BIO-MEDICAL RESEARCH
DOCUMENT DESCRIPTION FORM

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R&S 112381

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Title of Report; end with space-hyphen-hyphen-space. Follow with Index Terms, separated from each other with comma-space. Avoid other punctuation; do not abbreviate.

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CENTRAAL INSTITUUT VOOR VOEDINGSONDERZOEK TNO

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CENTRAL INSTITUTE FOR NUTRITION AND FOOD RESEARCH
INSTITUT CENTRAL DE LA NUTRITION ET DE L'ALIMENTATION
ZENTRALINSTITUT FÜR ERNÄHRUNGSFORSCHUNG

Carl Smith
Hugh Tafuri

Chronic (two-year) oral toxicity study with vinyl chloride in rats

(Interim information III)

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R&S 112382

1. Conduct of the study

See Interim Information of 15th December 1975, given in Enclosure 1.

Vinyl chloride-treatment by gavage was discontinued in week 84 because the condition of the rats given 300 mg vinylchloride/kg body weight was rapidly declining and mortality in this group was high (55 %). Moreover, most of the rats of this group that died or were killed in extremis showed extensive liver damage (haemorrhages, focal necrosis), liver tumours or tumours at other sites.

2. Results available after a test period of 90 weeks

2.1. Body weights

Not affected.

2.2. Food consumption

Not distinctly affected.

2.3. Mortality

VCM (mg/kg body wt)	Total number of deaths*) at week 90 males	females
0	2	5
1	3	4
3	6	16
9	20	40
300 (by gavage)	46	44

*) Initial number of rats: 60 animals/sex/group

2.4. Haematology

Slightly decreased haemoglobin values in males of the 9 mg/kg group after 78 weeks.

2.5. Blood biochemistry

No indications of an adverse effect of vinyl chloride.

See also Interim information II, given in enclosure 2, § 2.5.

2.6. Liver function

See Interim information II, given in enclosure 2, § 2.6.

2.7. Urine analyses

No indications of an adverse effect of vinyl chloride.
See also Interim information II, given in enclosure 2, § 2.7.

2.8. Liver and kidney weights

See Interim information II, given in enclosure 2, §2.8.

2.9. Pathology

2.9.1. Rats killed after 26 and 52 weeks

See Interim information II, given in enclosure 2, § 2.9.1

2.9.2. Rats found dead or killed when moribund

See above table for mortality figures.

Gross autopsy findings allow the following preliminary information on both the occurrence of presumable tumours and the number of rats bearing these lesions (in some cases the gross diagnosis was confirmed by histological examination):

Control group:	Thymic tumour	1
	Mammary tumour	1
	Leukaemia	1
	Cervix tumour	1 4/7
1 mg/kg group:	Thymic tumour	1
	Uterus tumour	1
	Lymphoreticular tumour	1
	Mammary tumour	1
	Abdominal tumour	1 5/7
3 mg/kg group:	Liver nodules (tumours ?)	7
	Subcutaneous tumour	1
	Uterus tumour	1
	Pituitary tumour	1
	Mammary tumour	2
	Ovarian tumour	1 10/22

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9 mg/kg group:	Liver nodules (tumours ?)	40
	Pancreas tumour	1
	Thymic tumour	1
	Lymphoreticular tumour	2
	Mammary tumour	2
	Pituitary tumour	1
	Subcutaneous tumour 48/60	1
300 mg/kg group:	Liver nodules/haemorrhagic cysts (tumours ??)	40
	Pancreas tumour	3
	Pituitary tumour	1
	Lymphoreticular tumour	4
	Pulmonary nodules/haemorrhagic lesions (tumours ?)	9
	Nodules aer-duct area	2
	Abdominal tumour	1
	Mammary tumour	10
	Kidney mass (tumour ?) 71/90	1

3. Preliminary conclusion

From the results so far available it appears that the administration of vinyl chloride monomer to rats at levels of 9 (as PVC-powder in diet) and 300 mg/kg body weight (in soyaoil by gavage) resulted in obvious liver changes which in many cases seem to be neoplastic in nature. Moreover, there are indications that similar lesions also occur at the 3 mg/kg level, but so far are absent at the 1 mg/kg level.

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BY V.J. FERON JAN 18, 1977, EUROPE, DOW

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Attachment Nr. 1

CENTRAL INSTITUTE FOR NUTRITION AND FOOD RESEARCH TNO

Chronic oral toxicity study with vinyl chloride in rats

(Interim information IV)

1. Conduct of the study

Six hundred weanling albino rats (Wistar strain from the SPF-colony of the Central Institute for the Breeding of Laboratory Animals TNO, Zeist, The Netherlands) were divided into five groups of 60 males and 60 females each. The control group is fed a diet containing 10% PVC-powder free from vinyl chloride monomer (VCM). Three of the test groups are fed increasing levels of VCM-containing PVC, which is added to the diet at the expense of VCM-free PVC at levels resulting in a daily intake of approximately 1, 3, and 9mg VCM/kg body weight. The diets are freshly prepared daily just prior to use and the animals are allowed to eat them during a period of four hours each day. The fourth test group fed on stock diet received VCM in soya bean oil by gavage at a relatively high level (300mg VCM/kg body weight) once a day, five days a week. This group was merely added to find out whether oral administration of VCM at a high level results in tumours. For this group a real control group is not available. Nevertheless, a number of criteria studied in the other groups are also examined in this high-dose group.

Both the control group and the 9 and 300mg VCM/kg body weight groups were extended with 20 male and 20 female rats, of which ten males and ten females are killed for interim information after six and twelve months respectively.

Body weights, food consumption, haematology, urine analyses, biochemistry of the blood, organ weights, gross pathology, extensive histopathology, enzyme histochemistry and electron microscopy are used as criteria to disclose possible harmful effects.

An extra control group of 60 males and 60 females was added. This group is fed on stock diet containing 10% PVC-powder without VCM. The animals are housed in a room separate from that used for the other rats in the VCM experiment, thus preventing any contact of the rats with VCM. Moreover, these rats are fed the PVC diet ad libitum. Organs and tissues of all animals are preserved in formalin, and examined histologically only if necessary.

Treatment by gavage with vinyl chloride was discontinued in week 84 because the condition of the rats given 300mg vinyl chloride/kg body weight was rapidly declining and mortality in this group was high (55%). Moreover, most of the rats of this group that died or were killed in extremis showed extensive liver damage (haemorrhages, focal necrosis), liver tumours or tumours at other sites.

2. Results available after 104 weeks

2.1. Body weights

VCM (mg/kg body wt)	Average body weights (g) at week 104 males	Females
0	380	231
1	399	231
3	395	238
9	381	224
300 (by gavage)	458	270
0 (extra group)	568	352

2.2. Food consumption

Not distinctly affected in main study.

2.3. Mortality

VCM (mg/kg body wt)	Total number of deaths*) at week 36	60	80	104	36	60	80	104
	males				females			
0	0	0	0	7	0	0	1	7
1	0	1	1	6	0	1	2	13*
3	0	1	2	13	1	2	7	31
9	1	5	9	40	0	2	7	60
300 (by gavage)**)	6	8	21	53	4	8	24	56
0 (extra group)	0	0	1	19	0	3	4	20

*) Initial number of rats: 60/sex/group

**) Treatment discontinued in week 84

2.4. Haematology

Slightly decreased haemoglobin values in males of the 9mg/kg group after 78 and 94 weeks.

Decreased packed cell volume, increased number of white blood cells, decreased % of lymphocytes and increased % of neutrophils in males of the 9mg/kg group after 94 weeks.

2.5. Blood biochemistry

No indications of an adverse effect of VCM (the results of several enzyme activity determinations after 104 weeks were not yet available).

2.6. Liver function (determined in rats killed after 26 and 52 weeks)

Slightly decreased clotting time and BSP-retention at the 9mg/kg level both after 26 and 52 weeks.

2.7. Urine analyses

Slightly increased UGOT-values were found in females of the 3 and 9mg/kg groups after 13 weeks, and in females of the 9mg/kg group after 52 and 94 weeks, but not after 26 and 78 weeks.

After 78 and 94 weeks the pH of the urine was slightly lower and the number of bacteria in the urine was slightly higher in the 9mg/kg group than in controls and lower-dose animals.

2.8. Liver and kidney weights (determined in rats killed after 26 and 52 weeks)

Liver-to-body weight ratios were slightly increased in males and females of the 9mg/kg group both after 26 and 52 weeks. Relative kidney weights were not affected after 26 weeks, but were slightly increased in females of the 9mg/kg group after 52 weeks.

2.9. Pathology

2.9.1. Rats killed after 26 and 52 weeks

The livers of several male and female rats of the 9 and 300mg/kg groups killed after 26 and 52 weeks showed one or a few foci of cellular

alteration mainly being "clear cell foci". Degree and incidence of these liver changes were slightly higher a) after 52 than after 26 weeks, and b) in animals of the 9mg/kg group than in those of the 300mg/kg group (receiving VCM in oil by stomach tube!). In addition, after 52 weeks one male and one female of the 9mg/kg group had a hepatocellular carcinoma. Moreover, several females of the 9mg/kg group showed focal cystic hyperplasia of bile ducts (cystadenomas or adenofibrosis?).

2.9.2. Rats found dead or killed when moribund

GROSS PATHOLOGY (at 110 weeks)

Preliminary information on gross autopsy findings concerning the occurrence of presumable tumours (=t). Numbers of rats examined are given in parentheses.

Control group

Males (8):	Thymic t	1
	Lymphoreticular lung t	1
Females (7):	Lymphoreticular abd. t	1
	Subcutaneous t	1
	Uterine t	1
	Cervix t	2
	Mammary t	2
	Enlarged adrenals	1 8T/7rats

1mg/kg group

Males (7):	Thymic t	1
	Subcutaneous t	1
Females (13):	Liver nodules (tumours ?)	5*
	Pancreas t	1
	Mammary t	5
	Uterine t	3
	Cervix t	1
	Thymic t	1
	Lymphoreticular abd. t	1
	Enlarged adrenals	3 3T/13rats

3mg/kg group		
Males (14):	Liver nodules (tumours?)	1
	Leukaemia	2
	Subcutaneous t	1
	Thyroid t	1
	Zymbal gland t	1
Females (31):	Liver nodules (tumours?)	20
	Pituitary t	1
	Cervix t	1
	Mammary t	6
	Subcutaneous t	1
	Ovarian t	1
	Zymbal gland t	1
	Uterine t	3
9mg/kg group		
Males (41):	Liver nodules (tumours?)	25
	Pulmonary nodules	6
	Lymphoreticular abd.t	4
	Thymic t	1
	Zymbal gland t	1
	Pancreas t	1
	Mammary t	1
	Subcutaneous t	1
Females (60):	Liver nodules (tumours?)	56
	Pituitary t	4
	Mammary t	13
	Pulmonary nodules	5
	Subcutaneous t	1
	Uterine t	6
	Abdominal t	3
	Pancreas t	2

300mg/kg group		
Males (60):	Liver nodules (tumours?)	32
	Pulmonary nodules	20
	Subcutaneous t	1
	Zymbal gland t	1
	Mammary t	2
	Kidney t (?)	2
	Abdominal t	3
	Thymic t	1
	Pituary t	1
	Enlarged thyroid	4
Females (60):	Liver nodules (tumours?)	31
	Pulmonary nodules	16
	Pituitary t	7
	Mammary t	14
	Pancreas t	1
	Kidney t	1
	Zymbal gland t	3
	Uterine t	2
	Abdominal t	1
	Subcutaneous t	1
	Enlarged adrenals	6
Extra control group		
Males (13):	Leukaemia	2
	Abscess in Liver (?)	1
	Lymphoreticular abd. t	1
	Enlarged adrenals	2
	Enlarged thyroid	1
Females (16):	Mammary t	4
	Pituitary t	3
	Uterine t	3
	Lymphoreticular lung t	1
	Enlarged adrenals	1

MICROSCOPIC PATHOLOGY

Preliminary information on histological examination of several tumours of animals of various groups. Number of animals examined are given in parentheses.

Control group

No microscopic examination.

1mg/kg group

Males (1):	Thymic fibrosarcoma	1
Females (1):	Uterine adenocarcinoma	1

3mg/kg group

Males (2):	Leukaemia	1
Females (5):	Uterine leiomyosarcoma	1
	Hyperplastic liver cell nodule with atypia	1
	Reticular cell sarcoma	1
	Pituitary carcinoma	1

9mg/kg group

Males (8):	Hyperplastic liver cell nodule with atypia	1
	Angiosarcoma in liver/pancreas	1
	Subcutaneous sarcoma	1
	Abdominal sarcoma	1
Females (21):	Hyperplastic liver cell nodule with atypia	6
	Hepatocellular carcinoma	8
	Hepatic angiosarcoma	5
	Pituitary adenoma	3
	Mammary adenocarcinoma	2
	Mammary fibroadenoma	2
	Mammary adenoma	1
	Uterine adenocarcinoma	1
	Uterine polyp	2
	Adrenocortical adenoma	1
	Mesothelioma	1

300mg/kg group

Males (16):	Hyperplastic liver cell nodule with atypia	1
	Hepatic angiosarcoma	5
	Leukaemia	1

Females (20):	Hepatic angiosarcoma	8
	Pulmonary angiosarcoma	1
	Mammary adenocarcinoma	2
	Mammary fibroadenoma	1
	Uterine polyp	1
	Abdominal lymphoreticular malignancy	1

Extra control group

No microscopic examination.

Remark:

Many of the hepatic angiosarcomas had metastasized to the lungs. Occasionally it was difficult to discriminate between primary pulmonary angiosarcoma and metastasis from hepatic angiosarcoma.

3. Preliminary conclusion

From the results so far available it appears that the administration of vinyl chloride monomer to rats at levels of 9 (as PVC-powder in diet) and 300mg/kg body weight (in soya oil by gavage) resulted in obvious liver changes including hepatocellular carcinomas and angiosarcomas. Similar lesions are, very probably, also present in rats of the 3mg/kg group. Whether this type of hepatic changes also occurs at the 1mg/kg level is not yet clear.

CIVO-TNO
4.2.1977 JF

Attachment Nr. 2

CENTRAAL INSTITUUT VOOR VOEDINGSONDERZOEK

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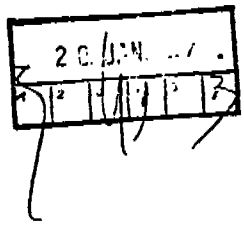

Verband Kunststofferzeugende Industrie e.V.
z.H. Herrn Dr. H. Bornemann
6 Frankfurt om Main
Karlstrasse 21 (Chemie-Haus)
Deutschland.

UW REF: UW DATUM: 21.12.1977 ONZE REF.: 7383 VF/F DATUM: 18th January, 1977

Dear Dr Bornemann,

Chronic oral toxicity study with VCM

Thank you for your letter of 21st December, 1976 authorizing us to continue the long-term oral study with VCM.

After discussions at CIVO and following contacts, by telephone with Dr Weigand (Hoechst), Dr Jager (Shell) and Drs van Esch (RIV) I should like to mention the following points:

1. Shell will continue to provide us with PVC powder.

2. The study will be terminated and the remaining animals killed and autopsied either, when only 25% of the controls are still alive, or when all test animals are dead. If there is an appreciable difference in mortality between males and females, the experiment will be stopped for males and females at different points of time. A complete histopathological examination is done on 20 males and 20 females of the control and two highest dose groups. The rats to be used for this examination are survivors and/or animals killed at a late stage of the experimental period. Histological examinations of the other animals are carried out according to the original plan.

cont.....

The additional costs are Dfl 30.-/rat/month. For the first month (10th Jan. to 10th Feb. 1977) the cost is estimated to be about Dfl 9,500.- . Bills covering the extra costs are sent once every three months.

3. Because many of the test animals still alive are expected to have liver nodules (tumours?), it might be important to determine once or twice (e.g. after 25 and 28 months) the α fetoprotein content of the blood serum.

The costs are at most Dfl 2,500.- for one determination in all rats and Dfl 4,500.- for two determinations in all rats.

4. Persorption of PVC particles has been reported to occur in rats, chickens, dogs, and pigs (Volkheimer, Ann. N.Y. Acad. Sci., 246, 1975, 164-171) following oral administration of PVC powder. We feel that it might be of interest to do some observations on possible persorption of the PVC powder used in our long-term study. Therefore, we propose to make an attempt to trace PVC particles in the blood and several other organs of a few rats given PVC powder suspended in soya been oil by gavage.

The costs are at most Dfl 2,500.-.

5. With reference to our letter of 24th April, 1975 (8875 FE/WW) I should like to bring to your attention the additional control group fed on stock diet containing 10% PVC powder without VCM and housed in a room separate from that used for the other rats in the long-term VCM experiment. So far, VKI and the other participating industries have not been charged for costs attached to the keeping of this group of rats. Therefore, we hope you have no objections to CIVO shortly sending bills together amounting to Dfl 19,200.-. This amount represents 40% of the maximum total costs going with the maintenance and complete examination of this extra group (see also the above mentioned letter). The mortality in this group is low, after

cont.....

an experimental period of two years, and we propose, therefore, to continue this group also. The additional costs are Dfl 20.-/rat/month. For the first month the costs are estimated to be Dfl 2,100.-.

We should highly appreciate your informing us at short notice whether you can agree to the above suggestions.

With kind regards,

Yours sincerely,

CENTRAL INSTITUTE FOR NUTRITION
AND FOOD RESEARCH TNO

Dr V.J. Feron
Dept Biological Toxicology