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FROM: T. G. Grumbles
DATE: June 12, 1990

VISTA

Interoffice Communication

SUBJ: PVC CARCINOGENICITY STUDY: ORAL ADMINISTRATION OF DOSE

Attached is a study conducted to assess the carcinogenic potential of PVC resin when administered by gavage (force feeding). In summary, PVC resin (suspension and emulsion), when suspended in olive oil and administered by gavage to rats every 2 weeks for 52 weeks, did not show any carcinogenic effects.

The attached is provided for your information. The Product Safety Assessment Group will review the study to determine if revisions should be made to our resin MSDS's.

T. G. Grumbles

dlj
.105

Attachment

Distribution: Brent White-OKC, Bruce Trego-Aber, Dave Penney, A. M. Nielsen, J. R. Roheim, Diana Fenton, Lee Matheson, Curt Elsik, John Kirkpatrick-Austin, W. L. McClain

cc: w/o attachment

T. H. Huffman

R. W. Seymour-Aber, H. Garrison-Okc

[redacted]

VVV 000013038

The Vinyl Institute

A Division of The Society of The Plastics Industry, Inc.

Roy T. Gottesman
Executive Director

Sec 1766

May 21, 1990

To: VI Health Safety & Environment Committee
VI Technical Committee's Medical Subcommittee
Jerome H. Heckman, Esq.

RE: Non Toxicite Du PVC -- Etude Maltoni 1989

Through the courtesy of Nancy Russotto of the European Council of Vinyl Manufacturers, I have received the enclosed document giving the results of a recent study by Professor Cesare Maltoni.

The report concludes that repeated administration of PVC dust in olive oil suspension by gavage to rats did not result in any carcinogenic effects.

Please note that the dissemination of this text must mention that the study will shortly be published in the Italian medical review, Acta Oncologia N° 1989/4. Further, it is required that the study must be circulated in its entirety, without omitting the curriculum vitae of the author.

Roy T. Gottesman

RTG:g

Enc.

VVV 000013039

SOLVAY & Cie
société anonyme

direction nationale pour le benelux
direction commerciale matières plastiques

24 AVR. 1990

NON TOXICITE DU PVC - ETUDE MALTONI 1989

Par notre téléfax du 12 octobre 1989, nous vous signalions l'existence de cette étude dont le résumé est :

"De la fine poudre de PVC, produite respectivement par polymérisation en suspension et en émulsion, a été administrée en suspension dans l'huile d'olive par gavage à deux groupes de 40 (20 mâles et 20 femelles) rats SPRAGUE-DAWLEY, âgés de 10 à 11 semaines au début de l'expérimentation. Deux mg de poudre de PVC ont été administrés en une fois toutes les 2 semaines durant 52 semaines (27 traitements). Le groupe contrôle était constitué d'animaux traités de la même façon et n'ingérant que de l'huile d'olive. Les animaux furent observés jusqu'à leur mort spontanée. Aucun effet cancérigène n'a été observé chez les animaux traités au PVC."

En bref, cela veut dire que l'on peut ingérer de la poudre de PVC sans encourir de risque de cancer.

Ainsi, contrairement au monomère chlorure de vinyle, dont le même Professeur MALTONI avait mis en évidence les effets cancérigènes, le polymère PVC est lui totalement inoffensif sur ce plan.

A présent, nous avons reçu, du Professeur MALTONI, l'autorisation d'utiliser et de communiquer son étude, à deux conditions :

- signaler que l'étude sera prochainement publiée dans la revue médicale italienne ACTA ONCOLOGICA n°1989/4,

- communiquer l'étude dans son entièreté, sans omettre le curriculum vitae de l'auteur.

VVV 000013040

Nous vous communiquons en annexe le texte de l'étude, tel que nous l'avons reçu, et la traduction française approuvée par le Professeur MALTONI.

ANNEXE

In stampa su Acta Oncologica 1989/4

# LONG-TERM CARCINOGENICITY BIOASSAYS OF POLYVINYLCHLORIDE (PVC) ADMINISTERED BY INGESTION (GAVAGE) ON SPRAGUE-DAWLEY RATS

Cesare MALTONI
Institute of Oncology "F. ADDARII", Bologna, Italy

## CURRICULUM VITAE OF PROFESSOR CESARE MALTONI, MD

Born in Faenza (Ravenna) Italy, on November 17, 1930. Graduated in Medicine and Surgery at the University of Bologna. Docent in General Pathology and Oncology. Director of the Institute of Oncology of Bologna since 1964. Professor at the school of Oncology of the University of Bologna.

Past President and Honorary President of Italian Society of Tumor Prevention, Detection and Therapy. Member of the Italian National Board of Health, and of the Italian Commission of Carcinogenesis, Teratogenesis and Mutagenesis. Past Chairman of International Committee of Human Tumor Characterisation. Member of the Académie Internationale de Lutèce, and of the "Académie des Sciences, des Arts et des Lettres". General Secretary of Collegium RAMAZZINI.

He is author of more than 320 scientific publications, and co-editor and contributing editor of several scientific series of books, and scientific journals.

His major contributions were :

1. the promotion of large scale screenings for early diagnosis of tumors,
2. the promotion of health surveillance of groups at carcinogenic risk,
3. the foundation of the Tumor Registry of Bologna, and,
4. the setting up of a large Experimental Unit of Industrial, Occupational and Environenmental Carcinogenesis (when it was shown that :
   1) vinyl chloride is experimentally a multipotential carcinogen, causing, among other tumors, angiosarcoma of the liver,
   2) benzene is an experimental multipotential carcinogen, and,
   3) many other widely produced and used compounds are carcinogens on experimental system.

## I. INTRODUCTION

A wide variey of vinyl chloride (VC) based resins, homopolymers (PVC) and copolymers, are available, with varying properties, for different, specific applications. The copolymers are made with low levels of other comonomers, such as vinyl acetate (PVCA) or ethylene. VC resins are used for the production of rigid, semirigid and flexible plastics. The rigid plastics are processed essentially without plasticizers. The semirigid, and flexible plastics contain plastizers, among which the most commonly used are the dialkyl phthalates. Other materials are alsc used in the production of VC plastics, such as pigments, fillers and light-and heat-stabilizers.

VC resins are among the most widely industrially produced polymers: world production may be evaluated in millions of tons (in some years over 10 millions).

The uses of VC plastics were as follows: building and construction industries, consumer goods, electrical appliances, packaging, transportation, and several other miscellaneous uses, which include plastic material for medical applications. The mayor uses of VC plastic packaging are in plasticized film, bottles and bottle-cap liners and gaskets.

VC plastics are largely used for packaging of food and of non alcoholic beverages. Packaging for alcoholic beverages was withdrawn because of the high migration of VC into the alcohol.

Implants of PVC and PVCA squares, discs or films in experimental rodents were shown to cause the onset of local sarcomas (IARC, 1979) (Table 1). The mechanism by which PVC and PVCA, as well as other solid materials (plastics, metals, etc.), can cause local tumors was and still is matter of debate. It may be hypothesyzed that the carcinogenic effect is due to physical change brought by solid material into the cellular environment (solid carcinogenesis ). It cannot be ruled out, however, that the carcinogenic effect is a consequence of the migration of soluble, reactive compounds (among which, in the case of polymers residual monomers) from the implanted material to the surrounding animal tissues. In the case of VC-based resins, this possibility is of particular relevance due to the fact that VC has been shown to be a multipotential carcinogen in experimental rodents and in humans (Maltoni et al., 1984).

Up to present the carcinogenic effects of PVC and PVCA have been studied only in experiments in which the material, under various forms, was implanted within the animal tissues.

In our opinion, the long-term biological effects of PVC deserve further and more specific research, also in consideration of its wide use for food and beverage packaging.

The present experiment was performed to study the long-term effects of PVC dust on rats, following repeated administrations by ingestion (gavage). With this type of treatment, gastro-intestinal mucosa is particularly exposed. However it must be also considered that after oral administration of PVC dust to experimental animals (including the rat), PVC particles are persorbed through the intestinal mucosa, can be found in the blood, and via the bloodstream they are

disseminated into all the organs (where individual particles can be found a long time later).

## II. MATERIALS, METHODS, PLAN AND CONDUCT OF THE EXPERIMENT

Fine PVC dust, produced by suspension and by emulsion polymerization, was tested on Sprague-Dawley rats, by ingestion (stomach tube).

Male and female Sprague-Dawley rats 10-11 week old at the start of the experiment were used. The animals, were of the breed currently employed at the Experimental Unit of the Bologna Institute of Oncology, in Bentivoglio (BT).

The plan of the experiment is shown in table 2.

Details on the conduct of the experiments are given in table 3.

Systematic and standardized histopathological examinations were performed on: brain and cerebellum, Zymbal glands, interscapular fat, salivary glands, Harderian glands, tongue, thymus, lungs, diaphragm, liver, kidneys, adrenals, spleen, oesophagus, stomach, various segments of the intestine, urinary bladder, uterus, gonads and any other organs with pathological lesions.

## III. RESULTS

The experiment ended after 130 weeks from start.

The treatment with PVC did not affect the survival rate and the body weight of the animals (Figures 1-4).

In rats of the strain used, the most frequently expected tumors on the basis of the literature and of the historical constrols of the BT Experimental Unit, are mammary tumors (benign and malignant), leukemias, pheochromocytomas and pheo-

chromoblastomas. Moreover, a variety of other miscellaneous tumors are also observed.

No tumors were observed in the digestive tract of rats administered with PVC. No increase was found in the treated groups, either in the percentage of animals with benign and malignant tumors, and of animals with malignant tumors, and in the number of malignant tumors per 100 animals (Table 4).

No differences in the incidence of benign and malignant mammary tumors, leukemias, pheochromocytomas, and pheochromoblastomas were observed among the various groups (Table 5).

The tratment did not affect the incidence of other benign and malignant tumors (Table 6).

No unexpected tumors were found in the tested animals.

## IV. CONCLUSIONS

Repeated administration of PVC dust in olive oil suspension, in the tested experimental conditions, did not show carcinogenic effects.

## SUMMARY

Fine PVC dust, produced by suspension and by emulsion polymerization, suspended in olive oil, was administered by gavage to two groups respectively of 40 (20 male and 20 female) Sprague-Dawley rats, 10-11 weeks old at the start of the experiment. Two mg of PVC dust were given once every 2 weeks for 52 weeks (27 treatments). Another group of animals, treated in the same way with olive oil alone served as a control. The animals were kept under observation until spontaneous death. No carcinogenic effects were observed in PVC dosed animals.

RIASSUNTO

Polvere fine di PVC, prodotta con polimerizzazione per sospensione ed emulsione, sospesa in olio di oliva, è stata somministrata per gavaggio, rispettivamente a due gruppi di 40 (20 maschi e 20 femmine) ratti Sprague-Dawley, di 10-11 settimane di età all'inizio dell'esperimento. Due mg di polvere di PVC sono stati somministrati una volta ogni 2 settimane, per 52 settimane (27 trattamenti). Un gruppo di animali, trattati nello stesso modo con solo olio di oliva, è stato usato come controllo. Gli animali sono stati tenuti sotto osservazione fino a morte spontanea. Negli animali trattati con PVC non sono stati riscontrati effetti cancerogeni.

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Table 1. Studies on PVC carcinogenicity

(first part)

| Test materials | | Animals | | | Site of implant | Tumors at the site of implant | | | References |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Bearing animals | | |
| Chemical characters | Physical characters | Species and strain | N. at start | N. corrected | | Type | N. | % | |
| PVC (commercial, with some additives) | Squares or disks (15 mm wide, 0.04 thick) | Wistar rats | 45 | 44 (1) | Abdominal wall | Sarcomas | 17 | 38.6 | Oppenheimer et al., 1952, 1953, 1955 |
| PVC (idem) | idem, perforated | Wistar rats | | 27 (2) | idem | – | 0 | – | |
| PVC (pure) | Film (0.03 mm thick) | Wistar rats | idem | | idem | Sarcomas | 4 (3) | | |
| Cotton | | Wistar rats | 50 | | idem | – | 0 | – | |
| PVC | Film (5X4 mm wide, 0.16 mm thick) | Wistar rats | 35 | 30 (4) | Intra-abdominal | Sarcomas<br>Fibromas | 1<br>1 | | Russel et al., 1959 |
| Glass | Similar size | Wistar rats | 25 | 20 (4) | idem | – | 0 | – | |

Table 1. Studies on PVC carcinogenicity

(second part)

| Test materials | | Animals | | | Site of implant | Tumors at the site of implant | | | References |
|---|---|---|---|---|---|---|---|---|---|
| Chemical characters | Physical characters | Species and strain | N. at start | N. corrected | | Type | Bearing animals N. | Bearing animals % | |
| PVC | Capsules | Rats | | 16 | Kidney | Sarcomas | 5 | 31 | Kogan and Tugarinova, 1959 |
| PVC | Film | Rats | | 5 | idem | Sarcomas | 2 | 40 | |
| PVC | Perforated film | Rats | | 5 | idem | Sarcomas | 1 | 20 | |
| PVC | Film | Albino rats | 80 | 16 (5) | Around kidney | Sarcomas | 6 | 37 | Raikhlin and Kogan, 1961 |
| PVCA | Film (15X22 mm which 0.2 mm thick) | CBA/H-T6 mice | 82 | | Sub-cutaneous tissue | Sarcomas | 60 | 65 (6)<br>≃100 (7) | Brand et al., 1967 a, b, 1975 |
| - | - | CBA/H-T6 mice | 80 | - | - | - | 0 | - | |
| PVCA | Particles (50-100 micron, corresponding by weight to 2 films 15X22X0.2 mm) | CBA mice | 76 | | Sub-cutaneous tissue | Sarcomas | 1 | | Brand et al., 1975 |

Table 1. Studies on PVC carcinogenicity

(third part)

| Test materials | | Animals | | | Site of implant | Tumors at the site of implant | | | References |
|---|---|---|---|---|---|---|---|---|---|
| Chemical characters | Physical characters | Species and strain | N. at start | N. corrected | | Type | Bearing animals N. | % | |
| PVCA | Film (15X22X0.2 mm) (15X7X0.2 mm) | Mice of 18 different strains | 9-124 | | Sub-cutaneous tissue | Tumors at the site of implant were observed in 16 of 18 strains. The incidence varied from strain to strain. The females were more responsive than the males (except in one strain) | | | Brand et al., 1967 |

(1) Alive at the appearance of the first tumor

(2) At risk

(3) Preliminary results after 533 days from implant

(4) Alive after 300 days

(5) Alive after 285-365 days

(6) In males, after 9-12 months

(7) In females, after 7-12 months

Table 2. Experiment BT28: Exposure by ingestion (stomach tube) to PVC dust in olive oil, at the single dose of 2 mg, once every 2 weeks, for 52 weeks

PLAN OF THE EXPERIMENT

| Group N. | Test material | Dose (every 2 weeks) (mg) | Animals (Sprague-Dawley rats, 10-11 weeks old) Sex | N. at start |
|---|---|---|---|---|
| I | PVC suspension granules | 2 | M | 20 |
| | | | F | 20 |
| | | | M+F | 40 |
| II | PVC emulsion granules | 2 | M | 20 |
| | | | F | 20 |
| | | | M+F | 40 |
| III | Olive oil (control) | - | M | 75 |
| | | | F | 75 |
| | | | M+F | 150 |
| Total | | | M | 115 |
| | | | F | 115 |
| | | | M+F | 230 |

Table 3. Experiment BT28: Exposure by ingestion (stomach tube) to PVC dust, in olive oil, at the single dose of 2 mg, once every 2 weeks, for 52 weeks

CONDUCT OF EXPERIMENT

- The animals were exposed by ingestion (stomach tube), to 2 mg of suspension or emulsion PVC, in 1 ml of olive oil, once every 2 weeks, for 52 weeks (27 treatments).
- All the animals were kept under control until spontaneous death.
- The status and behavieur of the animals were controlled twice daily.
- The animals were submitted to clinical examination for gross changes every 2 weeks.
- The animals were weighted every 2 weeks during the treatment period, and then every 8 weeks.
- Full necropsy and systemic histopathological examination were performed on all the animals.
- The housing and the diet of the animals were the same, highly standardized ones, adopted in the BT Experimental Unit over the last 15 years.

Table 4. Experiment BT20: Exposure by ingestion (stomach tube) to PVC dust in olive oil, at the single dose of 2 mg, once every 2 weeks, for 52 weeks
Duration of the biophase: 136 weeks

THE INCIDENCE (%) OF TOTAL TUMORS

| Group N. | Test material | Animals Sex | N. at start | % of animals bearing tumors TBMT(1) | MT(2) | N. of malignant tumors per 100 animals |
|---|---|---|---|---|---|---|
| I | PVC | M | 20 | 10.0 | 10.0 | 10.0 |
| | suspension granules | F | 20 | 55.0 | 20.0 | 20.0 |
| | | M+F | 40 | 32.5 | 15.0 | 15.0 |
| II | PVC | M | 20 | 10.0 | - | - |
| | emulsion granules | F | 20 | 65.0 | 10.0 | 10.0 |
| | | M+F | 40 | 37.5 | 5.0 | 5.0 |
| III | Olive oil | M | 75 | 17.3 | 8.0 | 8.0 |
| | (control) | F | 75 | 52.0 | 22.7 | 24.0 |
| | | M+F | 150 | 34.7 | 15.3 | 16.0 |

(1) Total benign and malignant tumors

(2) Malignant tumors

Table 5. Experiment DT20: Exposure by ingestion (stomach tube) to PVC dust in olive oil, at the single dose of 2 mg, once every 2 weeks, for 52 weeks
Duration of the biophase: 136 weeks

THE INCIDENCE (%) OF MAMMARY TUMORS, LEUKEMIAS, PHEOCHROMOCYTOMAS AND PHEOCHROMOBLASTOMAS

| Group N. | Test material | Animals Sex | N. at start | % of animals bearing tumors Mammary tumors BMT(1) | MT(2) | Leukemias | Pheochromocytomas | Pheochromoblastomas |
|---|---|---|---|---|---|---|---|---|
| I | PVC | M | 20 | - | - | - | - | - |
| | suspension granules | F | 20 | 50.0 | 10.0 | - | - | - |
| | | M+F | 40 | 25.0 | 5.0 | - | - | - |
| II | PVC | M | 20 | - | - | - | 5.0 | - |
| | emulsion granules | F | 20 | 60.0 | 5.0 | 5.0 | - | - |
| | | M+F | 40 | 30.0 | 2.5 | 2.5 | 2.5 | - |
| III | Olive oil | M | 75 | 2.7 | - | 5.3 | 2.7 | - |
| | (control) | F | 75 | 46.7 | 9.3 | 4.0 | 2.7 | - |
| | | M+F | 150 | 24.7 | 4.7 | 4.7 | 2.7 | - |

(1) Benign (fibromas and fibroadenomas) and malignant (adenocarcinomas) tumors

(2) Malignant tumors

Table 6. Experiment BT28: Exposure by ingestion (stomach tube) to PVC dust in olive oil, at the single dose of 2 mg, once every 2 weeks, for 52 weeks.
Duration of the biophase: 136 weeks

THE INCIDENCE (%) OF OTHER TYPES OF TUMORS

(first part)

| Group N. | Test material | Animals Sex | N. at start | % of animals bearing tumors Benign | | Malignant | |
|---|---|---|---|---|---|---|---|
| I | PVC suspension granules | M | 20 | Skin acanthoma | 5.0 | Cholangiocarcinoma | 5.0 |
| | | | | Neurilemmoma | 5.0 | Islet cell carcinoma | 5.0 |
| | | F | 20 | – | – | Skin carcinoma | 5.0 |
| | | M+F | 40 | Total | 5.0 | Total | 10.0 |
| II | PVC emulsion granules | M | 20 | Leydig cell tumor | 5.0 | – | – |
| | | F | 20 | Polypus of the uterus | 5.0 | – | – |
| | | M+F | 40 | Total | 5.0 | Total | – |

Table 6. Experiment RT28: Exposure by ingestion (stomach tube) to PVC dust in olive oil, at the single dose of 2 mg, once every 2 weeks, for 52 weeks.
Duration of the bioassay: 136 weeks

THE INCIDENCE (%) OF OTHER TYPES OF TUMORS

(second part)

| Group N. | Test material | Animals Sex | N. at start | % of animals bearing tumors Benign | | Malignant | |
|---|---|---|---|---|---|---|---|
| III | Olive oil (control) | M | 75 | Exocrine pancreas adenomas | 2.7 | Meningioma | 1.3 |
| | | | | Forestomach acanthomas | 2.7 | Oligodendroglioma | 1.3 |
| | | F | 75 | Polypus of the glandular stomach | 1.3 | Zymbal gland carcinoma | 1.3 |
| | | | | Cholangioma | 1.3 | Kidney adenocarcinoma | 1.3 |
| | | | | Adrenal gland cortical adenoma | 1.3 | Adenocarcinoma of the uterus | 1.3 |
| | | | | | | Fibrosarcoma of the uterus | 1.3 |
| | | | | | | Ependymoma | 1.3 |
| | | | | | | Meningioma | 1.3 |
| | | | | | | Oligodendrogliomas | 2.7 |
| | | M+F | 150 | Total | 4.7 | Total | 6.7 |

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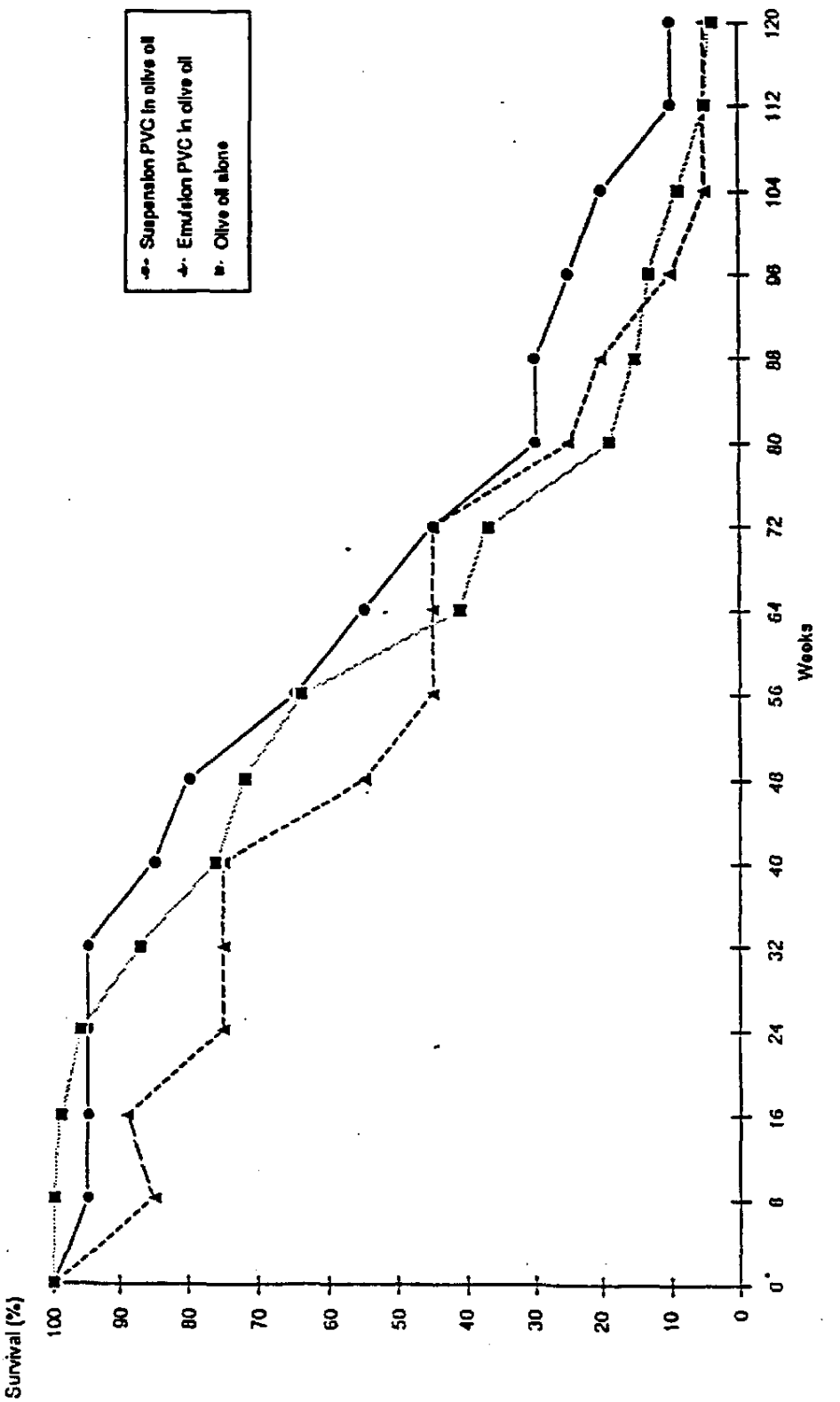
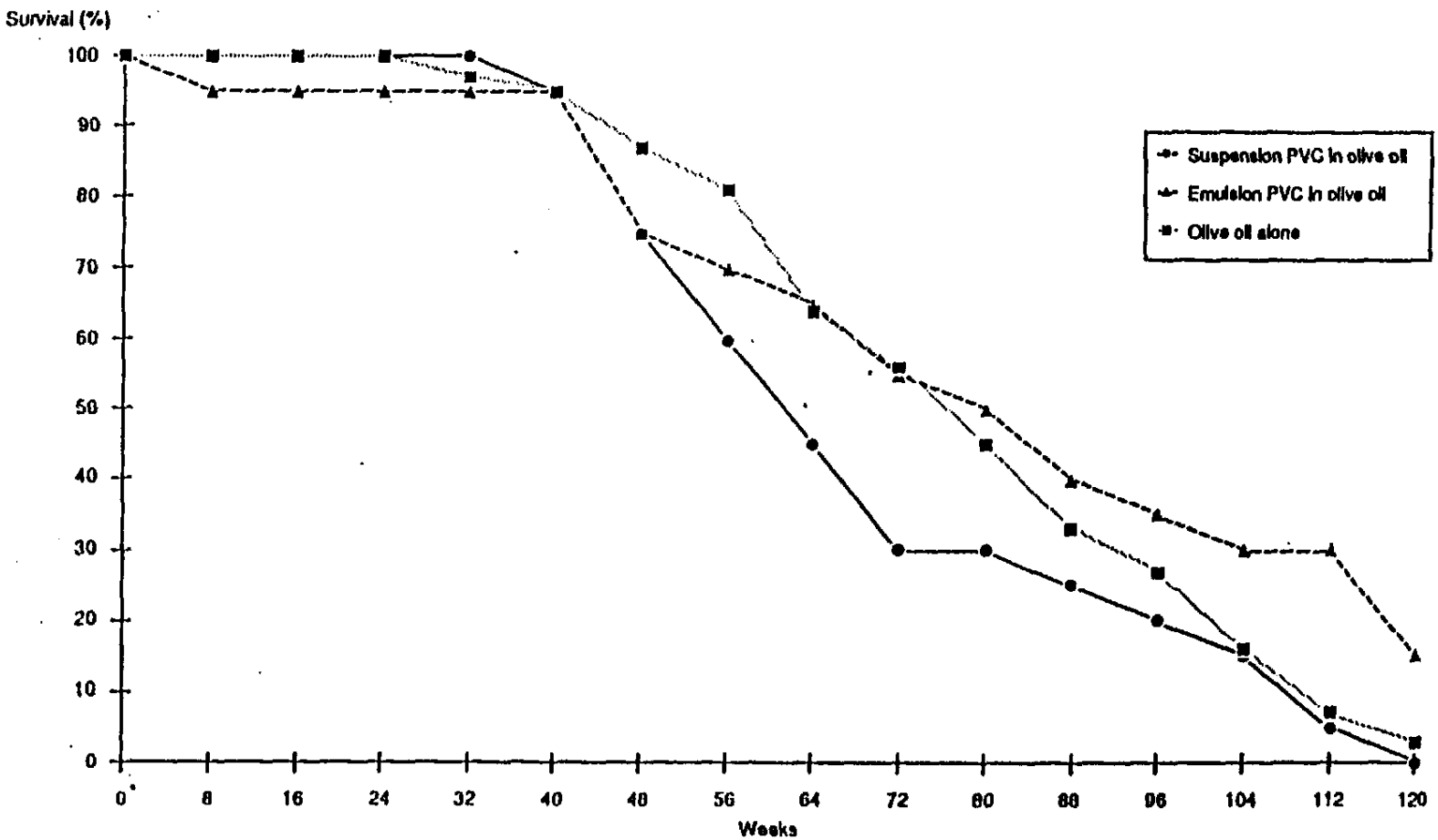



Figure 1. Experiment DT28: Survival of male Sprague-Dawley rats.

Figure 2. Experiment BT28: Survival of female Sprague-Dawley rats.




* Start of the treatment

Figure 3. Experiment DT28: Body weight of male Sprague-Dawley rats.

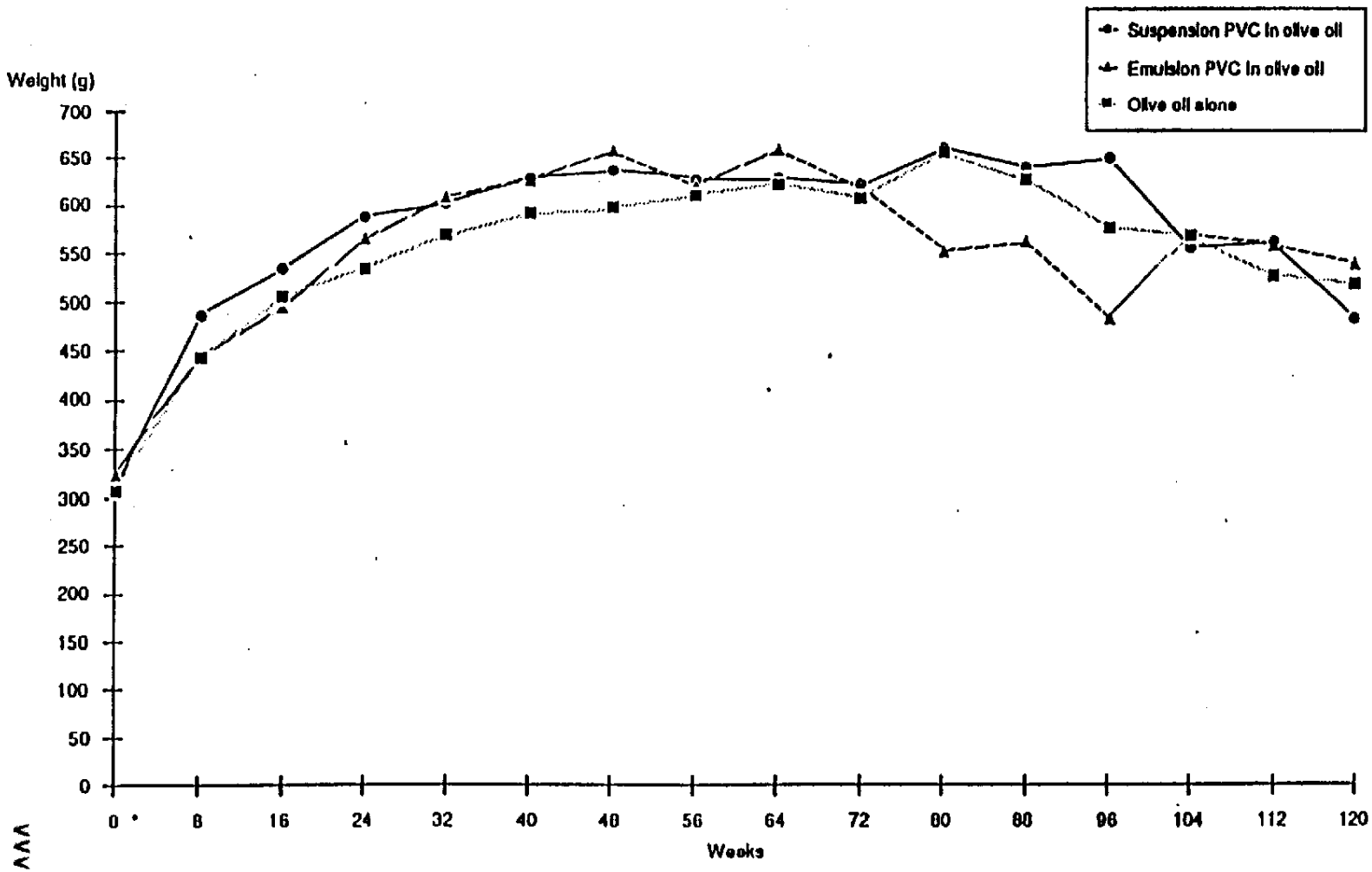


Figure 4. Experiment BT28: Body weight of female Sprague-Dawley rats.