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EXPERIMENTAL CONTRIBUTIONS IN IDENTIFYING BRAIN POTENTIAL CARCINOGENS IN THE PETROCHEMICAL INDUSTRY

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INTRODUCTION

Data on the correlation between brain tumors and exogenous (environmental and occupational) agents are scanty, but extremely striking.

Historically, Dr. Thomas F. Mancuso was the first to identify an epidemiological relationship between industrial employment in a specific industry (rubber) and the subsequent development of malignant tumors of the brain: In a series of studies, including demographic, retrospective, and cohort longitudinal investigations, a higher risk of death due to tumors of the central nervous system among rubber workers was established.[1-4]

Following the experimental results showing that vinyl chloride was producing brain tumors (neuroblastomas),[5] epidemiological studies demonstrated an increase in brain neoplasias among workers of the vinyl chloride—polyvinyl chloride industry,[6] which was confirmed by many further investigations.

Recently a two-fold increase in brain tumors in several petrochemical plants and refineries in Texas, was found by some U.S. epidemiological groups. This finding is still under debate (this volume).

So far, only in the case of VC-PVC workers has the direct casual agent been identified. In both the case of the rubber industry and that of Texas petrochemical plants and refineries, workers have been potentially exposed to a multitude of compounds (several known as human carcinogens): none of them, however, can at present be definitely linked to the excess of brain tumors.

Theoretically, the experimental approach to the study of brain environmental and occupational carcinogenesis may help to do the following:

1. to predict the carcinogenic action of environmental agents (identification);
2. to assess the degree of carcinogenic potential of environmental agents (quantification), in relation to concentration, length of exposure, and so on;
3. to provide the basis for the evaluation of the relative carcinogenic risk of various agents;
4. to evaluate the possibility of sincarcinogenetic effects of exposures to different carcinogenic agents;
5. to help to interpret epidemiological findings showing an increased brain tumor rate among people exposed to a multitude of compounds: namely, to identify the risky single agent(s);
6. and finally, to provide basic information on the mechanisms of brain carcinogenesis by environmental agents.

The possibility of producing brain tumors in laboratory animals is well known. Many chemical agents, of different types, following direct implantation and general administration, may produce different types of tumors in a variety of experimental rodents (TABLE 1). Rats, at present, appear to be the most suitable species.

Three industrial compounds, in recent years, have been experimentally shown to produce brain, and brain-correlated, tumors in rats of different histotypes: these are bis (chloromethyl) ether, vinyl chloride, and acrylonitrile (TABLE 2).

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TABLE 1

EXPERIMENTAL CHEMICALS USED TO PRODUCE EXPERIMENTAL BRAIN TUMORS

Chemical Substances	Experimental Systems		
	Route	Animal Species	Tumors
Aromatic hydrocarbons 20-Methylcholanthrene 3-Methylcholanthrene 3,4-Benzopyrene 1,2-Benzopyrene 3,4,8,9-Dibenzopyrene 1,2,5,6-Dibenzanthracene 1,2,6-Dibenzanthracene 9,10-Dimethyl-1,2-benzanthracene 6,9,10-Trimethyl-1,2-benzanthracene	Direct implantation	Rats Mice Syrian hamsters (Rabbits)	Gliomas Sarcomas
Derivatives of aromatic hydrocarbons *N*-2-Fluorenylacetamide *N,N'*-2,7-Fluorenylbisacetamide	General administration	Rats	Gliomas
N-Nitroso compounds *N*-Methyl-*N*-nitrosourea (MNU) *N,N*-Dimethyl-*N*-nitrosourea (DMNU) *N,N',N'*-Trimethyl-*N*-nitrosourea (TMNU) Ethyl-nitrosourea (ENU)	General administration	Rats Rabbits	Gliomas Sarcomas
Triazenes 1-Phenyl-3,3-dimethyltriazene	General administration	Rats	Gliomas
Hydrazines 1,2-Diethylhydrazine	General administration	Rats	Gliomas Sarcomas Neuro-esthesio-epitheliomas

TABLE 2

INDUSTRIAL CHEMICALS KNOWN TO PRODUCE BRAIN TUMORS IN EXPERIMENTAL ANIMALS

Compounds	Route	Animal Species	Tumors	References
Bis (chloromethyl) ether	Inhalation	Rats	Neuroesthesio-epitheliomas	7
Vinyl chloride	Inhalation	Rats	Neuroblastomas (similar to human medulloblastomas)	5,8,9
Acrylonitrile	Inhalation Ingestion	Rats	Gliomas mainly oligodendrogliomas	10,11

TABLE 3

THE INCIDENCE OF BRAIN TUMORS AMONG UNTREATED SPRAGUE-DAWLEY AND WISTAR RATS AT THE INSTITUTE OF ONCOLOGY AND TUMOR CENTER OF BOLOGNA (ITALY)

Animals			Tumors*											
			Ependymomas			Gliomas			Meningiomas			Total		
Rat Strain	Sex	No.	No.	%	Average Latency Time (Weeks)	No.	%	Average Latency Time (Weeks)	No.	%	Average Latency Time (Weeks)	No.	%	Average Latency Time (Weeks)
Sprague-Dawley	M	1,384	3	0.2	95.0	13	0.9	118.5	10	0.7	96.6	26	1.9	107.4
	F	1,412	4	0.3	105.5	8	0.6	81.3	9	0.6	117.1	21	1.5	101.3
	M & F	2,796	7	0.2	101.0	21	0.7	104.3	19	0.7	106.3	47	1.7	104.6
Wistar	M	170	0	—	—	6	3.5	102.5	1	0.6	119.0	7	4.1	104.9

* No neuroblastomas were found.

Sprague-Dawley	M	1,384	3	0.2	95.0	13	0.9	118.5		0.7	96.6	26	1.9	107.4					
	F	1,412	4	0.3	105.5	8	0.6	81.3	9	0.6	117.1	21	1.5	101.3					
	M & F	2,796	7	0.2	101.0	21	0.7	104.3	19	0.7	106.3	47	1.7	104.6					
Wistar	M	170	0	—	—	6	3.5	102.5	1	0.6	119.0	7	4.1	104.9					

[a] No neuroblastomas were found.

TABLE 4

THE INCIDENCE OF BRAIN TUMORS AMONG SPRAGUE-DAWLEY RATS, TREATED WITH 2 ML OF OLIVE OIL PER KG BODY WT BY GAVAGE, ONCE DAILY, 4–5 DAYS WEEKLY, FOR 52–57 WEEKS

Sprague-Dawley Rats		Tumors[a]											
		Ependymomas			Gliomas			Meningiomas			Total		
Sex	No.	No.	%	Average Latency Time (Weeks)	No.	%	Average Latency Time (Weeks)	No.	%	Average Latency Time (Weeks)	No	%	Average Latency Time (Weeks)
M	325	1	0.3	104.0	3	0.9	102.0	3	0.9	102.3	7	2.1	102.4
F	325	2	0.6	91.5	2	0.6	114.2	4	1.2	100.2	8	2.3	101.5
M & F	650	3	0.5	95.7	5	0.8	106.9	7	1.1	101.1	15	2.3	101.9

[a] No neuroblastomas were found.

To achieve the above-listed finalities, the experimental investigations, aimed at studying environmental and occupational carcinogenesis, should meet the following prerequisites:

1. a suitable animal model should be used;
2. the spontaneous background tumorigram of the animals employed must be known;
3. the experimental protocols and procedures must be kept highly standardized for the different experiments, performed in the same laboratory. In our opinion, in order to obtain natural, worthwhile, and comparable data, one must:
   - A. keep the animal alive until spontaneous death;
   - B. perform, at autopsy, careful gross examination;
   - C. trim the organs and make histological sections in a standard way;
   - D. make histological sections, highly representative of different parts of the brain, available; and
   - E. follow the same histological classification of tumors.

This report presents our data on the incidence of brain tumors in rats, following the treatment with a variety of industrial compounds, given by inhalation and or by ingestion, at different doses and, in some instances, for different durations and with different schedules.

These data have been collected in the framework of a long-term project on industrial carcinogenesis which was started in 1970 at the Institute of Oncology and Tumor Center of Bologna, and is still going on.

TABLE 5

THE INCIDENCE OF BRAIN TUMORS AMONG SPRAGUE-DAWLEY RATS EXPOSED BY INHALATION TO VINYL CHLORIDE IN AIR AT VARIOUS CONCENTRATIONS, FROM 30,000 TO 1 PPM, 4 HOURS DAILY, 5 DAYS WEEKLY, FOR 52 WEEKS[a]

Vinyl Chloride (ppm)	Animals		Tumors														
			Neuroblastomas			Ependymomas			Gliomas			Meningiomas			Total		
	Sex	No.	No.	%	Average Latency Time (Weeks)	No.	%	Average Latency Time (Weeks)	No.	%	Average Latency Time (Weeks)	No.	%	Average Latency Time (Weeks)	No.	%	Average Latency Time (Weeks)
30,000	M	30	1	3.3	80.0	0	—	—	0	—	—	0	—	—	1	3.3	80.0
	F	30	0	—	—	0	—	—	0	—	—	0	—	—	0	—	—
	MF	60	1	1.7	80.0	0	—	—	0	—	—	0	—	—	1	1.7	80.0
10,000	M	30	2	6.7	65.0	0	—	—	0	—	—	0	—	—	2	6.7	65.0
	F	30	5	16.7	67.2	0	—	—	0	—	—	0	—	—	5	16.7	67.2
	MF	60	7	11.7	66.6	0	—	—	0	—	—	0	—	—	7	11.7	66.0
6,000	M	30	2	6.7	75.0	0	—	—	0	—	—	0	—	—	2	6.7	75.0
	F	30	1	3.3	63.0	0	—	—	1	3.3	115.0	0	—	—	2	6.7	89.0
	MF	60	3	5.0	71.0	0	—	—	1	1.7	115.0	0	—	—	4	6.7	82.0
2,500	M	30	2	6.7	89.5	0	—	—	0	—	—	0	—	—	2	6.7	89.5
	F	30	2	6.7	97.0	2	6.7	99.5	0	—	—	0	—	—	4	13.3	98.2
	MF	60	4	6.7	93.2	2	3.3	99.5	0	—	—	0	—	—	6	10.0	95.3
500	M	30	0	—	—	0	—	—	1	3.3	105.0	0	—	—	1	3.3	105.0
	F	30	0	—	—	0	—	—	0	—	—	1	3.3	84.0	1	3.3	84.0
	MF	60	0	—	—	0	—	—	1	1.7	105.0	1	1.7	84.0	2	3.3	94.5
250	M	30	0	—	—	0	—	—	0	—	—	0	—	—	0	—	—
	F	30	0	—	—	0	—	—	0	—	—	0	—	—	0	—	—
	MF	60	0	—	—	0	—	—	0	—	—	0	—	—	0	—	—

10,000	M	30	2	6.7	65.0	0	—	—	0	—	—	0	—	—	1	1.7	80.0
	F	30	5	16.7	67.2	0	—	—	0	—	—	0	—	—	2	6.7	65.0
	MF	60	7	11.7	66.6	0	—	—	0	—	—	0	—	—	5	16.7	67.2
6,000	M	30	2	6.7	75.0	0	—	—	0	—	—	0	—	—	7	11.7	66.0
	F	30	1	3.3	63.0	0	—	—	1	3.3	115.0	0	—	—	2	6.7	75.0
	MF	60	3	5.0	71.0	0	—	—	1	1.7	115.0	0	—	—	2	6.7	89.0
2,500	M	30	2	6.7	89.5	0	—	—	0	—	—	0	—	—	4	6.7	82.0
	F	30	2	6.7	97.0	2	6.7	99.5	0	—	—	0	—	—	2	6.7	89.5
	MF	60	4	6.7	93.2	2	3.3	99.5	0	—	—	0	—	—	4	13.3	98.2
500	M	30	0	—	—	0	—	—	1	3.3	105.0	0	—	—	6	10.0	95.3
	F	30	0	—	—	0	—	—	0	—	—	1	3.3	84.0	1	3.3	105.0
	MF	60	0	—	—	0	—	—	1	1.7	105.0	1	1.7	84.0	2	3.3	84.0
250	M	90	0	—	—	0	—	—	0	—	—	0	—	—	0	—	94.5
	F	90	0			0			0			0			0		
	MF	60	0			0			0			0			0		
500	M	60	0			0			0			0			0		
	F	60	0	—	—	0	—	—	0	—	—	0	—	—	0	—	—
	MF	120	0	—	—	0	—	—	0	—	—	0	—	—	0	—	—
150	M	60	0	—	—	0	—	—	0	—	—	0	—	—	0	—	—
	F	60	0	—	—	0	—	—	1	1.7	120.0	1	1.7	94.0	2	3.3	107.0
	MF	120	0	—	—	0	—	—	1	0.8	120.0	1	0.8	94.0	2	1.7	107.0
100	M	60	0	—	—	0	—	—	1	1.7	82.0	1	1.7	102.0	2	3.3	92.0
	F	60	0	—	—	0	—	—	0	—	—	0	—	—	0	—	—
	MF	120	0	—	—	0	—	—	1	0.8	82.0	1	0.8	102.0	2	1.7	92.0
50	M	180	0	—	—	1	0.5	123.0	2	1.1	108.0	1	0.5	124.0	4	2.2	115.7
	F	180	0	—	—	0	—	—	2	1.1	90.5	0	—	—	2	1.1	90.5
	MF	360	0	—	—	1	0.3	123.0	4	1.1	99.2	1	0.3	124.0	6	1.7	107.3
25	M	60	0	—	—	0	—	—	0	—	—	0	—	—	0	—	—
	F	60	0	—	—	0	—	—	0	—	—	0	—	—	0	—	—
	MF	120	0	—	—	0	—	—	0	—	—	0	—	—	0	—	—
10	M	60	0	—	—	0	—	—	0	—	—	0	—	—	0	—	—
	F	60	0	—	—	0	—	—	0	—	—	1	1.7	91.0	1	1.7	91.0
	MF	120	0	—	—	0	—	—	0	—	—	1	0.8	91.0	1	0.8	91.0
5	M	60	0	—	—	0	—	—	1	1.7	132.0	0	—	—	1	1.7	132.0
	F	60	0	—	—	0	—	—	0	—	—	0	—	—	0	—	—
	MF	120	0	—	—	0	—	—	1	0.8	132.0	0	—	—	1	0.8	132.0
1	M	60	0	—	—	0	—	—	1	1.7	93.0	0	—	—	1	1.7	93.0
	F	60	0	—	—	0	—	—	0	—	—	0	—	—	0	—	—
	MF	120	0	—	—	0	—	—	1	0.8	93.0	0	—	—	1	0.8	93.0
Controlst	M	225	0	—	—	0	—	—	2	0.9	138.0	1	0.4	106.0	3	1.3	127.3
	F	240	0	—	—	1	0.4	122.0	0			3	1.2	113.0	4	1.7	115.5
	MF	465	0	—	—	1	0.2	122.0	2	0.4	138.0	4	0.9	111.2	7	1.5	120.4
Total		2,025															

* Age of the animals at start: 13–17 weeks
† No treatment.

TABLE 6

THE INCIDENCE OF BRAIN TUMORS AMONG SPRAGUE-DAWLEY RATS EXPOSED BY INHALATION TO VINYL CHLORIDE IN AIR AT VARIOUS CONCENTRATIONS, 4 HOURS DAILY, 5 DAYS WEEKLY, FOR 17 WEEKS*

Vinyl Chloride (ppm)	Animals		Tumors														
			Neuroblastomas			Ependymomas			Gliomas			Meningiomas			Total		
	Sex	No.	No.	%	Average Latency Time (Weeks)	No.	%	Average Latency Time (Weeks)	No.	%	Average Latency Time (Weeks)	No.	%	Average Latency Time (Weeks)	No.	%	Average Latency Time (Weeks)
10,000	M	30	3	10.0	62.3	0	—	—	0	—	—	0	—	—	3	10.0	62.3
	F	30	6	20.0	75.0	0	—	—	0	—	—	1	3.3	60.0	7	23.3	73.1
	MF	60	9	15.0	70.0	0	—	—	0	—	—	1	1.7	60.0	10	16.7	69.9
6,000	M	30	3	10.0	71.3	0	—	—	0	—	—	0	—	—	3	10.0	71.3
	F	30	9	30.0	78.3	0	—	—	0	—	—	0	—	—	9	30.0	78.3
	MF	60	12	20.0	76.6	0	—	—	0	—	—	0	—	—	12	20.0	76.6
2,500	M	30	4	13.3	85.7	0	—	—	0	—	—	0	—	—	4	13.3	85.7
	F	30	1	3.3	76.0	0	—	—	0	—	—	0	—	—	1	3.3	76.0
	MF	60	5	8.3	83.8	0	—	—	0	—	—	0	—	—	5	8.3	83.8
500	M	30	0	—	—	0	—	—	0	—	—	0	—	—	0	—	—
	F	30	0	—	—	0	—	—	0	—	—	0	—	—	0	—	—
	MF	60	0	—	—	0	—	—	0	—	—	0	—	—	0	—	—
250	M	30	0	—	—	0	—	—	0	—	—	0	—	—	0	—	—
	F	30	0	—	—	0	—	—	0	—	—	0	—	—	0	—	—
	MF	60	0	—	—	0	—	—	0	—	—	0	—	—	0	—	—
50	M	30	0	—	—	0	—	—	0	—	—	0	—	—	0	—	—
	F	30	0	—	—	0	—	—	0	—	—	1	3.3	130.0	1	3.3	130.0
	MF	60	0	—	—	0	—	—	0	—	—	1	1.7	130.0	1	1.7	130.0
Controls†	M	108	0	—	—	1	0.9	126.0	1	0.9	100.0	2	1.8	86.5	4	3.7	99.7
	F	82	0	—	—	0	—	—	3	3.7	81.7	1	1.2	71.0	4	4.9	79.0
	MF	190	0	—	—	1	0.5	126.0	4	2.1	86.2	3	1.6	81.3	8	4.2	89.4
Total		550															

* Age of the animals at start, 12 weeks.
† No treatment

	MF	60	5	8.3	83.8	0	—	—	0	—	—	0	—	—	1	3.3	76.0
500	M	30	0	—	—	0	—	—	0	—	—	0	—	—	5	8.3	83.8
	F	30	0	—	—	0	—	—	0	—	—	0	—	—	0	—	—
	MF	60	0	—	—	0	—	—	0	—	—	0	—	—	0	—	—
250	M	30	0	—	—	0	—	—	0	—	—	0	—	—	0	—	—
	F	30	0	—	—	0	—	—	0	—	—	0	—	—	0	—	—
	MF	60	0	—	—	0	—	—	0	—	—	0	—	—	0	—	—
50	M	30	0	—	—	0	—	—	0	—	—	0	—	—	0	—	—
	F	30	0	—	—	0	—	—	0	—	—	0	—	—	0	—	—
	MF	60	0	—	—	0	—	—	0	—	—	1	3.3	130.0	1	3.3	130.0
Controls†	M	108	0	—	—	1	0.9	126.0	1	0.9	100.0	1	1.7	130.0	1	1.7	130.0
	F	82	0	—	—	0	—	—	3	3.7	81.7	2	1.8	86.5	4	3.7	99.7
	MF	190	0	—	—	1	0.5	126.0	4	2.1	86.2	1	1.2	71.0	4	4.9	79.0
Total		550										3	1.6	81.3	8	4.2	89.4

* Age of the animals at start: 12 weeks
† [illegible]

Table 3

THE INCIDENCE OF BRAIN TUMORS AMONG SPRAGUE-DAWLEY RATS EXPOSED BY INHALATION TO VINYL CHLORIDE IN AIR AT 10,000 AND 6,000 PPM FOR VARIOUS EXPOSURE SCHEDULES (100 HOURS TOTAL)*

			Tumors														
			Neuroblastomas			Ependymomas			Gliomas			Meningiomas			Total		
VC Conc (ppm), Exposure†	Animals Sex	No.	No.	%	Average Latency Time (Weeks)	No.	%	Average Latency Time (Weeks)	No.	%	Average Latency Time (Weeks)	No.	%	Average Latency Time (Weeks)	No.	%	Average Latency Time (Weeks)
10,000	M	60	0	—	—	0	—	—	3	5.0	102.3	0	—	—	3	5.0	102.3
4 × 5 × 5	F	60	0	—	—	0	—	—	0	—	—	0	—	—	0	—	—
	MF	120	0	—	—	0	—	—	3	2.5	102.3	0	—	—	3	2.5	102.3
6,000	M	60	0	—	—	0	—	—	2	3.3	75.5	0	—	—	2	3.3	75.5
4 × 5 × 5	F	60	1	1.7	106.0	0	—	—	0	—	—	0	—	—	1	1.7	106.0
	MF	120	1	0.8	106.0	0	—	—	2	1.7	75.5	0	—	—	3	2.5	85.7
10,000	M	60	0	—	—	0	—	—	2	3.3	92.5	1	1.7	56.0	3	5.0	54.0
1 × 4 × 25	F	60	0	—	—	1	1.7	116.0	0	—	—	2	3.3	97.5	3	5.0	103.7
	MF	120	0	—	—	1	0.8	116.0	2	1.7	92.5	3	2.5	83.9	6	5.0	78.8
6,000	M	60	0	—	—	0	—	—	1	1.7	58.0	1	1.7	75.0	2	3.3	66.5
1 × 4 × 25	F	60	0	—	—	0	—	—	0	—	—	1	1.7	111.0	1	1.7	111.0
	MF	120	0	—	—	0	—	—	1	0.8	58.0	2	1.7	93.0	3	2.5	81.3
10,000	M	60	0	—	—	0	—	—	1	1.7	80.0	0	—	—	1	1.7	80.0
4 × 1 × 25	F	60	1	1.7	84.0	0	—	—	1	1.7	90.0	1	1.7	58.0	3	5.0	77.0
	MF	120	1	0.8	84.0	0	—	—	2	1.7	85.0	1	0.8	58.0	4	3.3	78.0
6,000	M	60	0	—	—	0	—	—	0	—	—	0	—	—	0	—	—
4 × 1 × 25	F	60	0	—	—	1	1.7	83.0	0	—	—	2	3.3	78.0	3	5.0	79.7
	MF	120	0	—	—	1	0.8	83.0	0	—	—	2	1.7	78.0	3	2.5	79.7
Controls‡	M	109	0	—	—	0	—	—	2	1.8	114.5	0	—	—	2	1.8	114.5
	F	120	0	—	—	0	—	—	1	0.8	94.0	0	—	—	1	0.8	94.0
	MF	229	0	—	—	0	—	—	3	1.3	107.7	0	—	—	3	1.3	107.7
Total		949															

* Age of animals at start: 13 weeks
† Exposure time (hr/day) × (day/wk) × (wk)
‡ No treatment

TABLE 8

THE INCIDENCE OF BRAIN TUMORS AMONG MALE WISTAR RATS EXPOSED BY INHALATION TO VINYL CHLORIDE IN AIR AT VARIOUS CONCENTRATIONS 4 HOURS DAILY, 5 DAYS WEEKLY, FOR 52 WEEKS*

			Tumors†											
			Neuroblastomas			Gliomas			Meningiomas			Total		
Group	Vinyl Chloride (ppm)	Animals	No.	%	Average Latency Time (Weeks)	No.	%	Average Latency Time (Weeks)	No.	%	Average Latency Time (Weeks)	No.	%	Average Latency Time (Weeks)
1	10,000	30	3	10.0	82.0	0	—	--	1	3.3	65.0	4	13.3	77.7
2	6,000	30	1	3.3	84.0	3	10.0	88.3	0	-		4	13.3	87.2
3	2,500	30	1	3.3	69.0	0	—	-	0	—	-	1	3.3	69.0
4	500	30	0	—	—	0	—	—	0	—	—	0	—	—
5	250	30	0	-	-	0	-		0	—	-	0	-	
6	50	30	0	—	—	0	—	-	1	3.3	93.0	1	3.3	93.0
7	1	120	0	—	—	5	4.2	107.6	1	0.8	110.0	6	5.0	108.0
8	Controls‡	170	0	—	—	6	3.5	102.5	1	0.6	119.0	7	4.1	104.9
Total		470												

* Age of animals at start, 11–13 weeks.
† No ependymomas were found.
‡ No treatment

															(Weeks)
	[illegible]	30	3	10.0	82.0	0	—	—	1	3.3	65.0	4	13.3	77.7
2	6,000	30	1	3.3	84.0	3	10.0	88	0	—	—	4	13.3	87.2
3	2,500	30	1	3.3	69.0	0	—	—	0	—	—	1	3.3	69.0
4	500	30	0	—	—	0	—	—	0	—	—	0	—	—
5	250	30	0	—	—	0	—	—	0	—	—	0	—	—
6	50	30	0	—	—	0	—	—	1	3.3	93.0	1	3.3	93.0
7	1	120	0	—	—	5	4.2	107.6	1	0.8	110.0	6	5.0	108.0
8	Controls‡	170	0	—	—	6	3.5	102.5	1	0.6	119.0	7	4.1	104.9
Total		470												

* Age of animals at start: 11–13 weeks.
† No ependymomas were found.
‡ No treatment.

TABLE 9

THE INCIDENCE OF BRAIN TUMORS AMONG SPRAGUE-DAWLEY RATS EXPOSED BY INHALATION TO VINYLIDENE CHLORIDE IN AIR AT 150, 100, 50, 25, AND 10 PPM, 4 HOURS DAILY, 4–5 DAYS WEEKLY, FOR 52 WEEKS*

				Tumors†											
				Ependymomas			Gliomas			Meningiomas			Total		
Group	Vinylidene Chloride (ppm)	Animals Sex	No.	No.	%	Average Latency Time (Weeks)	No.	%	Average Latency Time (Weeks)	No.	%	Average Latency Time (Weeks)	No.	%	Average Latency Time (Weeks)
1	150	M	60	0	—	—	0	—	—	0	—	—	0	—	—
		F	60	0	—	—	0	—	—	0	—	—	0	—	—
		M & F	120	0	—	—	0	—	—	0	—	—	0	—	—
2	100	M	30	0	—	—	0	—	—	0	—	—	0	—	—
		F	30	0	—	—	0	—	—	1	3.3	108.0	1	3.3	108.0
		M & F	60	0	—	—	0	—	—	1	1.7	108.0	1	1.7	108.0
3	50	M	30	0	—	—	1	3.3	111.0	1	3.3	127.0	2	6.7	119.0
		F	30	1	3.3	95.0	1	3.3	84.0	1	3.3	124.0	3	10.0	101.0
		M & F	60	1	1.7	95.0	2	3.3	97.0	2	3.3	125.0	5	8.3	102.2
4	25	M	30	0	—	—	0	—	—	0	—	—	0	—	—
		F	30	0	—	—	0	—	—	0	—	—	0	—	—
		M & F	60	0	—	—	0	—	—	0	—	—	0	—	—
5	10	M	30	0	—	—	1	3.3	111.0	0	—	—	1	3.3	111.0
		F	30	0	—	—	0	—	—	0	—	—	0	—	—
		M & F	60	0	—	—	1	1.7	111.0	0	—	—	1	1.7	111.0
6	Controls‡	M	100	0	—	—	2	2.0	132.5	1	1.0	52.0	3	3.0	105.7
		F	100	0	—	—	0	—	—	1	1.0	105.0	1	1.0	105.0
		M & F	200	0	—	—	2	1.0	132.5	2	1.0	78.5	4	2.0	105.5
Total			560												

* Age of the animals at start: 16 weeks
† No neuroblastomas were found
‡ No treatment.

TABLE 10

THE INCIDENCE OF BRAIN TUMORS AMONG SPRAGUE-DAWLEY RATS EXPOSED BY INHALATION TO ETHYLENE DICHLORIDE IN AIR AT 250, 150, 50, 10, AND 5 PPM, 7 HOURS DAILY, 5 DAYS WEEKLY, FOR 78 WEEKS*

				* Tumors†											
				Ependymomas			Gliomas			Meningiomas			Total		
Group	Ethylene Dichloride (ppm)	Animals Sex	Animals No.	No.	%	Average Latency Time (Weeks)	No.	%	Average Latency Time (Weeks)	No.	%	Average Latency Time (Weeks)	No.	%	Average Latency Time (Weeks)
1	250–150	M	90	0	—	—	0	—	—	0	—	—	0	—	—
		F	90	0	—	—	0	—	—	0	—	—	0	—	—
		M & F	180	0	—	—	0	—	—	0	—	—	0	—	—
2	50	M	90	0	—	—	1	1.1	155.0	0	—	—	1	1.1	155.0
		F	90	0	—	—	0	—	—	1	1.1	97.0	1	1.1	97.0
		M & F	180	0	—	—	1	0.5	155.0	1	0.5	97.0	2	1.1	126.0
3	10	M	90	0	—	—	0	—	—	0	—	—	0	—	—
		F	90	0	—	—	2	2.2	94.0	0	—	—	2	2.2	94.0
		M & F	180	0	—	—	2	1.1	94.0	0	—	—	2	1.1	94.0
4	5	M	90	0	—	—	0	—	—	0	—	—	0	—	—
		F	90	0	—	—	0	—	—	0	—	—	0	—	—
		M & F	180	0	—	—	0	—	—	0	—	—	0	—	—
5	Controls‡	M	180	0	—	—	0	—	—	1	0.5	86.0	1	0.5	86.0
		F	180	3	1.6	100.0	0	—	—	1	0.5	112.0	4	2.2	103.0
		M & F	360	3	0.8	100.0	0	—	—	2	0.5	99.0	5	1.4	99.6
Total			1,080												

* Age of the animals at start: 12 weeks.
† No neuroblastomas were found
‡ No treatment.

		F	90	0	—	—	[illegible]	[illegible]	[illegible]	0	—	—	1	1.1	155.0
		M & F	180	0	—	—	1	0.5	[illegible]	1	0.5	97.0	1	1.1	97.0
													2	1.1	126.0
3	10	M	90	0	—	—	0	—		0	—	—	0	—	—
		F	90	0	—	—	2	2.2	94.0	0	—	—	2	2.2	94.0
		M & F	180	0	—	—	2	1.1	94.0	0	—	—	2	1.1	94.0
4	5	M	90	0	—	—	0	—	—	0	—	—	0	—	—
		F	90	0	—	—	0	—	—	0	—	—	0	—	—
		M & F	180	0	—	—	0	—	—	0	—	—	0	—	—
5	Controls‡	M	180	0	—	—	0	—	—	1	0.5	86.0	1	0.5	86.0
		F	180	3	1.6	100.0	0	—	—	1	0.5	112.0	4	2.2	103.0
		M & F	360	3	0.8	100.0	0	—	—	2	0.5	99.0	5	1.4	99.6
Total			1,080												

* Age of the animals at start: 12 weeks
† [illegible] neuroblastomas were found.
‡ [illegible]

TABLE 11

THE INCIDENCE OF BRAIN TUMORS AMONG SPRAGUE-DAWLEY RATS EXPOSED BY INHALATION TO ACRYLONITRILE IN AIR AT 40, 20, 10, AND 5 PPM, 4 HOURS DAILY, 5 DAYS WEEKLY, FOR 52 WEEKS*

				Tumors†								
				Gliomas			Meningiomas			Total		
Group	Acrylonitrile Conc (ppm)	Animals Sex	Animals No.	No.	%	Average Latency Time (Weeks)	No.	%	Average Latency Time (Weeks)	No.	%	Average Latency Time (Weeks)
1	40	M	30	2	6.7	75.5	0	—	—	2	6.7	75.5
		F	30	1	3.3	108.0	0	—	—	1	3.3	108.0
		M & F	60	3	5.0	86.3	0	—	—	3	5.0	86.3
2	20	M	30	1	3.3	96.0	1	3.3	99.0	2	6.7	97.5
		F	30	1	3.3	121.0	0	—	—	1	3.3	121.0
		M & F	60	2	3.3	108.5	1	1.7	99.0	3	5.0	105.3
3	10	M	30	0	—	—	0	—	—	0	—	—
		F	30	0	—	—	1	3.3	115.0	1	3.3	115.0
		M & F	60	0	—	—	1	1.7	115.0	1	1.7	115.0
4	5	M	30	0	—	—	0	—	—	0	—	—
		F	30	0	—	—	1	3.3	98.0	1	3.3	98.0
		M & F	60	0	—	—	1	1.7	98.0	1	1.7	98.0
5	Controls‡	M	30	0	—	—	1	3.3	134.0	1	3.3	134.0
		F	30	0	—	—	0			0	—	—
		M & F	60	0	—	—	1	1.7	134.0	1	1.7	134.0
Total			300									

* Age of the animals at start: 12 weeks.
† No neuroblastomas or ependymomas were found.
‡ No treatment.

TABLE 12

THE INCIDENCE OF BRAIN TUMORS AMONG SPRAGUE-DAWLEY RATS EXPOSED BY INHALATION TO STYRENE IN AIR AT 300, 200, 100, 50, AND 25 PPM, 4 HOURS DAILY, 5 DAYS WEEKLY, FOR 52 WEEKS*

				Tumors†								
				Gliomas			Meningiomas			Total		
Group	Styrene Conc (ppm)	Animals Sex	No.	No.	%	Average Latency Time (Weeks)	No.	%	Average Latency Time (Weeks)	No.	%	Average Latency Time (Weeks)
1	300	M	30	0	—	—	0	—	—	0	—	—
		F	30	0	—	—	0	—	—	0	—	—
		M & F	60	0	—	—	0	—	—	0	—	—
2	200	M	30	0	—	—	0	—	—	0	—	—
		F	30	0	—	—	0	—	—	0	—	—
		M & F		0	—	—	0	—	—	0	—	—
3	100	M	30	0	—	—	1	3.3	120.0	1	3.3	120.0
		F	30	0	—	—	3	10.0	112.7	3	10.0	112.7
		M & F	60	0	—	—	4	6.7	114.5	4	6.7	114.5
4	50	M	30	0	—	—	0	—	—	0	—	—
		F	30	0	—	—	0	—	—	0	—	—
		M & F	60	0	—	—	0	—	—	0	—	—
5	25	M	30	0	—	—	1	3.3	132.0	1	3.3	132.0
		F	30	1	3.3	106.0	0	—	—	1	3.3	106.0
		M & F	60	1	1.7	106.0	1	1.7	132.0	2	3.3	119.0
6	Controls‡	M	60	0	—	—	0	—	—	0	—	—
		F	60	0	—	—	0	—	—	0	—	—
		M & F	120	0	—	—	0	—	—	0	—	—
Total			420									

* Age of the animals at start 11 weeks
† No neuroblastomas or ependymomas were found
‡ No treatment

		M & F	60	0	—	—	3	10.0	112.7	3	10.0	112.7
4	50	M	30	0	—	—	4	6.7	114.5	4	6.7	114.5
		F	30	0	—	—	0	—	—	0	—	—
		M & F	60	0	—	—	0	—	—	0	—	—
5	25	M	30	0	—	—	0	—	—	0	—	—
		F	30	1	3.3	106.0	1	3.3	132.0	1	3.3	132.0
		M & F	60	1	1.7	106.0	0	—	—	1	3.3	106.0
6	Controls‡	M	60	0	—	—	1	1.7	132.0	2	3.3	119.0
		F	60	0	—	—	0	—	—	0	—	—
		M & F	120	0	—	—	0	—	—	0	—	—
Total			420				0	—	—	0	—	—

* Age of the animals at start: 13 weeks.
† No neuroblastomas or ependymomas were found.
‡ No treatment

TABLE 13

THE INCIDENCE OF BRAIN TUMORS AMONG SPRAGUE-DAWLEY RATS EXPOSED BY INHALATION TO PROPYLENE IN AIR AT 5,000, 1,000, AND 200 PPM, 7 HOURS DAILY, 5 DAYS WEEKLY, FOR 104 WEEKS*

				Tumors†								
				Gliomas			Meningiomas			Total		
Group	Propylene Conc (ppm)	Animals Sex	No.	No.	%	Average Latency Time (Weeks)	No.	%	Average Latency Time (Weeks)	No.	%	Average Latency Time (Weeks)
1	5,000	M	120	0	—	—	0	—	—	0	—	—
		F	120	0	—	—	0	—	—	0	—	—
		M & F	240	0	—	—	0	—	—	0	—	—
2	1,000	M	100	0	—	—	0	—	—	0	—	—
		F	100	0	—	—	1	1.0	111.0	1	1.0	111.0
		M & F	200	0	—	—	1	0.5	111.0	1	0.5	111.0
3	200	M	100	0	—	—	0	—	—	0	—	—
		F	100	0	—	—	0	—	—	0	—	—
		M & F	200	0	—	—	0	—	—	0	—	—
4	Controls‡	M	120	2	1.7	108.5	0	—	—	2	1.7	108.5
		F	120	1	0.8	88.0	0	—	—	1	0.8	88.0
		M & F	240	3	1.2	101.7	0	—	—	3	1.2	101.7
Total			880									

* Age of the animals at start: 17 weeks.
† No neuroblastomas or ependymomas were found.
‡ No treatment.

TABLE 14

THE INCIDENCE OF BRAIN TUMORS AMONG SPRAGUE-DAWLEY RATS EXPOSED BY INHALATION TO TRICHLOROFLUOROMETHANE IN AIR AT 5,000 AND 1,000 PPM, 4 HOURS DAILY, 5 DAYS WEEKLY, FOR 104 WEEKS*

Group	Trichlorofluoromethane Conc (ppm)	Animals		Tumors†											
				Ependymomas			Gliomas			Meningiomas			Total		
		Sex	No.	No.	%	Average Latency Time (Weeks)	No.	%	Average Latency Time (Weeks)	No.	%	Average Latency Time (Weeks)	No.	%	Average Latency Time (Weeks)
1	5,000	M	90	0	—	-	0	—	-	0	—		0	—	
		F	90	0	—		0	—	—	2	2.2	90.0	2	2.2	90.0
		M & F	180	0	—	—	0	—	-	2	1.1	90.0	2	1.1	90.0
2	1,000	M	90	0	—	-	2	2.2	129.5	1	1.1	72.0	3	3.3	110.3
		F	90	1	1.1	103.0	1	1.1	75.0	1	1.1	88.0	3	3.3	88.7
		M & F	180	1	0.5	103.0	3	1.7	111.3	2	1.1	80.0	6	3.3	99.5
3	Controls‡	M	150	1	0.7	94.0	1	0.7	84.0	0	—	—	2	1.3	89.0
		F	150	0	—	—	2	1.3	82.5	0	—	-	2	1.3	82.5
		M & F	300	1	0.3	94.0	3	1.0	83.0	0	—	—	4	1.3	85.7
Total			660												

* Age of the animals at start 9–13 weeks.
† No neuroblastomas were found
‡ No treatment The same control group is common for the experiments FC12 and FC11.

		F	90	0	—	—	0	—	—	0	—	—	0	—	—
		M & F	180	0	—	—	0	—	—	2	2.2	90.0	2	2.2	90.0
2	1,000	M	90	0	—	—	0	—	—	2	1.1	90.0	2	1.1	90.0
		F	90	1	1.1	103.0	2	2.2	129.5	1	1.1	72.0	3	3.3	110.3
		M & F	180	1	0.5	103.0	1	1.1	75.0	1	1.1	88.0	3	3.3	88.7
3	Controls‡	M	150	1	0.7	94.0	3	1.7	111.3	2	1.1	80.0	6	3.3	99.5
		F	150	0	—	—	1	0.7	84.0	0	—	—	2	1.3	89.0
		M & F	300	1	0.3	94.0	2	1.3	82.5	0	—	—	2	1.3	82.5
Total			660				3	1.0	83.0	0	—	—	4	1.3	85.7

* Age of the animals at start: 9–13 weeks.
† No neuroblastomas were found.
‡ No treatment. The same control group is common for the experiments FC12 and FC11.

TABLE 15

THE INCIDENCE OF BRAIN TUMORS AMONG SPRAGUE-DAWLEY RATS EXPOSED BY INHALATION TO DICHLORODIFLUOROMETHANE IN AIR AT 5,000 AND 1,000 PPM, 4 HOURS DAILY, 5 DAYS WEEKLY, FOR 104 WEEKS*

				Tumors†								
				Ependymomas			Gliomas			Total		
Group	Dichloro-fluoro-methane (ppm)	Animals Sex	Animals No.	No.	%	Average Latency Time (Weeks)	No.	%	Average Latency Time (Weeks)	No.	%	Average Latency Time (Weeks)
1	5,000	M	90	0	—	—	1	1.7	109.0	1	1.7	109.0
		F	90	0	—	—	1	1.7	97.0	1	1.7	97.0
		M & F	180	0	—		2	1.7	133.0	2	1.7	103.0
2	1,000	M	90	0	—	—	3	3.3	100.4	3	3.3	100.4
		F	90	0	—	—	1	1.1	90.0	1	1.1	90.0
		M & F	180	0	—	—	4	2.2	97.8	4	2.2	97.8
3	Controls‡	M	150	1	0.7	94.0	1	0.7	84.0	2	1.3	89.0
		F	150	0	—	—	2	1.3	82.5	2	1.3	82.5
		M & F	300	1	0.3	94.0	3	1.0	83.0	4	1.3	85.7
Total			660									

* Age of the animals at start: 9–13 weeks.
† No neuroblastomas or meningiomas were found.
‡ No treatment. The same control group is common for the experiments FC12 and FC11.

TABLE 16

THE INCIDENCE OF BRAIN TUMORS AMONG SPRAGUE-DAWLEY RATS EXPOSED BY INHALATION TO CHLORODIFLUOROMETHANE IN AIR AT 5,000 AND 1,000 PPM, 4 HOURS DAILY, 5 DAYS WEEKLY, FOR 104 WEEKS*

Group	Chloro difluoro-methane (ppm)	Animals Sex	Animals No.	Tumors† Ependymomas No.	%	Average Latency Time (Weeks)	Gliomas No	%	Average Latency Time (Weeks)	Meningiomas No	%	Average Latency Time (Weeks)	Total No.	%	Average Latency Time (Weeks)
1	5,000	M	60	0	--	-	2	3.3	78.5	0	—	-	2	3.3	78.5
		F	60	1	1.7	96.0	0	-		2	3.3	99.5	3	5.0	101.7
		M & F	120	1	0.8	96.0	2	1.7	78.5	2	1.7	99.5	5	4.2	92.4
2	1,000	M	60	0	--		0	-		1	1.7	124.0	1	1.7	124.0
		F	60	0	—	-	0	--	--	0	—		0	--	--
		M & F	120	0	—	--	0	--		1	0.8	124.0	1	0.8	124.0
3	Controls‡	M	60	0	—		0	--	--	0	-	-	0	-	
		F	60	0	—	--	0	—	—	1	1.7	136.0	1	1.7	136.0
		M & F	120	0	—	—	0	—	—	1	0.8	136.0	1	0.8	136.0
Total			360												

* Age of animals at start 8 weeks.
† No neuroblastomas were found
‡ No treatment.

2	1,000	M	60	0	—	—	0	—	—	1	1.7	124.0	1	1.7	124.0
		F	60	0	—	—	0	—	—	0	—	—	0	—	—
		M & F	120	0	—	—	0	—	—	1	0.8	124.0	1	0.8	124.0
3	Controls‡	M	60	0	—	—	0	—	—	0	—	—	0	—	—
		F	60	0	—	—	0	—	—	1	1.7	136.0	1	1.7	136.0
		M & F	120	0	—	—	0	—	—	1	0.8	136.0	1	0.8	136.0
Total			360												

* Age of animals at start: 8 weeks.
† No neuroblastomas were found.
‡ No treatment.

TABLE 17

THE INCIDENCE OF BRAIN TUMORS AMONG SPRAGUE-DAWLEY RATS EXPOSED BY INGESTION TO VINYL CHLORIDE IN OLIVE OIL AT 50.00, 16.65, 3.33, 1.0, 0.3, AND 0.03 MG/KG BODY WT, ONCE DAILY, 4-5 DAYS WEEKLY, FOR 52-59 WEEKS*

				Tumors†											
				Ependymomas			Gliomas			Meningiomas			Total		
Group	Vinyl Chloride Ingested (mg/kg body wt)	Animals Sex	No. at Start	No.	%	Average Latency Time (Weeks)	No.	%	Average Latency Time (Weeks)	No.	%	Average Latency Time (Weeks)	No	%	Average Latency Time (Weeks)
1	50.00	M	40	0	—		0	—	—	0	—	—	0	—	—
		F	40	0	—	—	0	—	—	1	2.5	59.0	1	2.5	59.0
		MF	80	0	—	—	0	—	—	1	1.2	59.0	1	1.2	59.0
2	16.65	M	40	0	—		0	—	—	1	2.5	120.0	1	2.5	120.0
		F	40	0	—	—	0	—	—	0	—	—	0	—	—
		MF	80	0	—	—	0	—	—	1	1.2	120.0	1	1.2	120.0
3	3.33	M	40	1	2.5	92.0	0	—	—	0	—	—	1	2.5	92.0
		F	40	0	—		0	—	—	0	—	—	0	—	
		MF	80	1	1.2	92.0	0	—	—	0	—	—	1	1.2	92.0
4	1.0	M	75	1	1.3	115.0	1	1.3	121.0	0	—	—	2	2.7	118.0
		F	75	0	—	—	0	—	—	1	1.3	71.0	1	1.3	71.0
		MF	150	1	0.7	115.0	1	0.7	121.0	1	0.7	71.0	3	2.0	102.3
5	0.3	M	75	0	—	—	4	5.3	96.7	0	—	—	4	5.3	96.7
		F	75	0	—	—	2	2.7	96.5	0	—	—	2	2.7	96.5
		MF	150	0	—	—	6	4.0	96.7	0	—	—	6	4.0	96.7
6	0.03	M	75	0	—	—	0	—	—	0	—	—	0	—	—
		F	75	2	2.7	90.5	0	—	—	0	—	—	2	2.7	90.5
		MF	150	2	1.3	90.5	0	—	—	0	—	—	2	1.3	90.5
7	Controls‡	M	115	1	0.9	104.0	1	0.9	108.0	1	0.9	76.0	3	2.7	96.0
		F	115	1	0.9	87.0	2	1.7	114.2	1	0.9	92.0	4	3.4	101.8
		MF	230	2	0.9	95.5	3	1.3	112.0	2	0.9	84.0	7	3.0	99.3
Total			920												

* Age of animals at start: 10-13 weeks
† No neuroblastomas were found
‡ Olive oil

TABLE 18

THE INCIDENCE OF BRAIN TUMORS AMONG SPRAGUE-DAWLEY RATS, EXPOSED BY INGESTION TO VINYLIDENE CHLORIDE IN OLIVE OIL AT 20, 10, 5, 0.5 MG/KG BODY WT, ONCE DAILY, 4–5 DAYS WEEKLY, FOR 52–59 WEEKS*

Group	Vinylidene Chloride Ingested (mg/kg body wt)	Animals		Tumors†											
				Ependymomas			Gliomas			Meningiomas			Total		
		Sex	No. at Start	No.	%	Average Latency Time (Weeks)	No.	%	Average Latency Time (Weeks)	No.	%	Average Latency Time (Weeks)	No.	%	Average Latency Time (Weeks)
1	20	M	50	0	—	—	0	—	—	0	—	—	0	—	—
		F	50	0	—	—	0	—	—	0	—	—	0	—	—
		M & F	100	0	—	—	0	—	—	0	—	—	0	—	—
2	10	M	50	0	—	—	0	—	—	1	2.0	111.0	1	2.0	111.0
		F	50	0	—	—	0	—	—	0	—	—	0	—	—
		M & F	100	0	—	—	0	—	—	1	1.0	111.0	1	1.0	111.0
3	5	M	50	1	2.0	86.0	0	—	—	1	2.0	121.0	2	4.0	103.5
		F	50	0	—	—	0	—	—	1	2.0	118.0	1	2.0	118.0
		M & F	100	1	1.0	86.0	0	—	—	2	2.0	119.5	3	3.0	108.3
4	0.5	M	50	0	—	—	1	2.0	80.0	0	—	—	1	2.0	8.0
		F	50	0	—	—	0	—	—	0			0	—	
		M & F	100	0	—	—	1	1.0	80.0	0	—	—	1	1.0	8.0
5	Controls‡	M	175	0	—	—	2	1.1	109.5	2	1.1	113.0	4	2.3	111.2
		F	175	1	0.6	87.0	2	1.1	114.2	4	2.3	100.5	7	4.0	102.5
		M & F	350	1	0.3	87.0	4	1.1	111.8	6	1.7	104.7	11	3.1	105.8
Total			750												

* Age of animals at start: 9–10 weeks
† No neuroblastomas were found
‡ Olive oil

		M	50	1	2.0	86.0	0	—	—	1	2.0	121.0	2	4.0	103.5
		F	50	0	—	—	0	—	—	1	2.0	118.0	1	2.0	118.0
		M & F	100	1	1.0	86.0	0	—	—	2	2.0	119.5	3	3.0	108.3
4	0.5	M	50	0	—	—	1	2.0	80.0	0	—	—	1	2.0	8.0
		F	50	0	—	—	0	—	—	0	—	—	0	—	—
		M & F	100	0	—	—	1	1.0	80.0	0	—	—	1	1.0	8.0
5	Controls‡	M	175	0	—	—	2	1.1	109.5	2	1.1	113.0	4	2.3	111.2
		F	175	1	0.6	87.0	2	1.1	114.2	4	2.3	100.5	7	4.0	102.5
		M & F	350	1	0.3	87.0	4	1.1	111.8	6	1.7	104.7	11	3.1	105.8
Total			750												

* Age of animals at start: 9–10 weeks.
† No neuroblastomas were found.
‡ Olive oil.

TABLE 19.

THE INCIDENCE OF BRAIN TUMORS AMONG SPRAGUE-DAWLEY RATS, EXPOSED BY INGESTION TO ACRYLONITRILE IN OLIVE OIL AT 5 MG/KG BODY WT, 3 TIMES WEEKLY FOR 52 WEEKS

				Tumors†											
				Ependymomas			Gliomas			Meningiomas			Total		
Groups	Acrylonitrile Dose (mg/kg body wt)	Animals: Sex	Animals: No. at Start	No.	%	Average Latency Time (Weeks)	No.	%	Average Latency Time (Weeks)	No.	%	Average Latency Time (Weeks)	No.	%	Average Latency Time (Weeks)
1	5	M	40	0	—	—	0	—	—	0	—	—	0	—	—
		F	40	0	—	—	1	2.5	43.0	0	—	—	1	2.5	43.0
		M & F	80	0	—	—	1	1.3	43.0	0	—	—	1	1.3	43.0
2	Controls‡	M	75	0	—	—	1	1.3	108.0	1	1.3	76.0	2	2.7	92.0
		F	75	1	1.3	87.0	2	2.7	114.2	1	1.3	92.0	4	5.3	101.7
		M & F	150	1	0.7	87.0	3	2.0	112.0	2	1.3	84.0	6	4.0	98.5
Total			230												

* Age of the animals at start: 10 weeks.
† No neuroblastomas were found.
‡ Olive oil.

TABLE 20

THE INCIDENCE OF BRAIN TUMORS AMONG SPRAGUE-DAWLEY RATS, EXPOSED BY INGESTION TO STYRENE IN OLIVE OIL AT 250 AND 50 MG/KG BODY WT, ONCE DAILY, 4–5 DAYS WEEKLY FOR 52 WEEKS*

				Tumors†											
				Ependymomas			Gliomas			Meningiomas			Total		
Group	Styrene Dose Ingested (mg/kg body wt)	Animals Sex	Animals No. at Start	No.	%	Average Latency Time (Weeks)	No.	%	Average Latency Time (Weeks)	No.	%	Average Latency Time (Weeks)	No.	%	Average Latency Time (Weeks)
1	250	M	40	0	—	—	0	—	—	1	2.5	90.0	1	2.5	90.0
		F	40	0	—	—	0	—	—	1	2.5	103.0	1	2.5	103.0
		M & F	80	0	—	—	0	—	—	2	2.5	96.5	2	2.5	96.5
2	50	M	40	0	—	—	1	2.5	106.0	0	—	—	1	2.5	106.0
		F	40	1	2.5	82.0	0	—	—	3	7.5	132.0	4	10.0	119.5
		M & F	80	1	1.2	82.0	1	1.2	106.0	3	3.7	132.0	5	6.2	116.8
3	Controls‡	M	40	0	—	—	0	—	—	0	—	—	0	—	—
		F	40	1	2.5	96.0	0	—	—	0	—	—	1	2.5	96.0
		M & F	80	1	1.2	96.0	0	—	—	0	—	—	1	1.2	96.0
Total			240												

* Age of the animals at start: 13 weeks.
† No neuroblastomas were found
‡ Olive oil.

TABLE 21

THE INCIDENCE OF BRAIN TUMORS AMONG SPRAGUE-DAWLEY RATS, EXPOSED BY INGESTION TO STYRENE OXIDE IN OLIVE OIL AT 250 AND 50 MG KG BODY WT, ONCE DAILY, 4–5 DAYS WEEKLY, FOR 52 WEEKS*

Group	Styrene Oxide Dose (mg/kg body wt)	Animals		Meningiomas†		
		Sex	No. at Start	No.	%	Average Latency Time (Weeks)
1	250	M	40	0	—	—
		F	40	2	5.0	129.5
		M & F	80	2	2.5	129.5
2	50	M	40	1	2.5	107.0
		F	40	1	2.5	126.0
		M & F	80	2	2.5	116.0
3	Controls‡	M	40	1	2.5	81.0
		F	40	0	—	—
		M & F	80	1	1.3	81.0
Total			240			

* Age of the animals at start: 13 weeks.
† No neuroblastomas, ependymomas, or gliomas were found.
‡ Olive oil.

PLAN OF THE STUDIES: MATERIALS AND METHODS

The incidence of brain tumors has been systematically studied in our Laboratory for the following:

1. untreated rats (Sprague-Dawley and Wistar);
2. rats (Sprague-Dawley) treated with virgin olive oil, which is the vehicle used for the ingestion (gavage) experiments;
3. rats (Sprague-Dawley and, in the case of vinyl chloride, also Wistar), treated by inhalation at different doses (and, in the case of vinyl chloride, also for different times and with different schedules) with:
   - A. vinyl chloride,
   - B. vinylidene chloride,
   - C. ethylene dichloride,
   - D. acrylonitrile,
   - E. styrene,
   - F. propylene,
   - G. trichlorofluoromethane (FC 11),
   - H. dichlorodifluoromethane (FC 12),
   - I. chlorodifluoromethane (FC 22);
4. rats (Sprague-Dawley), treated by ingestion at different doses with:
   - A. vinyl chloride,
   - B. vinylidene chloride,
   - C. acrylonitrile,

D. styrene,
E. styrene-oxide,
F. vinylidene fluoride,
G. trichloroethylene,
H. benzene,
I. asbestos (Crocydolite),
J. polyvinyl chloride (PVC).

All the supplies of the compounds used were examined in order to determine whether they meet the required standards.

The concentrations, when the compound was administered by inhalation, were controlled by continuous gas chromatographic monitoring..

Treatment was always performed by the same people. This is particularly important for gavage, since the animals become accustomed to the same operator.

The animal breeds have been routinely employed in our Laboratory for many years. It should be pointed out that, whatever their use, all the animals of our colony undergo periodic examination and complete autopsy, giving us extensive information concerning their pathology.

The age of the animals in the experiments considered in this report, at the start of treatment, varied from 11 to 16 weeks.

The animals were kept alive until spontaneous death. Every two weeks, they were submitted to an examination for the detection of any gross changes.

Full autopsy was performed on each animal. All the different parts of the body were explored, and specimens for histology were taken from all major organs and any other organ with pathological lesions. As far as the brain was concerned, careful gross examination was made, and all lesions, either superficial or discovered by dissecting the organ (after fixation) were measured and described.

The brain was always trimmed in a standard way, and sections were routinely stained with hematoxylin-eosin and, when necessary, with special techniques.

The criteria for histopathological characterization and classification of brain tumors were kept standard for all the experiments.

The observed tumors were grouped in four major categories: neuroblastomas (similar to the human medulloblastomas), ependymomas, gliomas, and meningiomas.

Gliomas and meningiomas in the original records were also subclassified according to histotype. The distribution of the different histotypes in those two categories of tumors, however, did not seem to be relevant. Most of the gliomas are oligodendrogliomas.

Results*

The incidence and the latency time of brain tumors among 2,796 Sprague-Dawley and 170 Wistar untreated rats in our colony, and among 650 Sprague-Dawley rats following long-term treatment with olive oil, by gavage, are given in Tables 3 & 4, respectively.

The incidence of these tumors appears to be higher in Wistar rats (whose number, however, is lower). The treatment with olive oil does not appear to affect the onset of brain tumors.

Tables 5–16 give the results of the experiments studying the effects of the exposure by inhalation to the following: vinyl chloride (Tables 5–8), vinylidene

* The incidence of the tumors is referred to the total number of animals at start; the time of latency as age of the tumor-bearing animals.

sed were examined in order to determine

und was administered by inhalation, were
phic monitoring.
the same people. This is particularly im-
ne accustomed to the same operator.
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as far as the brain was concerned, careful
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s to be higher in Wistar rats (whose
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inyl chloride (TABLES 5–8), vinylidene

e total number of animals at start; the time

TABLE 22

THE INCIDENCE OF BRAIN TUMORS AMONG SPRAGUE-DAWLEY RATS, EXPOSED BY INGESTION TO VINYLIDENE FLUORIDE IN OLIVE OIL AT 8.25 AND 4.12 MG/KG BODY WT, ONCE DAILY, 4–5 DAYS WEEKLY, FOR 52 WEEKS *

				Tumors†											
				Ependymomas			Gliomas			Meningiomas			Total		
Group	Vinylidene Fluoride Dose (mg/kg body wt)	Animals Sex	Animals No. at Start	No.	%	Average Latency Time (Weeks)	No.	%	Average Latency Time (Weeks)	No.	%	Average Latency Time (Weeks)	No.	%	Average Latency Time (Weeks)
1	8.25	M	35	1	2.8	113.0	0	—	—	0	—	—	1	2.8	113.0
		F	35	0	—	—	0	—	—	0	—	—	0	—	—
		M & F	70	1	1.4	113.0	0	—	—	0	—	—	1	1.4	113.0
2	4.12	M	30	0	—	—	0		—	0	—	—	0	—	—
		F	30	0	—	—	1	3.3	116.0	0	—	—	1	3.3	116.0
		M & F	60	0	—	—	1	1.7	116.0	0	—	—	1	1.7	116.0
3	Controls	M	30	0	—	—	1	3.3	87.0	0	—	—	1	3.3	87.0
		F	30	0	—	—	0	—	—	0	—	—	0	—	—
		M & F	60	0	—	—	1	1.7	87.0	0	—	—	1	1.7	87.0
Total			190												

* Age of the animals at start: 13 weeks.
† No neuroblastomas were found.

TABLE 23

THE INCIDENCE OF BRAIN TUMORS AMONG SPRAGUE-DAWLEY RATS EXPOSED BY INGESTION TO TRICHLOROETHYLENE IN OLIVE OIL AT 250 AND 50 MG/KG BODY WT, ONCE DAILY, 4–6 DAYS WEEKLY, FOR 52 WEEKS*

Group	Trichloroethylene Dose (mg/kg body wt)	Animals		Tumors†								
				Gliomas			Meningiomas			Total		
		Sex	No. at Start	No.	%	Average Latency Time (Weeks)	No.	%	Average Latency Time (Weeks)	No.	%	Average Latency Time (Weeks)
1	250	M	30	0	—	—	0	—	—	0	—	—
		F	30	0	—	—	0	—	—	0	—	—
		M & F	60	0	—	—	0	—	—	0	—	—
2	50	M	30	1	3.3	100.0	0	—	—	1	3.3	100.0
		F	30	0	—	—	1	3.3	108.0	1	3.3	108.0
		M & F	60	1	1.7	100.0	1	1.7	108.0	2	3.3	104.0
3	Controls‡	M	30	1	3.3	87.0	0	—	—	1	3.3	87.0
		F	30	0	—	—	0	—	—	0	—	—
		M & F	60	1	1.7	87.0	0	—	—	1	1.7	87.0
Total			180									

* Age of the animals at start: 13 weeks.
† No neuroblastomas and ependymomas were found.
‡ Olive oil.

		M & F	60	0			0			0			
4	50	M	30	1	3.3	87.0	-			1	3.3	87.0	
		F	30	0						0			
		M & F	60	1	1.7	87.0	1	1.7	87.0	1	1.7	87.0	
5	Controls‡	M	30	1	3.3	87.0	0	--	--	1	3.3	87.0	
		F	30	0	—	--	0	—	—	0	—	—	
		M & F	60	1	1.7	87.0	0	—	—	1	1.7	87.0	
Total			180										

* Age of the animals at start: 13 weeks.
† No neuroblastomas and ependymomas were found.
‡ Olive oil.

TABLE 24

THE INCIDENCE OF BRAIN TUMORS AMONG SPRAGUE-DAWLEY RATS EXPOSED BY INGESTION TO BENZENE IN OLIVE OIL AT 250 AND 50 MG/KG BODY WT ONCE DAILY, 4–5 DAYS WEEKLY, FOR 52 WEEKS*

				Tumors†								
				Gliomas			Meningiomas			Total		
Group	Benzene Dose (mg/kg body wt)	Animals Sex	Animals No. at Start	No.	%	Average Latency Time (Weeks)	No.	%	Average Latency Time (Weeks)	No.	%	Average Latency Time (Weeks)
1	250	M	35	1	2.8	157.0	0	—	—	1	2.8	157.0
		F	35	0	—	--	1	2.8	123.0	1	2.8	123.0
		M & F	70	1	1.4	157.0	1	1.4	123.0	2	2.8	140.0
2	50	M	30	0	--	--	1	3.3	115.0	1	3.3	115.0
		F	30	0	—	—	0	—	-	0	—	-
		M & F	60	0	—	--	1	1.7	115.0	1	1.7	115.0
3	Controls‡	M	30	1	3.3	87.0	0	--	--	1	3.3	87.0
		F	30	0	—	—	0	—	-	0	—	-
		M & F	60	1	1.7	87.0	0	—	—	1	1.7	87.0
Total			190									

* Age of the animals at start: 13 weeks.
† No neuroblastomas or ependymomas were found.
‡ Olive oil.

TABLE 25

THE INCIDENCE OF BRAIN TUMORS AMONG SPRAGUE-DAWLEY RATS EXPOSED BY INGESTION TO 2 MG OF ASBESTOS (CROCYDOLITE) IN OLIVE OIL, ONCE EVERY TWO WEEKS, FOR 52 WEEKS*

			Tumors†											
			Ependymomas			Gliomas			Meningiomas			Total		
	Animals				Average Latency Time			Average Latency Time			Average Latency Time			Average Latency Time
Group	Sex	No. at Start	No.	%	(Weeks)	No.	%	(Weeks)	No.	%	(Weeks)	No.	%	(Weeks)
(1) 2 mg	M	40	0	—	—	0	—	—	0	—	—	0	—	—
Asbestos	F	40	0	—	—	0	—	—	0	—	—	0	—	—
(Crocy-dolite)	M & F	80	0	—	—	0	—	—	0	—	—	0	—	—
(2) Controls	M	75	0	—	—	1	1.3	108.0	1	1.3	76.0	2	2.7	92.0
(olive	F	75	1	1.3	87.0	2	2.7	114.2	1	1.3	92.0	4	5.3	101.7
oil)	M & F	150	1	0.7	87.0	3	2.0	112.0	2	1.3	84.0	6	4.0	98.5
Total		230												

* Age of the animals at start: 10 weeks.
† No neuroblastomas were found.

(1) 2 mg	M	40	0	—	—	0	—	—	0	—	—	0	—	—		
Asbestos	F	40	0	—	—	0	—	—	0	—	—	0	—	—		
(Crocy-	M & F	80	0	—	—	0	—	—	0	—	—	0	—	—		
dolite)																
(2) Controls	M	75	0	—	—	1	1.3	108.0	1	1.3	76.0	2	2.7	92.0		
(olive	F	75	1	1.3	87.0	2	2.7	114.2	1	1.3	92.0	4	5.3	101.7		
oil)	M & F	150	1	0.7	87.0	3	2.0	112.0	2	1.3	84.0	6	4.0	98.5		
Total		230														

* Age of the animals at start: 10 weeks.
† No neuroblastomas were found.

TABLE 26

THE INCIDENCE OF BRAIN TUMORS AMONG SPRAGUE-DAWLEY RATS, EXPOSED BY INGESTION TO POLYVINYL CHLORIDE (2 MG IN OLIVE OIL), ONCE EVERY TWO WEEKS FOR 52 WEEKS *

				Tumors†											
				Ependymomas			Gliomas			Meningiomas			Total		
		Animals				Average Latency Time			Average Latency Time			Average Latency Time			Average Latency Time
Group	PVC Dose	Sex	No. at Start	No.	%	(Weeks)	No.	%	(Weeks)	No.	%	(Weeks)	No.	%	(Weeks)
1	2 mg (suspension)	M	20	0	—	—	0	—	—	0	—	—	0	—	—
		F	20	0	—	—	0	—	—	0	—	—	0	—	—
		M & F	40	0	—	—	0	—	—	0	—	—	0	—	—
2	2 mg (emulsion)	M	20	0	—	—	0	—	—	0	—	—	0	—	—
		F	20	0	—	—	0	—	—	0	—	—	0	—	—
		M & F	40	0	—	—	0	—	—	0	—	—	0	—	—
3	Controls‡	M	75	0	—	—	1	1.3	108.0	1	1.3	76.0	2	2.7	92.0
		F	75	1	1.3	87.0	2	2.7	114.2	1	1.3	92.0	4	5.3	101.7
		M & F	150	1	0.7	87.0	3	2.0	112.0	2	1.3	84.0	6	4.0	98.5
Total			230												

* Age of the animals at start: 10 weeks.
† No neuroblastomas were found.
‡ Olive oil.

TABLE 27

THE INCIDENCE OF NEUROBLASTOMA IN SPRAGUE-DAWLEY RATS IN RELATION TO CONCENTRATION OF VINYL CHLORIDE ADMINISTERED BY INHALATION FOR 52 WEEKS

Experiments	Vinyl Chloride (ppm)	% Animals with Neuroblastoma		
		M	F	T
BT 6	30,000	3.3	—	1.7
BT 1	10,000	6.7	16.7	11.7
	6,000	6.9	3.3	5.1
	2,500	6.7	6.7	6.7
	500	—	—	—
	250	—	—	—
BT 2	200	—	—	—
	150	—	—	—
	100	—	—	—
BT 1, BT 9	50	—	—	
BT 15	25	—	—	—
	10	—	—	—
	5	—	—	—
	1	—	—	—
Controls BT 1, BT 2, BT 9, BT 15	0	—	—	—

chloride (TABLE 9), ethylene dichloride (TABLE 10), acrylonitrile (TABLE 11), styrene (TABLE 12), propylene (TABLE 13), trichlorofluoromethane (TABLE 14), dichlorodifluoromethane (TABLE 15), and chlorodifluoromethane (TABLE 16).

Under our experimental conditions, only two of the above-listed compounds, given by inhalation, appear to produce brain tumors, namely vinyl chloride and acrylonitrile.

Vinyl chloride appears to produce neuroblastomas both in Sprague-Dawley and Wistar rats, at a concentration of 30,000, 10,000, 6,000, and 2,500 ppm, when given for 52 weeks, 17 weeks, or less.

Acrylonitrile produces an increase in the incidence of gliomas (oligodendrogliomas) at 40 and 20 ppm.

TABLES 17–26 present the results of the experiments studying the effects of the exposure by ingestion to the following: vinyl chloride (TABLE 17), vinylidene chloride (TABLE 18), acrylonitrile (TABLE 19), styrene (TABLE 20), styrene oxide (TABLE 21), vinylidene fluoride (TABLE 22), trichloroethylene (TABLE 23), benzene (TABLE 24), asbestos (Crocydolite) (TABLE 25), and polyvinyl chloride (TABLE 26).

Under our experimental conditions none of the above-mentioned compounds, given by ingestion, seemed to produce brain tumors.

Conclusions and Discussion

In the reported experiments, two compounds, vinyl chloride and acrylonitrile, appeared to cause brain tumors, neuroblastomas and gliomas (oligodendrogliomas), respectively, when given by inhalation.

Such an effect is not seen with vinyl chloride at 500 ppm and below (Table 27) and with acrylonitrile at 10 ppm and below.

In Tables 28 and 29 the overall incidence of brain tumors (different types and totals) in Sprague-Dawley rats following exposure, respectively, by inhalation and ingestion to different industrial compounds, without taking into account concentrations and duration and schedule of treatment, is presented.

From Table 28 it appears that when the level of dose and the type of tumor are not considered, the incidence of brain tumors may be "lowered" to borderline levels.

Such an "artifact" finding, in our opinion, is extremely important, and it stresses the point that, in epidemiological investigations in humans, reference must always be made to defined types of tumors and to groups of individuals with the same level of exposure (homogeneous groups).

Our research in the field of carcinogenesis is now being extended to other industrial compounds.

Furthermore, in consideration of the higher responsiveness of embryos and newborn animals, we are now testing a series of compounds (including some of the ones considered in this report), by treating the breeders from the 12th day of pregnancy, and continuing the exposure of offsprings up to adult age.

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RAGUE-DAWLEY RATS IN RELATION TO NISTERED BY INHALATION, FOR 52 WEEKS

% Animals with Neuroblastoma		
M	F	T
3.3	—	1.7
6.7	16.7	11.7
6.9	3.3	5.1
6.7	6.7	6.7
—	—	—
—	—	—
—	—	—
—	—	—
—	—	—
—	—	
—	—	—
—	—	—
—	—	—
—	—	—
—	—	—

E 10), acrylonitrile (Table 11), styrene luoromethane (Table 14), dichlorodimethane (Table 16).
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TABLE 28

OVERALL INCIDENCE OF BRAIN TUMORS IN SPRAGUE-DAWLEY RATS, FOLLOWING THE EXPOSURE BY INHALATION TO DIFFERENT INDUSTRIAL COMPOUNDS

Agent	Animals Sex	Animals No. at Start	Tumors: Neuroblastomas No.	%	Average Latency Time (Weeks)	Ependymomas No.	%	Average Latency Time (Weeks)	Gliomas No.	%	Average Latency Time (Weeks)	Meningiomas No.	%	Average Latency Time (Weeks)	Total No.	%	Average Latency Time (weeks)
Vinyl chloride	M	780	7	0.9	77.0	1	0.1	123 0	6	0.8	104 7	2	0.2	113.0	16	2.0	94.7
	F	780	8	1.0	74.1	2	0.2	99.5	4	0.5	104.7	3	0 4	89.7	17	2.2	86.9
	MF	1,560	15	1.0	75.5	3	0.2	107.3	10	0.6	104.4	5	0.3	99.0	33	2.1	90.7
Vinylidene chloride	M	180	0	—	—	0	—	—	2	1.1	111.0	1	0.5	127.0	3	1.7	116.3
	F	180	0	—	—	1	0.5	95.0	1	0.5	84 0	2	1.1	116.0	4	2.2	102.7
	MF	360	0	—	—	1	0.3	95.0	3	0.8	102.0	3	0.8	119.7	7	1.9	108.6
Dichloro-ethane	M	360	0	—	—	0	—	—	1	0.3	155.0	0	—	—	1	0.3	155.0
	F	360	0	—	—	0	—	—	2	0.5	94.0	1	0.3	97.0	3	0.8	95.0
	MF	720	0	—	—	0	—	—	3	0.4	114.3	1	0.1	97.0	4	0.5	110.0
Acrylo-nitrile	M	120	0	—	—	0	—	—	3	2.5	82.3	1	0.8	99.0	4	3.3	86.5
	F	120	0	—	—	0	—	—	2	1.7	114.5	2	1.7	106.0	4	3.3	110 5
	MF	240	0	—	—	0	—	—	5	2.1	95.2	3	1.2	104 0	8	3.3	98 5

Vinyl loride	M	780	7	0.9	77.0	1	0.1	123.0	6	[illegible]	104.7	2	0.2	113.0	16	2.0	94.7
	F	780	8	1.0	74.1	2	0.2	99.5	4		104.7	3	0.4	89.7	17	2.2	86.9
	MF	1,560	15	1.0	75.5	3	0.2	107.3	10	0.6	104.4	5	0.3	99.0	33	2.1	90.7
Vinylidene chloride	M	180	0	—	—	0	—	—	2	1.1	111.0	1	0.5	127.0	3	1.7	116.3
	F	180	0	—	—	1	0.5	95.0	1	0.5	84.0	2	1.1	116.0	4	2.2	102.7
	MF	360	0	—	—	1	0.3	95.0	3	0.8	102.0	3	0.8	119.7	7	1.9	108.6
Dichloro-ethane	M	360	0	—	—	0	—	—	1	0.3	155.0	0	—	—	1	0.3	155.0
	F	360	0	—	—	0	—	—	2	0.5	94.0	1	0.3	97.0	3	0.8	95.0
	MF	720	0	—	—	0	—	—	3	0.4	114.3	1	0.1	97.0	4	0.5	110.0
Acrylo-nitrile	M	120	0	—	—	0	—	—	3	2.5	82.3	1	0.8	99.0	4	3.3	86.5
	F	120	0	—	—	0	—	—	2	1.7	114.5	2	1.7	106.0	4	3.3	110.5
	MF	240	0	—	—	0	—	—	5	2.1	95.2	3	1.2	104.0	8	3.3	98.5
Styrene	M	150	0	—	—	0	—	—	0	—	—	2	1.3	126.0	2	1.3	126.0
	F	150	0	—	—	0	—	—	1	0.7	106.0	3	2.0	112.7	4	2.7	111.0
	MF	300	0	—	—	0	—	—	1	0.3	106.0	5	1.7	118.0	6	2.0	116.0
Propylene	M	320	0	—	—	0	—	—	0	—	—	0	—	—	0	—	—
	F	320	0	—	—	0	—	—	0	—	—	1	0.3	111.0	1[•]	0.3	111.0
	MF	640	0	—	—	0	—	—	0	—	—	1	0.1	111.0	1	0.1	111.0
Trichloro-fluoro-methane	M	180	0	—	—	0	—	—	2	1.1	129.5	1	0.5	72.0	3	1.7	110.3
	F	180	0	—	—	1	0.5	103.0	1	0.5	75.0	3	1.7	89.3	5	2.8	89.2
	MF	360	0	—	—	1	0.3	103.0	3	0.8	111.3	4	1.1	85.0	8	2.2	97.1
Dichloro-difluoro-methane	M	180	0	—	—	0	—	—	4	2.2	102.5	0	—	—	4	2.2	102.5
	F	180	0	—	—	0	—	—	2	1.1	93.5	0	—	—	2	1.1	93.5
	MF	360	0	—	—	0	—	—	6	1.7	99.5	0	—	—	6	1.7	99.5
Chloro-difluoro-methane	M	120	0	—	—	0	—	—	2	1.7	78.5	1	0.8	124.0	3	2.5	93.7
	F	120	0	—	—	1	0.8	96.0	0	—	—	2	1.7	99.5	3	2.5	98.3
	MF	240	0	—	—	1	0.4	96.0	2	0.8	78.5	3	1.2	107.7	6	2.5	96.0
Controls	M	1,384	0	—	—	3	0.2	95.0	13	0.9	118.5	10	0.7	96.6	26	1.9	107.4
	F	1,412	0	—	—	4	0.3	105.5	8	0.6	81 3	9	0.6	117.1	21	1.5	101 3
	MF	2,796	0	—	—	7	0.2	101.0	21	0.7	104.3	19	0.7	106.3	47	1.7	104.6

TABLE 29

OVERALL INCIDENCE OF BRAIN TUMORS IN SPRAGUE-DAWLEY RATS FOLLOWING EXPOSURE BY INGESTION TO DIFFERENT INDUSTRIAL COMPOUNDS

Agent	Animals: Sex	Animals: No. at Start	Tumors*: Ependymomas: No.	Ependymomas: %	Ependymomas: Average Latency Time (Weeks)	Gliomas: No.	Gliomas: %	Gliomas: Average Latency Time (Weeks)	Meningiomas: No.	Meningiomas: %	Meningiomas: Average Latency Time (Weeks)	Total: No.	Total: %	Total: Average Latency Time (Weeks)
Vinyl chloride	M	345	2	0.6	103.5	5	1.4	101.6	1	0.3	120.0	8	2.3	104.4
	F	345	2	0.6	90.5	2	0.6	96.5	2	0.6	65.0	6	1.7	84.0
	M & F	690	4	0.6	97.0	7	1.0	100.1	3	0.4	83.3	14	2.0	95.6
Vinylidene chloride	M	200	1	0.5	86.0	1	0.5	80.0	2	1.0	116.0	4	2.0	99.5
	F	200	0	—	—	0	—	—	1	0.5	118.0	1	0.5	118.0
	M & F	400	1	0.2	86.0	1	0.2	80.0	3	0.7	116.7	5	1.2	103.2
Acrylonitrile	M	40	0	—	—	0	—	—	0	—	—	0	—	—
	F	40	0	—	—	1	2.5	43.0	0	—	—	1	2.5	43.0
	M & F	80	0	—	—	1	1.3	43.0	0	—	—	1	1.3	43.0
Styrene	M	80	0	—	—	1	1.2	106.0	1	1.2	90.0	2	2.5	98.0
	F	80	1	1.2	82.0	0	—	—	4	5.0	124.7	5	6.2	116.2
	M & F	160	1	0.6	82.0	1	0.6	106.0	5	3.1	117.8	7	4.4	111.0

Vinyl chloride	M	345	2	0.6	103.5	5	1.4		1	0.3	120.0	8	2.3	104.4
	F	345	2	0.6	90.5	2	0.6		2	0.6	65.0	6	1.7	84.0
	M & F	690	4	0.6	97.0	7	1.0	100.1	3	0.4	83.3	14	2.0	95.6
Vinylidene chloride	M	200	1	0.5	86.0	1	0.5	80.0	2	1.0	116.0	4	2.0	99.5
	F	200	0	—	—	0	—	—	1	0.5	118.0	1	0.5	118,0
	M & F	400	1	0.2	86.0	1	0.2	80.0	3	0.7	116.7	5	1.2	103.2
Acrylonitrile	M	40	0	—	—	0	—	—	0	—	—	0	—	—
	F	40	0	—	—	1	2.5	43.0	0	—	—	1	2.5	43.0
	M & F	80	0	—	—	1	1.3	43.0	0	—	—	1	1.3	43.0
Styrene	M	80	0	—	—	1	1.2	106.0	1	1.2	90.0	2	2.5	98.0
	F	80	1	1.2	82.0	0	—	—	4	5.0	124.7	5	6.2	116.2
	M & F	160	1	0.6	82.0	1	0.6	106.0	5	3.1	117.8	7	4.4	111.0
Styrene oxide	M	80	0	—	—	0	—	—	1	1.2	107.0	1	1.2	107.0
	F	80	0	—	—	0	—	—	3	3.7	128.3	3	3.7	128.3
	M & F	160	0	—	—	0	—	—	4	2.5	123.0	4	2.5	123.0
Vinylidene fluoride	M	65	1	1.5	113.0	0	—	—	0	—	—	1	1.5	113.0
	F	65	0	—	—	1	1.5	116.0	0	—	—	1	1.5	116.0
	M & F	130	1	0.8	113.0	1	0.8	116.0	0	—	—	2	1.5	114.5
Trichloro-ethylene	M	60	0	—	—	1	1.7	100.0	0	—	—	1	1.7	100.0
	F	60	0	—	—	0	—	—	1	1.7	108.0	1	1.7	108.0
	M & F	120	0	—	—	1	0.8	100.0	1	0.8	108.0	2	1.7	104.0
Benzene	M	65	0	—	—	1	1.5	157.0	1	1.5	115.0	2	3.1	136.0
	F	65	0	—	—	0	—	—	1	1.5	123.0	1	1.5	123.0
	M & F	130	0	—	—	1	0.8	157.0	2	1.5	119.0	3	2.3	131.7
Asbestos (Crocydolite)	M	40	0	—	—	0	—	—	0	—	—	0	—	—
	F	40	0	—	—	0	—	—	0	—	—	0	—	—
	M & F	80	0	—	—	0	—	—	0	—	—	0	—	—
Polyvinyl chloride	M	40	0	—	—	0	—	—	0	—	—	0	—	—
	F	40	0	—	—	0	—	—	0	—	—	0	—	—
	M & F	80	0	—	—	0	—	—	0	—	—	0	—	—
Controls†	M	325	1	0.3	104.0	3	0.9	102.0	3	0.9	102.3	7	2.1	102.4
	F	325	2	0.6	91.5	2	0.6	114.2	4	1.2	100.2	8	2.3	101.5
	M & F	650	3	0.5	95.7	5	0.8	106.9	7	1.1	101.1	15	2.3	101.9

* No neuroblastomas were found.
† Olive oil.