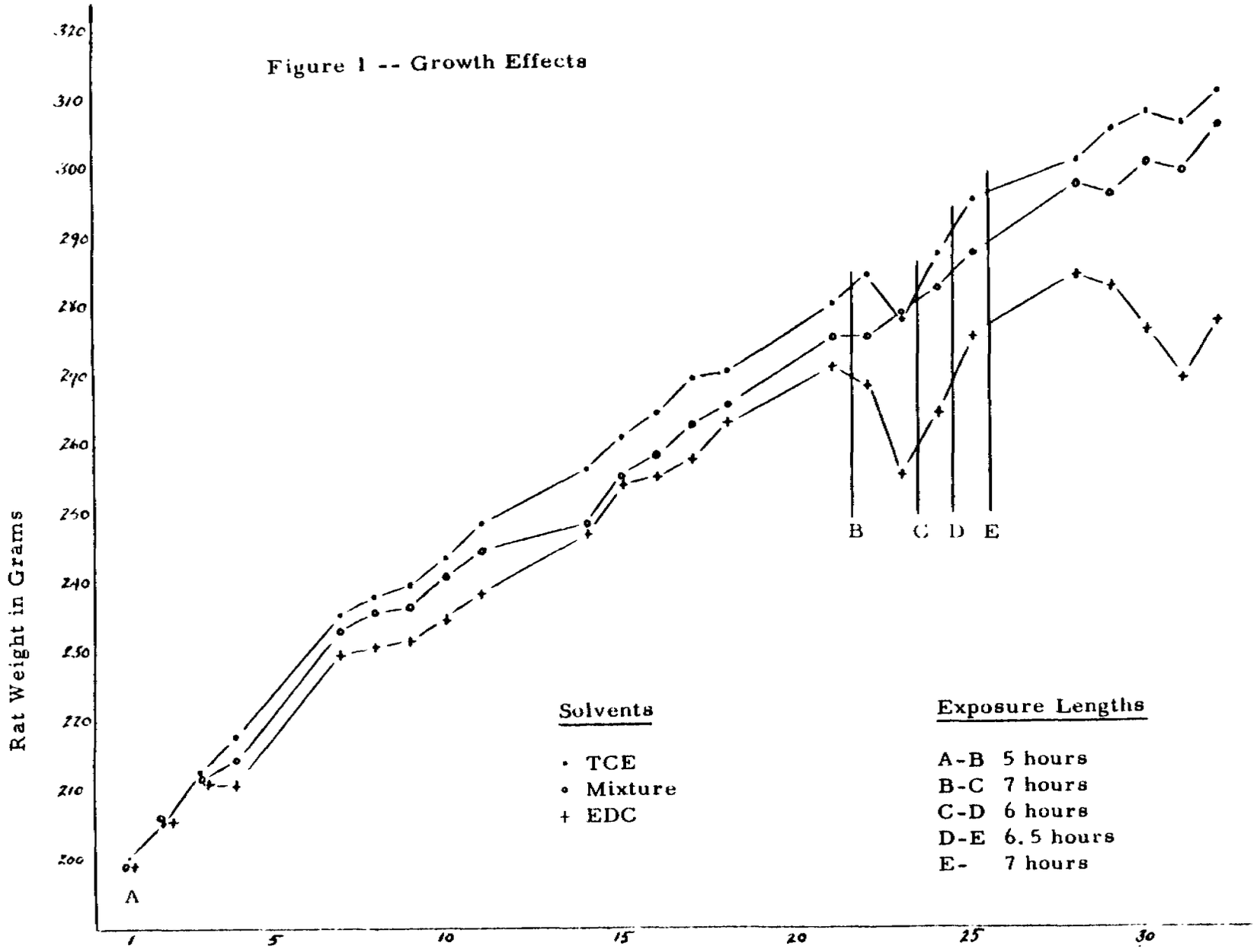

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TABLE 84 - Urinary leukocytes in control and ECD-exposed male rats.

Group 1		Group 2		Group 3		Group 4		Group 5	
Rat N°		Rat N°		Rat N°		Rat N°		Rat N°	
1215	1	1245	2	1275	1	1303	2	1333	1
1217	1	1246	1	1277	1	1304	1	1334	2
1218	1	1247	1	1278	2	1305	1	1335	3
1219	1	1248	2	1279	2	1306	2	1336	2
1220	1	1250	2	1280	2	1307	2	1338	2
1221	2	1251	1	1281	1	1308	2	1340	2
1222	2	1252	1	1282	1	1309	2	1341	1
1224	2	1253	1	1285	1	1310	3	1342	1
$\bar{X}$	1.38		1.38		1.38		1.88		1.75
S.E.									

0 = absent
1 = traces
2 = discrete quantitaties

TABLE 85 - Urinary crystals in control and ECD-exposed female rats.

Group 1		Group 2		Group 3		Group 4		Group 5	
Rat N°		Rat N°		Rat N°		Rat N°		Rat N°	
1201	1	1231	2	1262	2	1291	1	1321	3
1203	1	1233	1	1263	2	1292	2	1323	2
1204	0	1234	2	1264	2	1293	1	1325	2
1205	0	1235	2	1265	2	1294	0	1326	1
1208	2	1237	2	1266	1	1295	0	1327	3
1209	1	1238	2	1267	2	1297	2	1328	2
1210	2	1240	2	1270	2	1298	1	1330	2
1212	1	1242	1	1271	1	1299	2	1332	1
$\bar{X}$	1.00		1.75		1.75		1.13		2.00

0 = absent
1 = traces
2 = discrete quantitaties
3 = high quantity

SL 082920

TABLE 86 - Urinary crystals in control and ECD-exposed male rats.

Group 1		Group 2		Group 3		Group 4		Group 5	
Rat N°		Rat N°		Rat N°		Rat N°		Rat N°	
1215	2	1245	1	1273	2	1303	1	1333	3
1217	0	1246	2	1277	2	1304	1	1334	2
1218	0	1247	2	1278	2	1305	4	1335	2
1219	2	1248	1	1279	1	1306	2	1336	1
1220	1	1250	1	1280	2	1307	2	1338	1
1221	1	1251	1	1281	2	1308	1	1340	3
1222	1	1252	1	1282	2	1309	2	1341	3
1224	1	1253	1	1285	1	1310	2	1342	2
$\bar{X}$	1.00		1.25		1.75		1.88		2.13
S.E.									

0 = absent
1 = traces
2 = discrete quantitaties
3 = high quantity
4 = very high quantity

SL 082921

TABLE 87 - Urinary erythrocytes in control and ECD-exposed female rats.

Group 1		Group 2		Group 3		Group 4		Group 5	
Rat N°		Rat N°		Rat N°		Rat N°		Rat N°	
1201	0	1231	0	1262	0	1291	0	1321	0
1203	0	1233	0	1263	0	1292	0	1323	0
1204	0	1234	0	1264	0	1293	0	1325	0
1205	0	1235	0	1265	0	1294	0	1326	0
1208	0	1237	0	1266	0	1295	0	1327	0
1209	0	1238	0	1267	0	1297	0	1328	0
1210	0	1240	0	1270	0	1298	0	1330	0
1212	0	1242	0	1271	0	1299	0	1332	0
$\bar{X}$	0		0		0		0		0
S.E.									

0 = absent

TABLE 88 - Urinary erythrocytes in control and ECD-exposed male rats.

Group 1		Group 2		Group 3		Group 4		Group 5	
Rat N°		Rat N°		Rat N°		Rat N°		Rat N°	
1215	0	1245	0	1273	0	1303	0	1333	0
1217	0	1246	0	1277	0	1304	0	1334	0
1218	0	1247	0	1278	0	1305	2	1335	0
1219	0	1248	0	1279	0	1306	0	1336	0
1220	0	1250	0	1280	0	1307	0	1338	0
1221	0	1251	0	1281	0	1308	0	1340	0
1222	0	1252	0	1282	0	1309	0	1341	0
1224	0	1253	0	1285	0	1310	0	1342	0
$\bar{X}$	0		0		0		0		0
S.E.									

0 = absent
1 = traces
2 = discrete quantitaties

SL 082923

TABLE 89 - Urinary mucus in control and ECD-exposed female rats.

Group 1		Group 2		Group 3		Group 4		Group 5	
Rat N°		Rat N°		Rat N°		Rat N°		Rat N°	
1201	1	1231	1	1262	1	1291	1	1321	3
1203	1	1233	1	1263	2	1292	1	1323	1
1204	1	1234	2	1264	1	1293	1	1325	1
1205	2	1235	2	1265	2	1294	1	1326	3
1208	1	1237	1	1266	1	1295	0	1327	3
1209	1	1238	1	1267	1	1297	2	1328	2
1210	1	1240	2	1270	1	1298	2	1330	2
1212	2	1242	1	1271	1	1299	1	1332	3
$\bar{X}$	1.50		1.38		1.25		1.00		2.25

0 = absent
1 = traces
2 = discrete quantitaties
3 = high quantity

SL 082924

TABLE 90 - Urinary mucus in control and ECD-exposed male rats.

Group 1		Group 2		Group 3		Group 4		Group 5	
Rat N°		Rat N°		Rat N°		Rat N°		Rat N°	
1215	2	1245	1	1273	1	1303	1	1333	2
1217	2	1246	1	1277	1	1304	2	1334	2
1218	1	1247	2	1278	1	1305	1	1335	1
1219	1	1248	2	1279	3	1306	1	1336	1
1220	1	1250	1	1280	2	1307	1	1338	2
1221	2	1251	1	1281	1	1308	1	1340	1
1222	1	1252	1	1282	1	1309	1	1341	1
1224	1	1253	1	1285	1	1310	2	1342	3
$\bar{X}$	1.38		1.25		1.25		1.25		1.63

0 = absent
1 = traces
2 = discrete quantitaties
3 = high quantity

SL 082925

TABLE 91 - Urinary epithelial cells in control and ECD-exposed female rats.

Group 1		Group 2		Group 3		Group 4		Group 5	
Rat N°		Rat N°		Rat N°		Rat N°		Rat N°	
1201	1	1231	1	1262	2	1291	1	1321	1
1203	1	1233	1	1263	2	1292	1	1323	2
1204	1	1234	1	1264	2	1293	2	1325	2
1205	1	1235	2	1265	1	1294	1	1326	3
1208	2	1237	1	1266	1	1295	1	1327	1
1209	1	1238	1	1267	1	1297	1	1328	1
1210	2	1240	2	1270	1	1298	1	1330	2
1212	2	1242	1	1271	1	1299	2	1332	1
$\bar{X}$	1.38		1.25		1.38		1.25		1.63

0 = absent
1 = traces
2 = discrete quantitaties
3 = high quantity

SL 082926

TABLE 92 - Urinary epithelial cells in control and ECD-exposed male rats.

Group 1		Group 2		Group 3		Group 4		Group 5	
Rat N°		Rat N°		Rat N°		Rat N°		Rat N°	
1215	1	1245	1	1273	1	1303	0	1333	1
1217	1	1246	1	1277	1	1304	1	1334	2
1218	1	1247	2	1278	1	1305	2	1335	2
1219	2	1248	2	1279	1	1306	1	1336	1
1220	2	1250	1	1280	1	1307	1	1338	1
1221	1	1251	1	1281	1	1308	2	1340	2
1222	1	1252	2	1282	1	1309	2	1341	2
1224	1	1253	2	1285	1	1310	1	1342	1
$\bar{X}$	1.25		1.50		1.00		1.25		1.50

0 = absent

1 = traces

2 = discrete quantitaties

TABLE 93 - Urinary microorganisms in control and ECD-exposed female rats.

Group 1		Group 2		Group 3		Group 4		Group 5	
Rat N°		Rat N°		Rat N°		Rat N°		Rat N°	
1201	1	1231	1	1262	1	1291	1	1321	2
1203	1	1233	2	1263	2	1292	1	1323	2
1204	1	1234	2	1264	1	1293	1	1325	3
1205	2	1235	1	1265	1	1294	1	1326	4
1208	1	1237	1	1266	1	1295	1	1327	2
1209	1	1238	2	1267	1	1297	2	1328	2
1210	1	1240	1	1270	1	1298	1	1330	2
1212	1	1242	1	1271	1	1299	2	1332	2
$\bar{X}$	1.13		1.38		1.13		1.25		2.38

0 = absent
1 = traces
2 = discrete quantitaties
3 = high quantity
4 = very high quantity

SL 082928

TABLE 94 - Urinary microorganisms in control and ECD-exposed male rats.

Group 1		Group 2		Group 3		Group 4		Group 5	
Rat N°		Rat N°		Rat N°		Rat N°		Rat N°	
1215	2	1245	1	1273	2	1303	2	1333	2
1217	2	1246	2	1277	2	1304	1	1334	4
1218	1	1247	2	1278	2	1305	4	1335	2
1219	1	1248	1	1279	1	1306	1	1336	2
1220	1	1250	2	1280	1	1307	1	1338	4
1221	1	1251	1	1281	1	1308	1	1340	2
1222	1	1252	2	1282	1	1309	1	1341	4
1224	1	1253	1	1285	1	1310	2	1342	3
$\bar{X}$	1.25		1.50		1.38		1.63		2.88
S.E.									

0 = absent
1 = traces
2 = discrete quantitaties
3 = high quantity
4 = very high quantity

SL 082929

TABLE 1

Experiment BT501 : Exposure by inhalation to Dichloroethane in air at 250-150, 50, 10, 5 ppm, 7 hours daily, 5 days weekly, for 78 weeks.
Results after 104 weeks.

DISTRIBUTION OF THE DIFFERENT TYPES OF TUMOURS

(first part)

		ANIMALS (Sprague-Dawley rats, 12 weeks old at start)				ANIMALS WITH TUMOURS																
						Mammary tumours (c)			Zymbal gland carcinomas			Dermatofibromas			Leukaemias			Other tumours			Total (g)		
	Sex	No. at start	No. survivors	Corrected number (b)	Total No.	% (d)	Average latency time (weeks) (e)	Total No.	% (d)	Average latency time (weeks) (f)	Total No.	% (d)	Average latency time (weeks) (f)	Total No.	% (d)	Average latency time (weeks) (f)	Total No.	Benign No.	Malignant No.	No.	% (d)	No. of different tumours/ tumours bearing animals
250-150 ppm (a)	♂	90	1	89	10	11.2	91.2	0	–	–	4	4.5	57.0	0	–	–	3	2	1	15	16.8	1.1
	♀	90	1	90	52	57.7	78.6	2	2.2	78.0	0	–	–	0	–	–	8	3	5	52	57.7	1.2
	♂ and ♀	180	2	179	62	34.6	80.6	2	1.1	78.0	4	2.2	57.0	0	–	–	11	5	6	67	37.4	1.2
50 ppm	♂	90	8	90	8	8.9	67.5	0	–	–	6	6.7	66.0	1	1.1	80.0	7	6	1	17	18.9	1.3
	♀	90	7	90	55	61.1	76.7	1	1.1	86.0	0	–	–	1	1.1	48.0	5	3	2	59	65.5	1.0
	♂ and ♀	180	15	180	63	35.0	75.6	1	0.5	86.0	6	3.3	66.0	2	1.1	64.0	12	9	3	76	42.2	1.1
a	♂	90	2	89	5	5.6	60.8	0	–	–	1	1.1	58.0	2	2.2	34.0	4	1	3	11	12.3	1.1
	♀	90	7	90	43	47.8	79.9	0	–	–	0	–	–	0	–	–	3	2	1	43	47.8	1.1
	♂ and ♀	180	9	179	48	26.8	77.9	0	–	–	1	0.5	58.0	2	1.1	34.0	7	3	4	54	30.2	1.1
	♂	90	13	90	6	6.7	93.7	0	–	–	5	5.6	52.8	0	–	–	9	6	3	18	20.0	1.1
	♀	90	13	90	64	71.1	82.6	2	2.2	47.0	0	–	–	5	5.6	75.2	5	2	3	69	76.7	1.1
	♂ and ♀	180	26	180	70	38.9	83.6	2	1.1	47.0	5	2.8	52.8	5	2.8	75.2	14	8	6	87	48.3	1.1
rols in embers	♂	90	3	90	7	7.8	87.4	1	1.1	78.0	2	2.2	53.0	1	1.1	37.0	6	4	2	14	15.5	1.2
	♀	90	3	90	36	40.0	81.2	0	–	–	0	–	–	3	3.3	66.3	4	2	2	38	42.2	1.1
	♂ and ♀	180	6	180	43	23.9	82.2	1	0.5	78.0	2	1.1	53.0	4	2.2	59.5	10	6	4	52	28.9	1.1
Controls	♂	90	2	90	4	4.4	84.5	1	1.1	74.0	0	–	–	0	–	–	6	6	0	11	12.2	1.0
	♀	90	12	90	47	52.2	82.7	0	–	–	0	–	–	3	3.3	79.3	5	2	3	49	54.4	1.1
	♂ and ♀	180	14	180	51	28.3	82.8	1	0.5	74.0	0	–	–	3	1.7	79.3	11	8	3	60	33.3	1.1
V and VI Controls	♂	180	5	180	11	6.1	86.3	2	1.1	76.0	2	1.1	53.0	1	0.5	37.0	12	10	2	25	13.9	1.1
	♀	180	15	180	83	46.1	82.0	0	–	–	0	–	–	6	3.3	72.0	9	4	5	87	48.3	1.1
	♂ and ♀	360	20	360	94	26.1	82.5	2	0.5	76.0	2	0.5	53.0	7	1.9	67.7	21	14	7	112	31.1	1.1
Total		1.080	72	1.078																		

TABLE 1

Experiment BT501 : Exposure by inhalation to Dichloroethane in air at 250-150, 50, 10, 5 ppm, 7 hours daily, 5 days weekly, for 78 weeks.
Results after 104 weeks.

DISTRIBUTION OF THE DIFFERENT TYPES OF TUMOURS

(second part)

(a) After few weeks the dose was reduced to 150 ppm, because of the too high toxicity at 250 ppm level.

(b) Alive animals after 12 weeks, when the first tumour (a mammary carcinoma) was observed.

(c) Two or more tumours of the same and/or different types (fibroadenomas, carcinomas, sarcomas, carcinosarcomas) may be present in the same animal.

(d) The percentages are referred to the corrected number.

(e) Average age at the onset of the first mammary tumour per animal, detected at the periodic control or at autopsy.

(f) Average time from the start of the experiment to the detection at the periodic control or at autopsy.

(g) Several animals with two or more tumours.

TABLE 2

Experiment BT501 : Exposure by inhalation to Dichloroethane in air at 250-150, 50, 10, 5 ppm
7 hours daily, 5 days weekly, for 78 weeks.
Results after 104 weeks.

DISTRIBUTION OF THE DIFFERENT TYPES OF MAMMARY TUMOURS

(second part)

(a) After few weeks the dose was reduced to 150 ppm, because of the too high toxicity at 250 ppm level.

(b) Alive animals after 12 weeks, when the first tumour (a mammary carcinoma) was observed.

(c) Two or more tumours of the same and/or different types (fibroadenomas, carcinomas, sarcomas, carcinosarcomas) may be present in the same animal.

(d) The percentages are referred to the corrected number.

(e) Average age at the onset of the first mammary tumour per animal, detected at the periodic control or at autopsy.

(f) The percentages are referred to total number of animals bearing mammary tumours.

(g) The percentages are referred to total number of animals bearing mammary tumours, histologically examined.

TABLE 3

Experiment BT501 : Exposure by inhalation to Dichloroethane in air at 250-150, 50, 10, 5 ppm, 7 hours daily, 5 days weekly, for 78 weeks. Results after 104 weeks.

DISTRIBUTION OF THE DIFFERENT TYPES OF MISCELLANEOUS ("OTHER") TUMOURS

	Sex	ANIMALS BEARING OTHER TUMOURS				
		Benign		Malignant		Total
		No.	Distribution of histotypes	No.	Distribution of histotypes	
	♂	2	1 Zymbal gland adenoma 1 pheochromocytoma	1	1 peritoneal fibrosarcoma	3
	♀	3	1 Zymbal gland adenoma 1 luteoma 1 adenoma of the uterus	5	1 adenocarcinoma of stomach 1 adrenal gland cortical adenocarcinoma 1 granulosa cells carcinoma of ovary 1 adenocarcinoma of the uterus 1 squamous carcinoma of the uterus	8
	♂	6	2 skin cystic acanthomas 1 forestomach papilloma 1 adrenal gland cortical adenoma 1 pheochromocytoma 1 Leydig cells tumour	1	1 skin basocellular carcinoma	7
	♀	3	1 skin cystic acanthoma 1 Zymbal gland adenoma 1 polypus of the colon	2	1 fibrosarcoma of the uterus 1 peritoneal mesothelioma	5
III	♂	1	1 adrenal gland cortical adenoma	3	1 skin squamous carcinoma 1 adrenal gland cortical adenocarcinoma 1 pleural mesothelioma	4
	♀	2	1 forestomach papilloma 1 pheochromocytoma	1	1 adenocarcinoma of the uterus	3
IV	♂	6	1 forestomach acanthoma 1 cholangioma 1 adrenal gland cortical adenoma 2 Leydig cells tumours 1 ganglioneuroma	3	1 subcutaneous fibrosarcoma 1 nephroblastoma 1 neurilemoma	9
	♀	2	1 Zymbal gland adenoma 1 liver histiocytosis	3	1 intestinal fibrosarcoma 1 granulosa cells carcinoma of ovary 1 adenocarcinoma of the uterus	5
V	♂	4	1 skin cystic acanthoma 1 subcutaneous lipoma 1 forestomach acanthoma 1 pheochromocytoma	2	1 skin fibrosarcoma 1 meningioma	6
	♀	2	1 skin cystic acanthoma 1 forestomach acanthoma	2	1 subcutaneous rhabdomyosarcoma 1 squamous carcinoma of the uterus	4
VI	♂	6	1 skin acanthoma 1 skin cystic acanthoma 2 Zymbal gland adenomas 1 subcutaneous lipoma 1 benign neurilemoma	0		6
	♀	2	2 adrenal gland cortical adenomas	3	1 liver fibrosarcoma 1 adenocarcinoma of the uterus 1 neurilemoma	5
V and VI	♂	10	1 skin acanthoma 2 skin cystic acanthomas 2 Zymbal gland adenomas 2 subcutaneous lipomas 1 forestomach acanthoma 1 pheochromocytoma 1 benign neurilemoma	2	1 skin fibrosarcoma 1 meningioma	12
	♀	4	1 skin cystic acanthoma 1 forestomach acanthoma 2 adrenal gland cortical adenomas	5	1 subcutaneous rhabdomyosarcoma 1 liver fibrosarcoma 1 adenocarcinoma of the uterus 1 squamous carcinoma of the uterus 1 neurilemoma	9

TABLE 4

Experiment BT501 : Exposure by inhalation to Dichloroethane in air at 250-150, 50, 10, 5 ppm, 7 hours daily, 5 days weekly, for 78 weeks.
Results after 104 weeks.

INCIDENCE OF PITUITARY ADENOMATOUS GROWTH

GROUPS NO.	CONCEN-TRATION	ANIMALS (Sprague-Dawley rats, 12 weeks old at start)				PITUITARY ADENOMATOUS GROWTH	
		Sex	No.at start	No.survivors	Corrected number (b)	No.	%
I	250-150 ppm (a)	♂	90	1	89	1	1.1
		♀	90	1	90	0	-
		♂ and ♀	180	2	179	1	0.5
II	50 ppm	♂	90	8	90	0	-
		♀	90	7	90	7	7.8
		♂ and ♀	180	15	180	7	3.9
III	10 ppm	♂	90	2	89	0	-
		♀	90	7	90	3	3.3
		♂ and ♀	180	9	179	3	1.7
IV	5 ppm	♂	90	13	90	3	3.3
		♀	90	13	90	8	8.9
		♂ and ♀	180	26	180	11	6.1
V	Controls in chambers	♂	90	3	90	2	2.2
		♀	90	3	90	5	5.5
		♂ and ♀	180	6	180	7	3.9
VI	Controls	♂	90	2	90	1	1.1
		♀	90	12	90	7	7.8
		♂ and ♀	180	14	180	8	4.4
V and VI	Controls	♂	180	5	180	3	1.7
		♀	180	15	180	12	6.7
		♂ and ♀	360	20	360	15	4.2
Total			1.080	72	1.078		

(a) After few weeks the dose was reduced to 150 ppm, because of the too high toxicity at 250 ppm level.

(b) Alive animals after 12 weeks, when the first tumour (a mammary carcinoma) was observed.

SI 082935

TABLE 5

Experiment BT501 : Exposure by inhalation to Dichloroethane in air at 250-150, 50, 10, 5 ppm, 7 hours daily, 5 days weekly, for 78 weeks.
Results after 104 weeks.

INCIDENCE OF TERMINAL BRONCHIOLI HYPERPLASIA

GROUPS NO.	CONCEN-TRATION	ANIMALS (Sprague-Dawley rats, 12 weeks old at start)				TERMINAL BRONCHIOLI HYPERPLASIA (TBH)	
		Sex	No.at start	No.survivors	Corrected number (b)	No.	% (c)
I	250-150 ppm (a)	♂	90	1	89	0	-
		♀	90	1	90	2	2.2
		♂ and ♀	180	2	179	2	1.1
II	50 ppm	♂	90	8	90	2	2.2
		♀	90	7	90	5	5.5
		♂ and ♀	180	15	180	7	3.9
III	10 ppm	♂	90	2	89	0	-
		♀	90	7	90	10	11.1
		♂ and ♀	180	9	179	10	5.6
IV	5 ppm	♂	90	13	90	4	4.4
		♀	90	13	90	2	2.2
		♂ and ♀	180	26	180	6	3.3
V	Controls in chambers	♂	90	3	90	3	3.3
		♀	90	3	90	3	3.3
		♂ and ♀	180	6	180	6	3.3
VI	Controls	♂	90	2	90	4	4.4
		♀	90	12	90	6	6.7
		♂ and ♀	180	14	180	10	5.5
V and VI	Controls	♂	180	5	180	7	3.9
		♀	180	15	180	9	5.0
		♂ and ♀	360	20	360	16	4.4
Total			1.080	72	1.078		

(a) After few weeks the dose was reduced to 150 ppm, because of the too high toxicity at 250 ppm level.

(b) Alive animals after 12 weeks, when the first tumour (a mammary carcinoma) was observed.

SL 082936

TABLE 6

. Experiment BT502 : Exposure by inhalation to Dichloroethane in air at 250-150, 50, 10, 5 ppm, 7 hours daily, 5 days weekly, for 78 weeks.
Results after 104 weeks.

DISTRIBUTION OF THE DIFFERENT TYPES OF TUMOURS

1 (first part)

GROUPS NO.	CONCENTRATION	ANIMALS (Swiss mice, 11 weeks old at start)				ANIMALS WITH TUMOURS														
						Mammary tumours			Pulmonary adenomas			Leukaemias			Other tumours			Total (e)		
		Sex	No. at start	No. survivors	Corrected number (b)	Total No.	% (c)	Average latency time (weeks) (d)	Total No.	% (c)	Average latency time (weeks) (d)	Total No.	% (c)	Average latency time (weeks) (d)	Total No.	Benign No.	Malignant No.	No.	% (c)	No. of different tumours/ tumours bearing animals
I	250-150 ppm (a)	♂	90	2	83	0	-	-	0	-	-	1	1.2	77.0	1	0	1	2	2.4	1.0
		♀	90	0	85	5	5.9	68.8	2	2.3	84.5	1	1.2	65.0	1	1	0	9	10.6	1.3
		♂ and ♀	180	2	168	5	3.0	68.8	2	1.2	84.5	2	1.2	71.0	2	1	1	11	6.5	1.3
II	50 ppm	♂	90	0	86	0	-	-	2	2.3	73.0	4	4.6	64.7	1	0	1	7	8.1	1.0
		♀	90	7	88	3	3.4	70.3	2	2.3	75.5	3	3.4	60.0	3	1	2	10	11.4	1.0
		♂ and ♀	180	7	174	3	1.7	70.3	4	2.3	74.2	7	4.0	62.7	4	1	3	17	9.8	1.0
III	10 ppm	♂	90	5	89	1	1.1	33.0	3	3.4	78.3	3	3.4	58.3	1	0	1	8	9.0	1.0
		♀	90	1	89	4	4.5	69.5	2	2.2	53.5	5	5.6	65.8	2	1	1	12	13.5	1.1
		♂ and ♀	180	6	178	5	2.8	62.2	5	2.8	68.4	8	4.5	63.0	3	1	2	20	11.2	1.0
IV	5 ppm	♂	90	1	71	0	-	-	1	1.4	44.0	1	1.4	80.0	0	0	0	2	2.8	1.0
		♀	90	7	89	4	4.5	80.0	4	4.5	73.5	5	5.6	69.0	1	0	1	14	12.5	1.0
		♂ and ♀	180	8	160	4	2.5	80.0	5	3.1	67.5	6	3.7	70.8	1	0	1	16	10.0	1.0
V	Controls	♂	90	2	88	0	-	-	3	3.4	66.7	2	2.3	35.5	3	3	0	7	7.9	1.1
		♀	90	5	90	4	4.4	70.7	3	3.3	53.3	6	6.7	50.2	2	0	2	14	15.5	1.1
		♂ and ♀	180	7	178	4	2.2	70.7	6	3.4	60.0	8	4.5	46.7	5	3	2	21	11.8	1.1
Total			900	30	858															

SL 082937

TABLE 6 (follows)

Experiment BT502 : Exposure by inhalation to Dichloroethane in air at 250-150, 50, 10, 5 ppm, 7 hours daily, 5 days weekly, for 78 weeks.
Results after 104 weeks.

DISTRIBUTION OF THE DIFFERENT TYPES OF TUMOURS

GROUPS NO.	CONCENTRATION	ANIMALS (Swiss mice, 11 weeks old at start)				ANIMALS WITH TUMOURS														
						Mammary tumours			Pulmonary adenomas			Leukaemias			Other tumours			Total (e)		
		Sex	No. at start	No. survivors	Corrected number (b)	Total No.	% (c)	Average latency time (weeks) (d)	Total No.	% (c)	Average latency time (weeks) (d)	Total No.	% (c)	Average latency time (weeks) (d)	Total No.	Benign No.	Malignant No.	No.	% (c)	No. of different tumours/ tumours bearing animals
VI	Controls	♂	25	0	25	0	-	-	0	-	-	0	-	-	1	1	0	1	4.0	1.0
		♀	44	4	44	1	2.3	65.0	1	2.3	45.0	5	11.4	74.0	0	0	0	7	15.9	1.0
		♂ and ♀	69	4	69	1	1.4	65.0	1	1.4	45.0	5	7.2	74.0	1	1	0	8	11.6	1.0
V and VI	Controls	♂	115	2	113	0	-	-	3	2.6	66.7	2	1.8	36.5	4	4	0	8	7.1	1.1
		♀	134	9	134	5	3.7	69.6	4	3.0	51.2	11	8.2	61.0	2	0	2	21	15.7	1.0
		♂ and ♀	249	11	247	5	2.0	69.6	7	2.8	57.8	13	5.3	57.2	6	4	2	29	11.7	1.1

TABLE 6

Experiment BT502 : Exposure by inhalation to Dichloroethane in air at 250-150, 50, 10, 5 ppm, 7 hours daily, 5 days weekly, for 78 weeks.
Results after 104 weeks.

DISTRIBUTION OF THE DIFFERENT TYPES OF TUMOURS

(second part)

(a) After few weeks the dose was reduced to 150 ppm, because of the too high toxicity at 250 ppm level.

(b) Alive animals after 23 weeks, when the first tumour (a leukaemia) was observed.

(c) The percentages are referred to the corrected number.

(d) Average time from the start of the experiment to the detection at the periodic control or at autopsy.

(e) Several animals with two or more tumours.

TABLE 7

Experiment BT502 : Exposure by inhalation to Dichloroethane in air at 250-150, 50, 10, 5 ppm, 7 hours daily, 5 days weekly, for 78 weeks.
Results after 104 weeks.

DISTRIBUTION OF THE DIFFERENT TYPES OF MAMMARY TUMOURS

(first part)

GROUPS NO.	CONCENTRATION	ANIMALS (Swiss mice, 11 weeks old at start)				MAMMARY TUMOURS																	
										Histologically examined													
												Histotype											
												Fibromas and fibroadenomas			Carcinomas			Sarcomas			Carcinosarcomas		
		Sex	No. at start	No. survivors	Corrected number (b)	Total No.	% (c)	Average latency time (weeks) (d)	No. of tumours/ tumours bearing animals	Total No.	% (e)	No.	% (f)	Average latency time (weeks) (d)	No.	% (f)	Average latency time (weeks) (d)	No.	% (f)	Average latency time (weeks) (d)	No.	% (f)	Average latency time (weeks) (d)
I	250-150 ppm (a)	♂	90	2	83	0	-	-	-	0	-	0	-	-	0	-	-	0	-	-	0	-	-
		♀	90	0	85	5	5.9	68.8	1.0	5	100.0	0	-	-	5	100.0	68.8	0	-	-	0	-	-
		♂ and ♀	180	2	168	5	3.0	68.8	1.0	5	100.0	0	-	-	5	100.0	68.8	0	-	-	0	-	-
II	50 ppm	♂	90	6	86	0	-	-	-	0	-	0	-	-	0	-	-	0	-	-	0	-	-
		♀	90	7	88	3	3.4	70.3	1.0	2	66.6	0	-	-	2	100.0	57.0	0	-	-	0	-	-
		♂ and ♀	180	7	174	3	1.7	70.3	1.0	2	66.6	0	-	-	2	100.0	57.0	0	-	-	0	-	-
III	10 ppm	♂	90	5	89	1	1.1	33.0	1.0	1	100.0	1	100.0	33.0	0	-	-	0	-	-	0	-	-
		♀	90	1	89	4	4.5	69.5	1.0	4	100.0	0	-	-	4	100.0	69.5	0	-	-	0	-	-
		♂ and ♀	180	6	178	5	2.8	62.2	1.0	5	100.0	1	20.0	33.0	4	80.0	69.5	0	-	-	0	-	-
IV	5 ppm	♂	90	1	71	0	-	-	-	0	-	0	-	-	0	-	-	0	-	-	0	-	-
		♀	90	7	89	4	4.5	80.0	1.0	4	100.0	0	-	-	4	100.0	80.0	0	-	-	0	-	-
		♂ and ♀	180	8	160	4	2.5	80.0	1.0	4	100.0	0	-	-	4	100.0	80.0	0	-	-	0	-	-
y	Controls	♂	90	2	83	0	-	-	-	0	-	0	-	-	0	-	-	0	-	-	0	-	-
		♀	90	5	90	4	4.4	70.7	1.0	4	100.0	0	-	-	3	75.0	74.0	0	-	-	1	25.0	61.0
		♂ and ♀	180	7	178	4	2.2	70.7	1.0	4	100.0	0	-	-	3	75.0	74.0	0	-	-	1	25.0	61.0
Total			900	30	858																		

TABLE 7 (follows)

Experiment BT502 : Exposure by inhalation to Dichloroethane in air at 250-150, 50, 10, 5 ppm, 7 hours daily, 5 days weekly, for 78 weeks.
Results after 104 weeks.

DISTRIBUTION OF THE DIFFERENT TYPES OF MAMMARY TUMOURS

GROUPS NO.	CONCEN-TRATION	ANIMALS (Swiss mice; 11 weeks old at start)				MAMMARY TUMOURS																	
										Histologically examined													
												Histotype											
												Fibromas and fibroadenomas			Carcinomas			Sarcomas			Carcinosarcomas		
		Sex	No. at start	No. survivors	Corrected number (b)	Total No.	% (c)	Average latency time (weeks) (d)	No. of tumours/ tumours bearing animals	Total No.	% (e)	No.	% (f)	Average latency time (weeks) (d)	No.	% (f)	Average latency time (weeks) (d)	No.	% (f)	Average latency time (weeks) (d)	No.	% (f)	Average latency time (weeks) (d)
VI	Controls	♂	25	0	25	0	-	-	-	0	-	0	-	-	0	-	-	0	-	-	0	-	-
		♀	44	4	44	1	2.3	65.0	1.0	1	100.0	0	-	-	1	100.0	65.0	0	-	-	0	-	-
		♂ and ♀	69	4	69	1	1.4	65.0	1.0	1	100.0	0	-	-	1	100.0	65.0	0	-	-	0	-	-
V and VI	Controls	♂	115	2	113	0	-	-	-	0	-	0	-	-	0	-	-	0	-	-	0	-	-
		♀	134	9	134	5	3.7	69.5	1.0	5	100.0	0	-	-	4	80.0	71.7	0	-	-	1	20.0	61.0
		♂ and ♀	249	11	247	5	2.0	69.5	1.0	5	100.0	0	-	-	4	80.0	71.7	0	-	-	1	20.0	61.0

TABLE 7

Experiment BT501 : Exposure by inhalation to Dichloroethane in air at 250-150, 50, 10, 5 ppm, 7 hours daily, 5 days weekly, for 78 weeks.
Results after 104 weeks.

DISTRIBUTION OF THE DIFFERENT TYPES OF MAMMARY TUMOURS

(second part)

(a) After few weeks the dose was reduced to 150 ppm, because of the too high toxicity at 250 ppm level.

(b) Alive animals after 23 weeks, when the first tumour (a leukaemia) was observed.

(c) The percentages are referred to the corrected number.

(d) Average time from the start of the experiment to the onset of the first mammary tumour per animal, detected at the periodic control or at autopsy.

(e) The percentages are referred to total number of animals bearing mammary tumours.

(f) The percentages are referred to total number of animals bearing mammary tumours, histologically examined.

TABLE 8

Experiment BT502 : Exposure by inhalation to Dichloroethane in air at 250-150, 50, 10, 5 ppm, 7 hours daily, 5 days weekly, for 78 weeks.
Results after 104 weeks.

DISTRIBUTION OF THE DIFFERENT TYPES OF MISCELLANEOUS ("OTHER") TUMOURS

GROUPS NO.	SEX	ANIMALS BEARING OTHER TUMOURS				
		Benign		Malignant		Total
		No.	Distribution of histotypes	No.	Distribution of histotypes	
I	♂	0		1	1 subcutaneous angiosarcoma	1
	♀	1	1 spleen angioma	0		1
II	♂	0		1	1 adrenal gland cortical carcinoma	1
	♀	1	1 ovary leiomioma	2	1 Harderian gland adenocarcinoma 1 granulosa cell tumour of the ovary	3
III	♂	0		1	1 subcutaneous fibrosarcoma	1
	♀	1	1 peritoneal angioma	1	1 fibrosing liposarcoma	2
IV	♂	0		0		0
	♀	0		1	1 skin squamous carcinoma	1
V	♂	3	2 hepatomas 1 spleen angioma	0		3
	♀	0		2	1 skin squamous carcinoma 1 intestinal fibrosarcoma	2

Experiment BT502 : Exposure by inhalation to Dichloroethane in air at 250-150, 50, 10, 5 ppm, 7 hours daily, 5 days weekly, for 78 weeks.
Results after 104 weeks.

DISTRIBUTION OF THE DIFFERENT TYPES OF MISCELLANEOUS ("OTHER") TUMOURS

GROUPS NO.	SEX	ANIMALS BEARING OTHER TUMOURS				
		Benign		Malignant		Total
		No.	Distribution of histotypes	No.	Distribution of histotypes	
VI	♂	1	1 hepatoma	0		0
	♀	0		0		0
V and VI	♂	4	3 hepatomas 1 spleen angioma	0		4
	♀	0		2	1 skin squamous carcinoma 1 intestinal fibrosarcoma	2