# Results of a Long-term Experimental Study on the Carcinogenicity of Vinyl Acetate Monomer in Mice

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## INTRODUCTION

Vinyl acetate monomer (VAM) is an important monomer of the plastics industry. It is a colorless liquid, insoluble in water, soluble in ethanol, ether, acetone, benzene, chloroform, and carbon tetrachloride, with a vapor pressure of 115 mm Hg at 25°C. VAM was produced for the first time in 1912. It is produced commercially mainly by two processes: in one, used since 1920, acetylene and acetic acid are reacted in the vapor phase over a catalyst bed; in the other the ethylene is reacted with acetic acid in the presence of oxygen. Commercial production of VAM was first reported in the United States in 1928.[1,2]

VAM is produced in many countries: Japan (6 companies), China and the United States (5 companies), Germany and the Russian Federation (2 companies), and Brazil, Canada, France, Mexico, Poland, Romania, Spain, Thailand, the United Kingdom and Venezuela. The total world capacity of VAM production was about 1,000,000 tonnes in 1965. World production rose to 3,000,000 tonnes in 1982, but had decreased to 2,500,000 tonnes by 1988. In the United States, VAM ranks 40th among the 50 most highly produced (by volume) chemicals.[3]

VAM is used primarily to produce polyvinyl acetate emulsions and polyvinyl alcohol (these uses account for about 75% of the total VAM produced worldwide). It is also used for the production of polyvinyl-acetals, of ethylene-vinyl acetate copolymers, and polyvinyl-acetate chloride copolymers. The multiple uses of the various VAM products have been recently reviewed.[3]

Polyvinyl acetate is an intermediate in the conversion to polyvinyl alcohol and acetals. Its principal use is in adhesives for paper, wood, glass, metals, and porcelain. It is also used: in latex water paint; for paper coating, for textile and leather finishing; as a base for inks and lacquers, in heat-sealing films, in shatterproof photographic

bulbs; as an emulsifying agent in cosmetics, pesticide formulations and pharmaceuticals; and as a food additive.

Polyvinyl acetate is used as a component in the production of chewing gum; the amount of the polymer used in chewing gum varies from country to country: in some European countries it is higher than average, while in the United States it seems to be lower (around 5% of the final product in the United States).

Polyvinyl alcohol is used in sizing for textile warp and yarn, in laminating adhesives, photosensitive films and cements, as a binder for cosmetics, ceramics, leather, nonwoven fabrics and paper, and as an emulsifying agent, thickener, and stabilizer. It is the most highly produced (by volume) synthetic water-soluble plastic in the world.

Polyvinyl acetals are produced by the condensation of polyvinyl alcohol with an aldehyde. Commonly used aldehydes are formaldehyde, acetaldehyde, and butyralhyde. Polyvinyl formal, polyvinyl acetal, and polyvinyl butyral are mainly used in adhesives, paints, lacquers, and films. Polyvinyl butyral is used in sheet form as an interlayer in safety glasses and as shatter-resistant acrylic protection in aircraft.

Ethylene-vinyl acetate copolymers improve the adhesive properties of hot-melt and pressure-sensitive adhesives. They are also used in medical tubing, milk packaging, and beer-dispensing equipment. Plastic containers with barrier layers of ethylene-vinyl alcohol copolymers are replacing many glass and metal containers for packaging food.

Polyvinyl chloride-acetate copolymers, compounded with plasticizers, are used for cable and wire coverings, in chemical plants, and in protective garments.

The occupational exposure limits for vinyl acetate in various industrial countries range from 10 to 70 mg/m$^3$.[3] Polyvinyl acetate, ethylene-vinyl acetate-vinyl alcohol copolymers, ethylene-vinyl acetate copolymers, vinyl acetate-vinyl chloride copolymers, and vinyl acetate-crotonic acid copolymers have been approved for use by the United States Food and Drug Administration[4] as components of surfaces in contact with food and beverages.

VAM has an irritative effect on the upper respiratory system in humans. After subchronic and chronic exposure by inhalation it causes, in experimental animals, hyperplasia, metaplasia of the respiratory epithelium, and bronchitis and bronchiolitis.[3]

Experimental studies on reproductive and prenatal effects have shown that VAM causes parental toxicity (including decreased fertility), developmental toxicity, and minor skeletal alterations.[3]

VAM shows genotoxic effects both in human and rodent cells.[3]

*In vitro,* VAM is metabolized, mainly by hydrolysis, to acetaldehyde and acetic acid.[5,6] Rats exposed to VAM exhaled acetaldehyde as a result of hydrolysis by esterase.[6,7] Acetaldehyde is known to be carcinogenic in experimental animals,[8] and its carcinogenic potential was clearly demonstrated by a recent research performed on rats in our laboratory.[9]

Although VAM has been commercially produced for more than 60 years and represents a major monomer of the plastics industry, the carcinogenicity studies on this monomer are, in our opinion, still inadequate.

To date, five experimental studies on VAM carcinogenicity are reported in the scientific literature. In a first experiment, performed in our laboratory in the early '70s, a group of 96 male and female Sprague-Dawley rats was exposed by inhalation

for 4 hours per day, 5 days per week, for 52 weeks, to 2,500 ppm (maximum tolerated concentration) of VAM. Early mortality was high: only 49 animals survived for 26 or more weeks. No tumors related to VAM were reported during 135 weeks.[10–12] Because of the poor survival of the animals, this study was not adequate for exposing the carcinogenic potential of the monomer.

In a second experiment VAM was administered at the doses of 2500, 1000, and 0 mg/l in drinking water for 100 weeks, to groups of 20 male and 20 female Fischer F344 rats, 7 to 8 weeks of age, which were then kept under observation for the rest of their life span (130 weeks). An increase of liver neoplastic nodules, of uterine adenocarcinomas and polyps, and of thyroid C-cell adenomas was observed.[13] It must be noted that the number of the animals tested was small, and that the histopathological examination was limited to gross lesions and major organs only.

The results of three further carcinogenicity experiments, in which VAM was administered by inhalation to mice and rats, and by drinking water, *in utero,* to rats, were published in 1994.

In the inhalation experiment on mice, groups each of 60 male and 60 female Swiss mice, about 7 weeks of age, were exposed to 600, 200, 50, and 0 ppm vinyl acetate (purity >99%) for 6 hours per day, 5 days a week, for about 104 weeks. No treatment-related increase in tumor incidence was observed.[14]

In the inhalation experiment on rats, groups of 60 male and 60 female Sprague-Dawley rats, about 7 weeks of age, were exposed to 600, 200, 50, and 0 ppm vinyl acetate (purity >99%) for 6 hours per day, 5 days a week, for about 104 weeks. A slightly increased incidence of nasal cavity tumors (benign and malignant) was found in animals of each sex.[14]

In the *in utero* drinking water experiment on rats, a total of 72 male and 144 female Sprague-Dawley rats (age unspecified) were divided into 4 groups and received vinyl acetate (purity >99%) at 5000, 1000, 200, and 0 mg/l in the drinking water. Treatment commenced 10 weeks before mating; treatment of males was continued for an additional 4 weeks and that of females throughout mating, gestation, and lactation. Two males of the $F_0$ generation in each group were paired with one female from the same group for up to 15 days. After weaning, groups of 60 male and 60 female $F_1$ pups were selected and were administered 5000, 1000, 200, and 0 mg/l vinyl acetate in drinking water for 104 weeks. No treatment-related increase in tumor incidence was observed.[15]

One must note that in these last three experiments the biophase was truncated at 104 weeks, thus not allowing the animals to express to the possible maximum extent their neoplastic potentialities.

Two studies on the carcinogenicity of VAM were performed in humans. In a cohort study aimed at identifying the specific exposure associated with an excess of lung cancer risk in a United States synthetic chemical plant, 19 chemicals were considered, one of which was VAM: the subgroup with undifferentiated large-cell lung cancer had had slightly higher cumulative exposure to VAM.[16]

A nested case-control study was conducted in a cohort of 29,139 men, employed in two large chemical manufacturing facilities and a research and development center in the United States, who had died in 1940-78 with non-Hodgkin's lymphoma, multiple myeloma, lymphocytic leukemia, or nonlymphocytic leukemia as the underlying or contributing cause of death. Exposure to 21 chemicals was assessed on the

basis of information about work activity, work area, and production over time. Potential exposure to vinyl acetate was reported for 7 of 52 men who had died with non-Hodgkin's lymphoma (odds ratio 1.2), 3 of 20 with multiple myeloma (odds ratio 1.6), 2 of 39 with nonlymphocytic leukemia (odds ratio 0.5), and 2 of 18 with lymphocytic leukemia (odd ratio 1.8).[17]

These two studies on workers do not allow any conclusions to be drawn on the carcinogenic potential of VAM.

The International Agency for Research on Cancer (IARC) Monograph of 1995[3] concludes that VAM is possibly carcinogenic to humans (Group 2B), on the basis of the available results both of carcinogenicity studies and of other information relevant to an evaluation of carcinogenicity of the monomer—namely, the evidence that: (1) VAM is biotransformed into acetaldehyde; (2) VAM and acetaldehyde are genotoxic in human and animal cells; (3) acetaldehyde is carcinogenic in experimental animals; and (4) VAM and acetaldehyde induce nasal tumors after administration by inhalation.

In the '80s we started a project of three long-term bioassays for assessing the carcinogenic potential of VAM. These studies were performed with a similar protocol on Sprague-Dawley rats, Wistar rats, and Swiss mice. This report deals with the results of the experiment on mice.

## MATERIALS AND METHODS

VAM was supplied by an Italian chemical plant. The analyses of the sample of VAM supplied showed the following impurities:

- benzene 30-45 ppm
- methyl and ethyl acetate 50 ppm
- crotonaldehyde 6-16 ppm
- acetaldehyde 2-11 ppm
- acetone 330-500 ppm

Male and female Swiss mice were used.

VAM was administered in drinking water at two concentrations for 78 weeks. The experiment included breeders and offspring. The treatment of male and female breeders and of male and female offspring started when the female breeders were at the 12th day of pregnancy.

The plan of the experiment is shown in TABLE 1.

All animals were kept under control for their life span. The drinking water with or without the monomer was changed every morning. The solutions of VAM were prepared just before the daily water supply was provided.

The mice were submitted daily to observation and weighed periodically, weekly within the first 13 weeks of the experiment, every 2 weeks until the treatment was

**TABLE 1.** Long-term Carcinogenicity Bioassays on Vinyl acetate (VAM), Administered to Swiss Mice in Drinking Water Supplied ad Libitum (BT 52): Plan of the Experiment

| Group No. | Concentration (ppm, v/v) | Animals | | |
|---|---|---|---|---|
| | | Age at Start (weeks) | Sex | No. |
| I | 5,000 | 17 (breeders) | M | 13 |
| | | | F | 37 |
| | | | M + F | 50 |
| | | Embryos (offspring) | M | 49 |
| | | | F | 48 |
| | | | M + F | 97 |
| II | 1,000 | 17 (breeders) | M | 13 |
| | | | F | 37 |
| | | | M + F | 50 |
| | | Embryos (offspring) | M | 37 |
| | | | F | 44 |
| | | | M + F | 81 |
| III | 0[a] | 17 (breeders) | M | 14 |
| | | | F | 37 |
| | | | M + F | 51 |
| | | Embryos (offspring) | M | 38 |
| | | | F | 48 |
| | | | M + F | 86 |

[a] Drinking water alone.

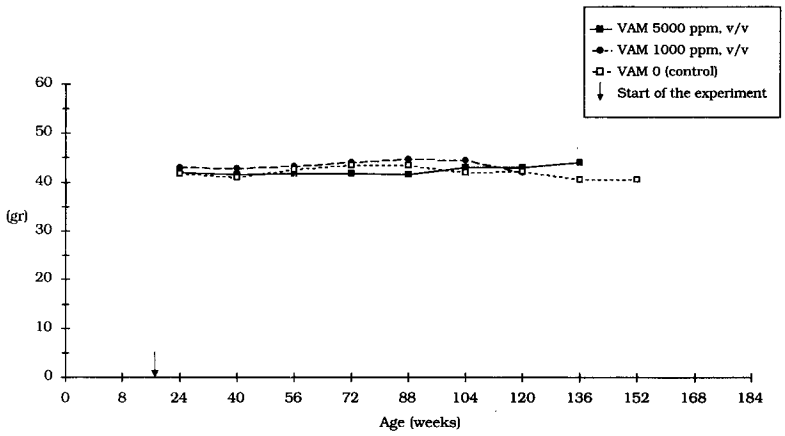


**FIGURE 1.** Mean body weight in male breeder mice.

stopped, and then every 8 weeks until the end of the experiment. In order to detect and register all gross lesions, the animals were examined every week for the first 13 weeks, and then every 2 weeks until the end of the experiment.

At death all animals were submitted to systemic necropsy. Specimens for histopathology include: brain, pituitary gland, Zymbal glands, salivary glands, Herderian glands, head (5 sections) (only in animals that survived more than 100 weeks), tongue, thyroid, thymus and mediastinal lymph nodes, lung, heart, diaphragm, liver, spleen, pancreas, kidneys and adrenal glands, esophagus, stomach, intestine (4 levels), bladder, prostate, uterus, gonads, interscapular fat pad, subcutaneous and mesenteric lymph nodes, and any other organs and tissues with pathological lesions. All organs and tissues were preserved in 70% ethyl alcohol, except bones, which were fixed in 10% formalin and then decalcified with a 10% formaldehyde and 20% formic acid in water solution. The normal specimens were trimmed, following the standard procedures of the Bentivoglio laboratory: i.e., parenchymal organs were dissected through the hilus to expose the widest surface, and hollow organs were sectioned across the greatest diameter(s). The pathological tissue was trimmed to allow for the largest surface, including normal adjacent tissues. The trimmed specimens were processed as paraffin blocks, and 3-5-micron sections of every specimen were obtained. Sections were routinely stained with hematoxylin-eosin. Specific stainings were performed when needed. All slides were examined microscopically by the same group of pathologists; a senior pathologist reviewed all the tumors and any other lesion of oncological interest. All pathologists followed the same criteria of histopathological evaluation and classification.

## RESULTS

*Body Weight.* There were no differences in mean body weight in treated and control groups of male and female breeders (FIGS. 1, 2). In the treated offspring at

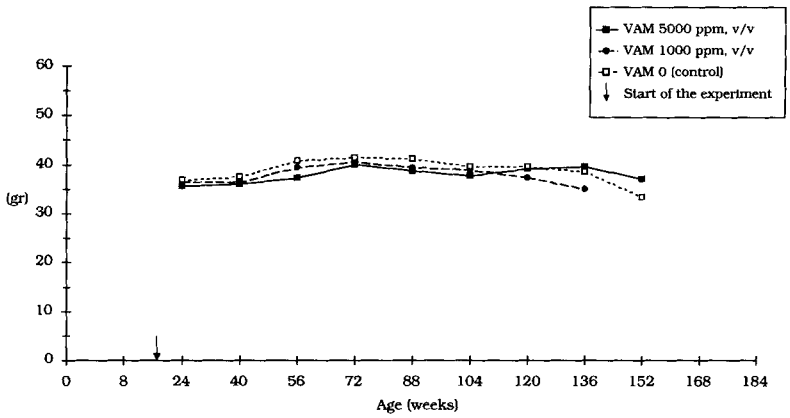


**FIGURE 2.** Mean body weight in female breeder mice.

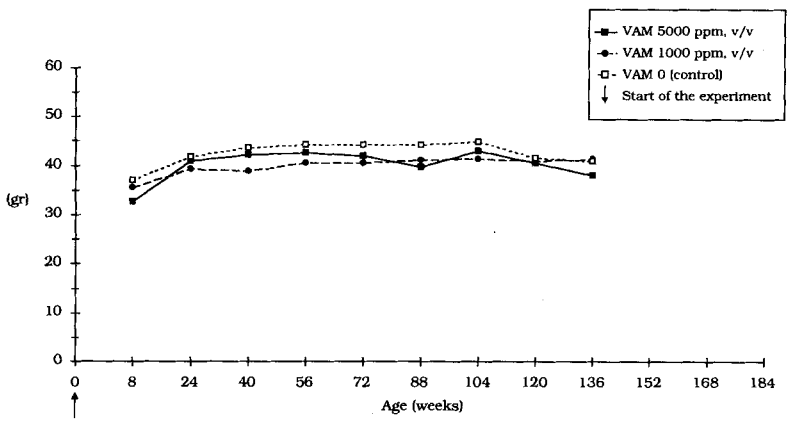


**FIGURE 3.** Mean body weight in male offspring mice.

both tested doses, there is a slight decrease in mean body weight in the animals of both sexes, more evident in females (FIGS. 3, 4).

*Survival.* In male breeders up to 72 weeks of age, there was a decrease in survival of treated animals at both doses; then from 72 to 120 weeks an increase of survival was observed among the animals treated with the higher dose (FIG. 5). The female breeders treated with the lower dose had a slight decrease in survival (FIG. 6). In male and female offspring treated with the higher dose an increase in survival was observed (FIGS. 7, 8).

*Nononcological Changes.* No evident behavioral changes were observed in VAM treated animals. No treatment-related nononcological pathological changes were detected by gross inspection and histological examination.

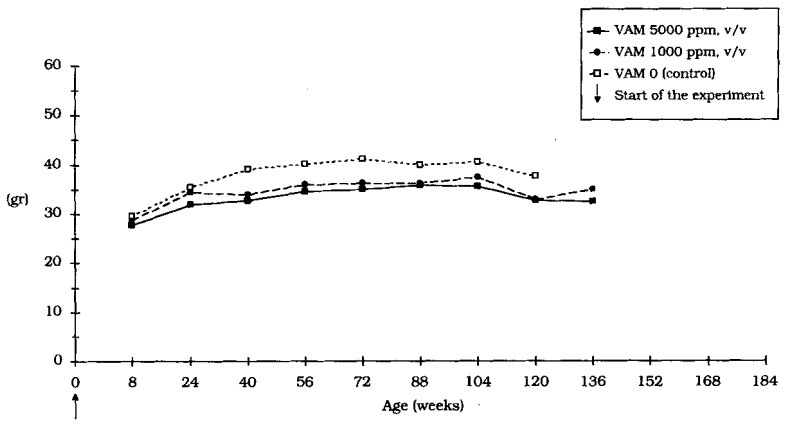


**FIGURE 4.** Mean body weight in female offspring mice.

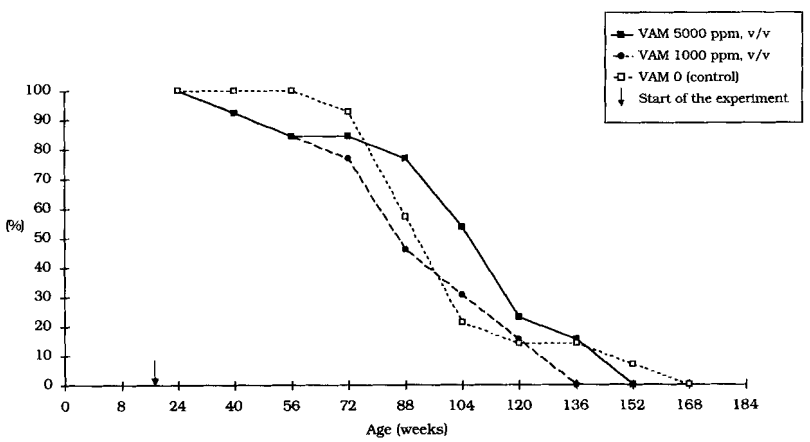


**FIGURE 5.** Survival in male breeder mice.

*Tumors.* The entire results are shown in TABLES 2 and 3. Multiple tumors of the same site (monolateral and bilateral organs) and type were plotted only once, apart from mammary and pulmonary tumors of the same type, whose multiplicity has been taken into account.

At the higher dose VAM increases the incidence of total benign tumors in female breeders and offspring (TABLE 4). An increase of total malignant tumors has been observed in male and female breeders and offspring treated with the higher dose (TABLE 5). Such increase was sharper among offspring.

Zymbal gland carcinomas were more numerous among female breeders treated with the higher dose, among female and male offspring treated with the higher dose,

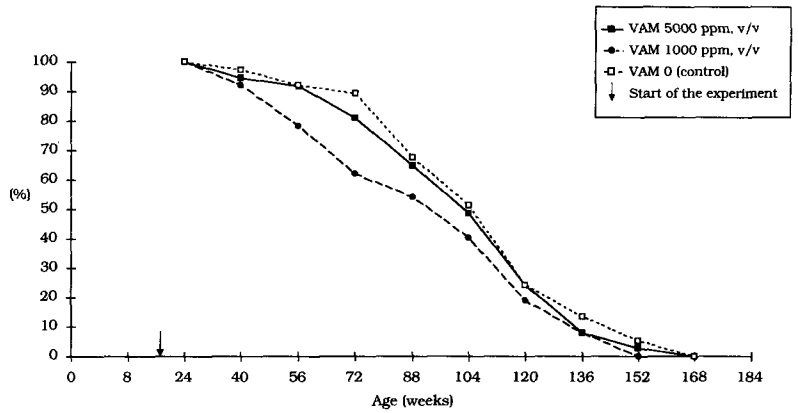


**FIGURE 6.** Survival in female breeder mice.

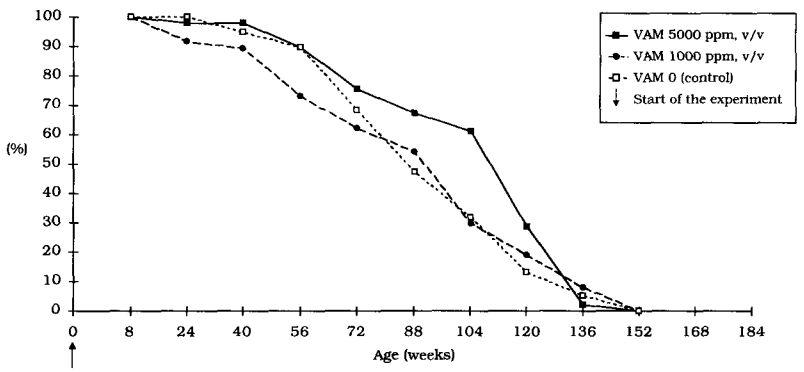


**FIGURE 7.** Survival in male offspring mice.

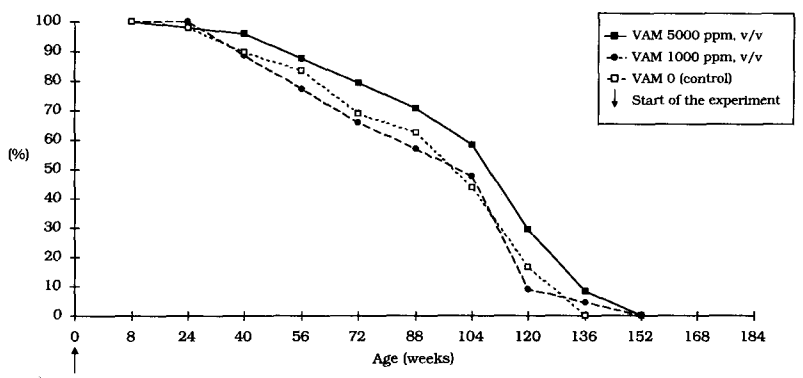


**FIGURE 8.** Survival in female offspring mice.

TABLE 2. Long-term Carcinogenicity Bioassays on Vinyl Acetate (VAM), Administered to Swiss Mice in Drinking Water Supplied ad Libitum (Experiment BT 52): Number and Percentage of Male Swiss Mice Bearing Various Types of Benign and Malignant Tumors[a]

| | | Groups | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | I: 5000 ppm | | | | II: 1000 ppm | | | | III: 0 (Control) | | | |
| | | Breeders | | Offspring | | Breeders | | Offspring | | Breeders | | Offspring | |
| Site | Histotype | No. | % | No. | % | No. | % | No. | % | No. | % | No. | % |
| Skin | Squamous cell carcinoma | 0 | – | 0 | – | 0 | – | 0 | – | 0 | – | 1 | 2.6 |
| Mammary gland[b] | Adenocarcinoma | 0 | – | 0 | – | 0 | – | 1 | 2.7 | 0 | – | 0 | – |
| Harderian glands | Adenoma | 1 | 7.7 | 1 | 2.0 | 0 | – | 1 | 2.7 | 1 | 7.1 | 4 | 10.5 |
| | Adenocarcinoma | 0 | – | 1 | 2.0 | 0 | – | 0 | – | 0 | – | 0 | – |
| Zymbal glands[c] | Carcinoma | 0 | – | 2 | 4.1 | 0 | – | 0 | – | 0 | – | 0 | – |
| Oral cavity[d] | Squamous cell carcinoma | 1 | 7.7 | 10 | 20.4 | 0 | – | 0 | – | 0 | – | 0 | – |
| Tongue[e] | Squamous cell carcinoma | 1 | 7.7 | 7 | 14.3 | 0 | – | 0 | – | 0 | – | 1 | 2.6 |
| Lung[f] | Adenoma | 3 (4) | 23.1 | 11 (19) | 22.4 | 2 | 15.4 | 6 (9) | 16.2 | 2 (3) | 14.3 | 6 (7) | 15.8 |
| | Adenocarcinoma | 2 (4) | 15.4 | 2 | 4.1 | 2 | 15.4 | 0 | – | 2 | 14.3 | 1 | 2.6 |
| Esophagus[g] | Squamous cell carcinoma | 0 | – | 12 | 24.5 | 0 | – | 0 | – | 0 | – | 0 | – |
| Stomach | | | | | | | | | | | | | |
| Forestomach[h] | Acanthoma | 1 | 7.7 | 8 | 16.3 | 0 | – | 1 | 2.7 | 0 | – | 0 | – |
| | Squamous cell carcinoma | 0 | – | 2 | 4.1 | 0 | – | 0 | – | 0 | – | 0 | – |
| Glandular stomach[i] | Adenomatous polyp | 0 | – | 0 | – | 0 | – | 1 | 2.7 | 0 | – | 0 | – |
| | Adenocarcinoma | 1 | 7.7 | 0 | – | 0 | – | 0 | – | 0 | – | 1 | 2.6 |
| Intestine | Adenocarcinoma | 0 | – | 0 | – | 0 | – | 0 | – | 0 | – | 1 | 2.6 |
| Liver[j] | Angioma and fibroangioma | 1 | 7.7 | 0 | – | 0 | – | 0 | – | 1 | 7.1 | 1 | 2.6 |
| | Hepatocarcinoma | 2 | 15.4 | 17 | 34.7 | 4 | 30.7 | 8 | 21.6 | 3 | 21.4 | 10 | 26.3 |
| | Angiosarcoma | 1 | 7.7 | 2 | 4.1 | 0 | – | 0 | – | 0 | – | 2 | 5.3 |
| Pancreas | Islet cell adenoma | 1 | 7.7 | 0 | – | 0 | – | 0 | – | 1 | 7.1 | 1 | 2.6 |
| Kidneys | Adenoma | 0 | – | 0 | – | 0 | – | 0 | – | 0 | – | 1 | 2.6 |
| | Adenocarcinoma | 0 | – | 2 | 4.1 | 0 | – | 1 | 2.7 | 0 | – | 1 | 2.6 |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Seminal vesicles | Adenoma | 0 | – | 0 | – | 0 | – | 0 | – | 0 | – | 2 | 5.3 |
| | Adenocarcinoma | 0 | – | 1 | 2.0 | 0 | – | 0 | – | 0 | – | 0 | – |
| Testes | Leydig cell tumor | 0 | – | 1 | 2.0 | 0 | – | 2 | 5.4 | 0 | – | 1 | 2.6 |
| | Angioma | 0 | – | 0 | – | 0 | – | 0 | – | 0 | – | 1 | 2.6 |
| Peritoneum | Angiosarcoma | 0 | – | 1 | 2.0 | 0 | – | 1 | 2.7 | 0 | – | 0 | – |
| Thyroid gland | C-cell carcinoma | 1 | 7.7 | 0 | – | 0 | – | 0 | – | 0 | – | 0 | – |
| Adrenal glands | Cortical adenoma | 0 | – | 0 | – | 0 | – | 1 | 2.7 | 0 | – | 0 | – |
| | Pheochromocytoma | 0 | – | 0 | – | 0 | – | 0 | – | 0 | – | 3 | 7.9 |
| | Pheochromoblastoma | 0 | – | 0 | – | 1 | 7.7 | 0 | – | 0 | – | 0 | – |
| Bones | | | | | | | | | | | | | |
| Cranium | Osteosarcoma | 0 | – | 1 | 2.0 | 0 | – | 0 | – | 0 | – | 0 | – |
| Heart | Angiosarcoma | 0 | – | 0 | – | 0 | – | 0 | – | 0 | – | 1 | 2.6 |
| Mediastinum | Fibroangioma | 0 | – | 0 | – | 0 | – | 0 | – | 1 | 7.1 | 0 | – |
| Spleen | Angioma and fibroangioma | 0 | – | 2 | 4.1 | 0 | – | 1 | 2.7 | 0 | – | 0 | – |
| | Angiosarcoma | 0 | – | 2 | 4.1 | 0 | – | 1 | 2.7 | 0 | – | 1 | 2.6 |
| Mesenteric lymph nodes | Fibroangioma | 0 | – | 0 | – | 1 | 7.7 | 0 | – | 0 | – | 0 | – |
| Hemolymphoreticular tissues[k,l] | Lymphomas and leukemias | 4 | 30.8 | 23 | 46.9 | 2 | 15.4 | 17 | 45.9 | 4 | 28.6 | 15 | 39.5 |

[a] The numbers in parentheses indicate the number of tumors (one animal can bear more than one tumor).
[b] See TABLE 15.
[c] See TABLE 6.
[d] See TABLE 7.
[e] See TABLE 8.
[f] See TABLE 12.
[g] See TABLE 9.
[h] See TABLE 10.
[i] See TABLE 11.
[j] See TABLE 13.
[k] See TABLE 16.
[l] Including spleen and mesenteric lymph nodes.

TABLE 3. Long-term Carcinogenicity Bioassays on Vinyl Acetate (VAM), Administered to Swiss Mice in Drinking Water Supplied ad Libitum (Experiment BT 52): Number and Percentage of Female Swiss Mice Bearing Various Types of Benign and Malignant Tumors[a]

| | | Groups | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | I: 5000 ppm | | | | II: 1000 ppm | | | | III: 0 (Control) | | | |
| | | Breeders | | Offspring | | Breeders | | Offspring | | Breeders | | Offspring | |
| Site | Histotype | No. | % | No. | % | No. | % | No. | % | No. | % | No. | % |
| Skin | Squamous cell carcinoma | 0 | – | 1 | 2.1 | 0 | – | 0 | – | 0 | – | 0 | – |
| Subcutaneous tissue | Angiosarcoma | 0 | – | 0 | – | 0 | – | 1 | 2.3 | 0 | – | 1 | 2.1 |
| Interscapular fat pad | Angiosarcoma | 0 | – | 1 | 2.1 | 0 | – | 0 | – | 0 | – | 0 | – |
| Mammary gland[b] | Adenocarcinoma | 6 | 16.2 | 7 | 14.6 | 4 | 10.8 | 5 | 11.4 | 6 (7) | 16.2 | 9 (10) | 18.8 |
| | Liposarcoma | 0 | – | 3 | 6.3 | 1 | 2.7 | 0 | – | 0 | – | 0 | – |
| | Angiosarcoma | 0 | – | 0 | – | 0 | – | 2 | 4.5 | 0 | – | 0 | – |
| Harderian glands | Adenoma | 1 | 2.7 | 4 | 8.3 | 0 | – | 2 | 4.5 | 1 | 2.7 | 2 | 4.2 |
| | Adenocarcinoma | 0 | – | 1 | 2.1 | 0 | – | 1 | 2.3 | 0 | – | 0 | – |
| Zymbal glands[c] | Carcinoma | 1 | 2.7 | 4 | 8.3 | 0 | – | 2 | 4.5 | 0 | – | 0 | – |
| Oral cavity[d] | Carcinoma | 1 | 2.7 | 9 | 18.8 | 0 | – | 0 | – | 0 | – | 0 | – |
| Tongue[e] | Carcinoma | 3 | 8.1 | 12 | 25.0 | 1 | 2.7 | 0 | – | 0 | – | 0 | – |
| Lung[f] | Adenoma | 6 (10) | 16.2 | 11 (21) | 22.9 | 6 (8) | 16.2 | 3 | 6.8 | 3 | 8.1 | 6 (7) | 12.5 |
| | Adenocarcinoma | 1 | 2.7 | 3 (4) | 6.3 | 1 | 2.7 | 1 | 2.3 | 0 | – | 0 | – |
| Esophagus[g] | Acanthoma | 1 | 2.7 | 3 | 6.3 | 0 | – | 0 | – | 0 | – | 0 | – |
| | Squamous cell carcinoma | 6 | 16.2 | 18 | 37.5 | 0 | – | 0 | – | 0 | – | 0 | – |
| Stomach | | | | | | | | | | | | | |
| Forestomach[h] | Acanthoma | 5 | 13.5 | 11 | 22.9 | 0 | – | 0 | – | 0 | – | 0 | – |
| | Squamous cell carcinoma | 3 | 8.1 | 7 | 14.6 | 0 | – | 0 | – | 0 | – | 0 | – |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Glandular stomach[i] | Adenocarcinoma | 1 | 2.7 | 1 | 2.1 | 0 | – | 0 | – | 0 | – | – |
| Intestine | Adenocarcinoma | 0 | – | 1 | 2.1 | 0 | – | 0 | – | 0 | – | – |
| Liver[d] | Cholangioma | 1 | 2.7 | 4 | 8.3 | 0 | – | 1 | 2.3 | 0 | – | 1 | 2.1 |
| | Angioma | 1 | 2.7 | 0 | – | 0 | – | 1 | 2.3 | 0 | – | 1 | 2.1 |
| | Hepatocarcinoma | 0 | – | 2 | 4.2 | 0 | – | 0 | – | 0 | – | 1 | 2.1 |
| | Angiosarcoma | 0 | – | 1 | 2.1 | 0 | – | 0 | – | 1 | 2.7 | 1 | 2.1 |
| Pancreas | Islet cell adenoma | 1 | 2.7 | 2 | 4.2 | 1 | 2.7 | 3 | 6.8 | 2 | 5.4 | 0 | – |
| Kidneys | Adenoma | 0 | – | 0 | – | 1 | 2.7 | 0 | – | 0 | – | 0 | – |
| Ovaries | Cystadenoma | 0 | – | 3 | 6.2 | 1 | 2.7 | 2 | 4.5 | 0 | – | 3 | 6.2 |
| | Granulosa cell tumor | 0 | – | 0 | – | 0 | – | 1 | 2.3 | 0 | – | 1 | 2.1 |
| | Theca cell tumor | 0 | – | 0 | – | 0 | – | 0 | – | 0 | – | 1 | 2.1 |
| | Sertoli cell tumor | 0 | – | 1 | 2.1 | 0 | – | 1 | 2.3 | 0 | – | 0 | – |
| | Angioma and fibroangioma | 1 | 2.7 | 0 | – | 2 | 5.4 | 2 | 4.5 | 1 | 2.7 | 0 | – |
| | Adenocarcinoma | 1 | 2.7 | 1 | 2.1 | 0 | – | 1 | 2.3 | 0 | – | 0 | – |
| | Granulosa cell malignant tumor | 1 | 2.7 | 0 | – | 0 | – | 0 | – | 0 | – | 0 | – |
| Uterus[k] | Polyp | 3 | 8.1 | 7 | 14.6 | 2 | 5.4 | 4 | 9.1 | 5 | 13.5 | 5 | 10.4 |
| | Leiomyoma | 2 | 5.4 | 6 | 12.5 | 0 | – | 3 | 6.8 | 1 | 2.7 | 2 | 4.2 |
| | Angioma and fibroangioma | 0 | – | 1 | 2.1 | 1 | 2.7 | 2 | 4.5 | 1 | 2.7 | 2 | 4.2 |
| | Squamous cell carcinoma | 0 | – | 1 | 2.1 | 0 | – | 0 | – | 0 | – | 0 | – |
| | Adenocarcinoma | 6 | 16.2 | 7 | 14.6 | 2 | 5.4 | 6 | 13.6 | 1 | 2.7 | 5 | 10.4 |
| | Leiomyosarcoma | 2 | 5.4 | 4 | 8.3 | 0 | – | 2 | 4.5 | 1 | 2.7 | 0 | – |
| | Angiosarcoma | 0 | – | 0 | – | 0 | – | 1 | 2.3 | 0 | – | 0 | – |
| Peritoneum | Mesothelioma | 1 | 2.7 | 0 | – | 0 | – | 0 | – | 0 | – | 0 | – |
| Pituitary gland | Adenoma | 0 | – | 1 | 2.1 | 0 | – | 1 | 2.3 | 0 | – | 0 | – |
| Thyroid gland | C-cell adenoma | 0 | – | 0 | – | 0 | – | 0 | – | 0 | – | 1 | 2.1 |
| Adrenal glands | Pheochromocytoma | 0 | – | 2 | 4.2 | 0 | – | 1 | 2.3 | 0 | – | 0 | – |
| Bones | Osteosarcoma | 0 | – | 0 | – | 0 | – | 1 | 2.3 | 1 | 2.7 | 0 | – |

TABLE 3. Long-term Carcinogenicity Bioassays on Vinyl Acetate (VAM), Administered to Swiss Mice in Drinking Water Supplied ad Libitum (Experiment BT 52): Number and Percentage of Female Swiss Mice Bearing Various Types of Benign and Malignant Tumors[a] (*continued*)

| | | Groups | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | I: 5000 ppm | | | | II: 1000 ppm | | | | III: 0 (Control) | | | |
| | | Breeders | | Offspring | | Breeders | | Offspring | | Breeders | | Offspring | |
| Site | Histotype | No. | % | No. | % | No. | % | No. | % | No. | % | No. | % |
| Spleen | Angioma and fibroangioma | 1 | 2.7 | 0 | – | 0 | – | 2 | 4.5 | 1 | 2.7 | 0 | – |
| | Angiosarcoma | 0 | – | 1 | 2.1 | 0 | – | 1 | 2.3 | 0 | – | 2 | 4.2 |
| Mesenteric lymph nodes | Fibroangioma | 1 | 2.7 | 0 | – | 0 | – | 0 | – | 0 | – | 0 | – |
| Hemolymphoreticular tissues[l,m] | Lymphomas and leukemias | 18 | 48.6 | 33 | 68.8 | 22 | 59.5 | 28 | 63.6 | 18 | 48.6 | 27 | 56.3 |

[a] The numbers in parentheses indicate the number of tumors (one animal can bear more than one tumor).
[b] See TABLE 15.
[c] See TABLE 6.
[d] See TABLE 7.
[e] See TABLE 8.
[f] See TABLE 12.
[g] See TABLE 9.
[h] See TABLE 10.
[i] See TABLE 11.
[j] See TABLE 13.
[k] See TABLE 14.
[l] See TABLE 16.
[m] Including spleen and mesenteric lymph nodes.

**TABLE 4.** Results of Long-term Carcinogenicity Bioassays on Vinyl Acetate (VAM), Administered to Swiss Mice in Drinking Water Supplied ad Libitum (BT 52): Total Benign Tumors

| Group No. | Concentration (ppm, v/v) | Animals | | | Benign tumors | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | Animals Bearing Tumors | | Tumors | |
| | | Age at Start (weeks) | Sex | No. | No. | % | No. | Per 100 Animals |
| I | 5,000 | 17 | M | 13 | 5 | 38.5 | 8 | 61.5 |
| | | (breeders) | F | 37 | 20 | 54.1 | 28 | 75.7 |
| | | | M + F | 50 | 25 | 50.0 | 36 | 72.0 |
| | | Embryos | M | 49 | 17 | 34.7 | 31 | 63.3 |
| | | (offspring) | F | 48 | 29 | 60.4 | 66 | 137.5 |
| | | | M + F | 97 | 46 | 47.4 | 97 | 100.0 |
| II | 1,000 | 17 | M | 13 | 3 | 23.1 | 3 | 23.1 |
| | | (breeders) | F | 37 | 10 | 27.0 | 16 | 43.2 |
| | | | M + F | 50 | 13 | 26.0 | 19 | 38.0 |
| | | Embryos | M | 37 | 10 | 27.0 | 16 | 43.2 |
| | | (offspring) | F | 44 | 16 | 36.4 | 29 | 65.9 |
| | | | M + F | 81 | 26 | 32.1 | 45 | 55.6 |
| III | 0[a] | 17 | M | 14 | 5 | 35.7 | 7 | 50.0 |
| | | (breeders) | F | 37 | 12 | 32.4 | 15 | 40.5 |
| | | | M + F | 51 | 17 | 33.3 | 22 | 43.1 |
| | | Embryos | M | 38 | 14 | 36.8 | 21 | 55.3 |
| | | (offspring) | F | 48 | 16 | 33.3 | 26 | 54.2 |
| | | | M + F | 86 | 30 | 34.9 | 47 | 54.7 |

[a] Drinking water alone.

**TABLE 5.** Results of Long-term Carcinogenicity Bioassays on Vinyl Acetate (VAM), Administered to Swiss Mice in Drinking Water Supplied ad Libitum (BT 52): Total Malignant Tumors

| Group No. | Concentration (ppm, v/v) | Animals | | | Malignant Tumors | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | Animals Bearing Tumors | | | Tumors | |
| | | Age at Start (weeks) | Sex | No. | No. | % | | No. | Per 100 Animals |
| I | 5,000 | 17 (breeders) | M | 13 | 11 | 84.6 | | 15 | 115.4 |
| | | | F | 37 | 26 | 70.3 | | 51 | 137.8 |
| | | | M + F | 50 | 37 | 74.0 | | 66 | 132.0 |
| | | Embryos (offspring) | M | 49 | 41 | | 83.7 | 85 | 173.5 |
| | | | F | 48 | 45 | | 93.8 | 119 | 247.9 |
| | | | M + F | 97 | 86 | | 87.7 | 204 | 210.3 |
| II | 1,000 | 17 (breeders) | M | 13 | 6 | 46.2 | | 9 | 69.2 |
| | | | F | 37 | 28 | 75.7 | | 31 | 83.8 |
| | | | M + F | 50 | 34 | 68.0 | | 40 | 80.0 |
| | | Embryos (offspring) | M | 37 | 24 | | 64.9 | 29 | 78.4 |
| | | | F | 44 | 33 | | 75.0 | 52 | 118.2 |
| | | | M + F | 81 | 57 | | 70.4 | 81 | 100.0 |
| III | 0[a] | 17 (breeders) | M | 14 | 7 | 50.0 | | 9 | 64.3 |
| | | | F | 37 | 21 | 56.8 | | 29 | 78.4 |
| | | | M + F | 51 | 28 | 54.9 | | 38 | 74.5 |
| | | Embryos (offspring) | M | 38 | 26 | | 68.4 | 35 | 92.1 |
| | | | F | 48 | 30 | | 62.5 | 47 | 97.9 |
| | | | M + F | 86 | 56 | | 65.1 | 82 | 95.3 |

[a] Drinking water alone.

and among female offspring treated with the lower dose (TABLE 6). The incidence of the squamous cell dysplasia of the gland was higher among male and female breeders treated with the higher dose, among male and female offspring treated with the higher dose, and among female breeders treated with the lower dose (TABLE 6). Such increase was sharper among females.

At the higher dose, in male and female breeders and offspring, VAM causes squamous cell carcinomas of the oral cavity (TABLE 7).

The incidence of tongue carcinomas is increased among male and female breeders and offspring treated with the higher dose (TABLE 8). The incidence of squamous cell dysplasia also increased among female breeders and among male and female offspring treated with the higher dose (TABLE 8).

Squamous carcinomas and squamous cell dysplasia of the esophagus are increased among male and female breeders and offspring treated with the higher dose of VAM (TABLE 9). A marginal increase of acanthomas in this organ has been found among female breeders and offspring treated with the higher dose (TABLE 9).

Also the incidence of squamous cell carcinomas and acanthomas of the forestomach has been found enhanced among female breeders and male and female offspring treated with the higher dose (TABLE 10). The forestomach acanthomas are more numerous among male and female breeders and offspring treated with the higher dose (TABLE 10).

A borderline increase of oncological lesions of the stomach was found among all treated animals (TABLE 11).

The number of lung tumors per 100 animals was increased among male and female breeders and offspring treated with the higher dose and among female breeders treated with the lower dose (TABLE 12).

A slight increase of hepatocarcinomas was observed among male offspring treated with the higher dose (TABLE 13).

The incidence of malignant tumors (leiomyosarcomas and adenocarcinomas) of the uterus was found to be increased in treated groups: the increase was dose correlated (TABLE 14). Uterine leiomyomas were found to be enhanced in offspring treated with the higher dose (TABLE 14).

No correlation between the treatment with VAM and the incidence of mammary cancers (TABLE 15) and lymphomas and leukemias (TABLE 16) was found.

Altogether the results indicate that the neoplastic response to treatment was more pronounced among female animals and in offspring.

## CONCLUSIONS

In the tested experimental conditions, VAM has been shown to cause tumors in several body sites: therefore it must be considered a multipotential carcinogen.

Of particular significance is the increase of squamous cell carcinomas of the oral cavity, tongue, esophagus, and forestomach, and of the tumors of the stomach. The sites of these tumors were the most directly exposed, since VAM was administered by oral route.

The results of our bioassays of VAM on Sprague-Dawley and Wistar rats are now been elaborated and will soon be published. However, already, on the basis of

**TABLE 6.** Results of Long-term Carcinogenicity Bioassays on Vinyl Acetate (VAM), Administered to Swiss Mice in Drinking Water Supplied ad Libitum (BT 52): Adenomas, Squamous Cell Dysplasias, and Carcinomas of the Zymbal Glands

| Group No. | Concentration (ppm, v/v) | Animals | | | Animals Bearing Lesions of the Zymbal Glands | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Adenomas | | Squamous Cell Dysplasias | | Carcinomas | |
| | | Age at Start (weeks) | Sex | No. | No. | % | No. | % | No. | % |
| I | 5,000 | 17 (breeders) | M | 13 | 0 | – | 1[a] | 7.7 | 0 | – |
| | | | F | 37 | 0 | – | 6[a] | 16.2 | 1 | 2.7 |
| | | | M + F | 50 | 0 | – | 7 | 14.0 | 1 | 2.0 |
| | | Embryos (offspring) | M | 49 | 0 | – | 4[a] | 8.2 | 2 | 4.1 |
| | | | F | 48 | 0 | – | 11[b] | 22.9 | 4 | 8.3 |
| | | | M + F | 97 | 0 | – | 15 | 15.5 | 6 | 6.2 |
| II | 1,000 | 17 (breeders) | M | 13 | 0 | – | 0 | – | 0 | – |
| | | | F | 37 | 0 | – | 3[a] | 8.1 | 0 | – |
| | | | M + F | 50 | 0 | – | 3 | 6.0 | 0 | – |
| | | Embryos (offspring) | M | 37 | 0 | – | 0 | – | 0 | – |
| | | | F | 44 | 0 | – | 2 | 4.5 | 2[a] | 4.5 |
| | | | M + F | 81 | 0 | – | 2 | 2.5 | 2 | 2.5 |
| III | 0[c] | 17 (breeders) | M | 14 | 0 | – | 0 | – | 0 | – |
| | | | F | 37 | 0 | – | 1 | 2.7 | 0 | – |
| | | | M + F | 51 | 0 | – | 1 | 2.0 | 0 | – |
| | | Embryos (offspring) | M | 38 | 0 | – | 2 | 5.3 | 0 | – |
| | | | F | 48 | 0 | – | 3 | 6.3 | 0 | – |
| | | | M + F | 86 | 0 | – | 5 | 5.8 | 0 | – |

[a] One animal is bearing a bilateral tumor.
[b] Five animals are bearing bilateral tumors.
[c] Drinking water alone.

**TABLE 7.** Results of Long-term Carcinogenicity Bioassays on Vinyl Acetate (VAM), Administered to Swiss Mice in Drinking Water Supplied ad Libitum (BT 52): Acanthomas, Squamous Cell Dysplasias, and Squamous Cell Carcinomas of the Oral Cavity

| | | Animals | | | Animals Bearing Lesions of the Oral Cavity | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Acanthomas | | Squamous Cell Dysplasias | | Squamous Cell Carcinomas | |
| Group No. | Concentration (ppm, v/v) | Age at Start (weeks) | Sex | No. | No. | % | No. | % | No. | % |
| I | 5,000 | 17 (breeders) | M | 13 | 0 | – | 0 | – | 1 | 7.7 |
| | | | F | 37 | 0 | – | 0 | – | 1 | 2.7 |
| | | | M + F | 50 | 0 | – | 0 | – | 2 | 4.0 |
| | | Embryos (offspring) | M | 49 | 0 | – | 0 | – | 10 | 20.4 |
| | | | F | 48 | 0 | – | 0 | – | 9 | 18.8 |
| | | | M + F | 97 | 0 | – | 0 | – | 19 | 19.6 |
| II | 1,000 | 17 (breeders) | M | 13 | 0 | – | 0 | – | 0 | – |
| | | | F | 37 | 0 | – | 0 | – | 0 | – |
| | | | M + F | 50 | 0 | – | 0 | – | 0 | – |
| | | Embryos (offspring) | M | 37 | 0 | – | 0 | – | 0 | – |
| | | | F | 44 | 0 | – | 0 | – | 0 | – |
| | | | M + F | 81 | 0 | – | 0 | – | 0 | – |
| III | 0[a] | 17 (breeders) | M | 14 | 0 | – | 0 | – | 0 | – |
| | | | F | 37 | 0 | – | 0 | – | 0 | – |
| | | | M + F | 51 | 0 | – | 0 | – | 0 | – |
| | | Embryos (offspring) | M | 38 | 0 | – | 0 | – | 0 | – |
| | | | F | 48 | 0 | – | 0 | – | 0 | – |
| | | | M + F | 86 | 0 | – | 0 | – | 0 | – |

[a] Drinking water alone.

**TABLE 8.** Results of Long-term Carcinogenicity Bioassays on Vinyl Acetate (VAM), Administered to Swiss Mice in Drinking Water Supplied ad Libitum (BT 52): Acanthomas, Squamous Cell Dysplasias, and Squamous Cell Carcinomas of the Tongue

| Group No. | Concentration (ppm, v/v) | Animals | | | Animals Bearing Lesions of the Tongue | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Acanthomas | | Squamous Cell Dysplasias | | Squamous Cell Carcinomas | |
| | | Age at Start (weeks) | Sex | No. | No. | % | No. | % | No. | % |
| I | 5,000 | 17 (breeders) | M | 13 | 0 | – | 0 | – | 1 | 7.7 |
| | | | F | 37 | 0 | – | 3 | 8.1 | 3 | 8.1 |
| | | | M + F | 50 | 0 | – | 3 | 6.0 | 3 | 6.0 |
| | | Embryos (offspring) | M | 49 | 0 | – | 4 | 8.2 | 7 | 14.3 |
| | | | F | 48 | 0 | – | 7 | 14.6 | 12 | 25.0 |
| | | | M + F | 97 | 0 | – | 11 | 11.3 | 19 | 19.6 |
| II | 1,000 | 17 (breeders) | M | 13 | 0 | – | 0 | – | 0 | – |
| | | | F | 37 | 0 | – | 0 | – | 1 | 2.7 |
| | | | M + F | 50 | 0 | – | 0 | – | 1 | 2.0 |
| | | Embryos (offspring) | M | 37 | 0 | – | 0 | – | 0 | – |
| | | | F | 44 | 0 | – | 1 | 2.3 | 0 | – |
| | | | M + F | 81 | 0 | – | 1 | 1.2 | 0 | – |
| III | 0[a] | 17 (breeders) | M | 14 | 0 | – | 0 | – | 0 | – |
| | | | F | 37 | 0 | – | 0 | – | 0 | – |
| | | | M + F | 51 | 0 | – | 0 | – | 0 | – |
| | | Embryos (offspring) | M | 38 | 0 | – | 0 | – | 1 | 2.6 |
| | | | F | 48 | 0 | – | 0 | – | 0 | – |
| | | | M + F | 86 | 0 | – | 0 | – | 1 | 1.2 |

[a] Drinking water alone.

**TABLE 9.** Results of Long-term Carcinogenicity Bioassays on Vinyl Acetate (VAM), Administered to Swiss Mice in Drinking Water Supplied ad Libitum (BT 52): Acanthomas, Squamous Cell Dysplasias, and Squamous Cell Carcinomas of the Esophagus

| Group No. | Concentration (ppm, v/v) | Animals | | | Animals Bearing Lesions of the Esophagus | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Acanthomas | | Squamous Cell Dysplasias | | Squamous Cell Carcinomas | |
| | | Age at Start (weeks) | Sex | No. | No. | % | No. | % | No. | % |
| I | 5,000 | 17 | M | 13 | 0 | – | 4 | 30.8 | 0 | – |
| | | (breeders) | F | 37 | 1 | 2.7 | 6 | 16.2 | 6 | 16.2 |
| | | | M + F | 50 | 1 | 2.0 | 10 | 20.0 | 6 | 12.0 |
| | | Embryos | M | 49 | 0 | – | 4 | 8.2 | 12 | 24.5 |
| | | (offspring) | F | 48 | 3 | 6.3 | 7 | 14.6 | 18 | 37.5 |
| | | | M + F | 97 | 3 | 3.1 | 11 | 11.3 | 30 | 30.9 |
| II | 1,000 | 17 | M | 13 | 0 | – | 0 | – | 0 | – |
| | | (breeders) | F | 37 | 0 | – | 0 | – | 0 | – |
| | | | M + F | 50 | 0 | – | 0 | – | 0 | – |
| | | Embryos | M | 37 | 0 | – | 0 | – | 0 | – |
| | | (offspring) | F | 44 | 0 | – | 0 | – | 0 | – |
| | | | M + F | 81 | 0 | – | 0 | – | 0 | – |
| III | 0[a] | 17 | M | 14 | 0 | – | 0 | – | 0 | – |
| | | (breeders) | F | 37 | 0 | – | 0 | – | 0 | – |
| | | | M + F | 51 | 0 | – | 0 | – | 0 | – |
| | | Embryos | M | 38 | 0 | – | 0 | – | 0 | – |
| | | (offspring) | F | 48 | 0 | – | 0 | – | 0 | – |
| | | | M + F | 86 | 0 | – | 0 | – | 0 | – |

[a] Drinking water alone.

**TABLE 10.** Results of Long-term Carcinogenicity Bioassays on Vinyl Acetate (VAM), Administered to Swiss Mice in Drinking Water Supplied ad Libitum (BT 52): Acanthomas, Squamous Cell Dysplasias, and Squamous Cell Carcinomas of the Forestomach

| | | Animals | | | Animals Bearing Lesions of the Forestomach | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Acanthomas | | Squamous Cell Dysplasias | | Squamous Cell Carcinomas | |
| Group No. | Concentration (ppm, v/v) | Age at Start (weeks) | Sex | No. | No. | % | No. | % | No. | % |
| I | 5,000 | 17 (breeders) | M | 13 | 1 | 7.7 | 0 | – | 0 | – |
| | | | F | 37 | 5 | 13.5 | 0 | – | 3 | 8.1 |
| | | | M + F | 50 | 6 | 12.0 | 0 | – | 3 | 6.0 |
| | | Embryos (offspring) | M | 49 | 8 | 16.3 | 1 | 2.0 | 2 | 4.1 |
| | | | F | 48 | 11 | 22.9 | 0 | – | 7 | 14.6 |
| | | | M + F | 97 | 19 | 19.6 | 1 | 1.0 | 9 | 9.3 |
| II | 1,000 | 17 (breeders) | M | 13 | 0 | – | 0 | – | 0 | – |
| | | | F | 37 | 0 | – | 0 | – | 0 | – |
| | | | M + F | 50 | 0 | – | 0 | – | 0 | – |
| | | Embryos (offspring) | M | 37 | 1 | 2.7 | 0 | – | 0 | – |
| | | | F | 44 | 0 | – | 0 | – | 0 | – |
| | | | M + F | 81 | 1 | 1.2 | 0 | – | 0 | – |
| III | 0[a] | 17 (breeders) | M | 14 | 0 | – | 0 | – | 0 | – |
| | | | F | 37 | 0 | – | 0 | – | 0 | – |
| | | | M + F | 51 | 0 | – | 0 | – | 0 | – |
| | | Embryos (offspring) | M | 38 | 0 | – | 0 | – | 0 | – |
| | | | F | 48 | 0 | – | 0 | – | 0 | – |
| | | | M + F | 86 | 0 | – | 0 | – | 0 | – |

[a] Drinking water alone.

TABLE 11. Results of Long-term Carcinogenicity Bioassays on Vinyl Acetate (VAM), Administered to Swiss Mice in Drinking Water Supplied ad Libitum (BT 52): Adenomatous Polyps, Glandular Dysplasias, and Adenocarcinomas of the Stomach

| Group No. | Concentration (ppm, v/v) | Animals | | | Animals Bearing Lesions of the Stomach | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Adenomatous Polyps | | Glandular Dysplasias | | Adenocarcinomas | |
| | | Age at Start (weeks) | Sex | No. | No. | % | No. | % | No. | % |
| I | 5,000 | 17 (breeders) | M | 13 | 0 | – | 0 | – | 1 | 7.7 |
| | | | F | 37 | 0 | – | 0 | – | 1 | 2.7 |
| | | | M + F | 50 | 0 | – | 0 | – | 2 | 4.0 |
| | | Embryos (offspring) | M | 49 | 0 | – | 3 | 6.1 | 0 | – |
| | | | F | 48 | 0 | – | 0 | – | 1 | 2.1 |
| | | | M + F | 97 | 0 | – | 3 | 3.1 | 1 | 1.0 |
| II | 1,000 | 17 (breeders) | M | 13 | 0 | – | 0 | – | 0 | – |
| | | | F | 37 | 0 | – | 0 | – | 0 | – |
| | | | M + F | 50 | 0 | – | 0 | – | 0 | – |
| | | Embryos (offspring) | M | 37 | 1 | 2.7 | 0 | – | 0 | – |
| | | | F | 44 | 0 | – | 1 | 2.3 | 0 | – |
| | | | M + F | 81 | 1 | 1.2 | 1 | 1.2 | 0 | – |
| III | 0[a] | 17 (breeders) | M | 14 | 0 | – | 0 | – | 0 | – |
| | | | F | 37 | 0 | – | 0 | – | 0 | – |
| | | | M + F | 51 | 0 | – | 0 | – | 0 | – |
| | | Embryos (offspring) | M | 38 | 0 | – | 0 | – | 1 | 2.6 |
| | | | F | 48 | 0 | – | 0 | – | 0 | – |
| | | | M + F | 86 | 0 | – | 0 | – | 1 | 1.2 |

[a] Drinking water alone.

**TABLE 12.** Results of Long-term Carcinogenicity Bioassays on Vinyl Acetate (VAM), Administered to Swiss Mice in Drinking Water Supplied ad Libitum (BT 52): Adenomas and Adenocarcinomas of the Lung

| | | Animals | | | Animals Bearing Tumors | | | | Total Tumors | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Adenomas | | Adenocarcinomas | | Animals Bearing Tumors | | Tumors | |
| Group No. | Concentration (ppm, v/v) | Age at Start (weeks) | Sex | No. | No. | % | No. | % | No. | % | No. | Per 100 Animals |
| I | 5,000 | 17 | M | 13 | 3 | 23.1 | 2 | 15.4 | 4 | 30.8 | 8 | 61.5 |
| | | (breeders) | F | 37 | 6 | 16.2 | 1 | 2.7 | 7 | 18.9 | 11 | 29.7 |
| | | | M + F | 50 | 9 | 18.0 | 3 | 6.0 | 11 | 22.0 | 19 | 38.0 |
| | | Embryos | M | 49 | 11 | 22.4 | 2 | 4.1 | 13 | 26.5 | 21 | 42.9 |
| | | (offspring) | F | 48 | 11 | 22.9 | 3 | 6.3 | 11 | 22.9 | 25 | 52.1 |
| | | | M + F | 97 | 22 | 22.7 | 5 | 5.2 | 24 | 24.7 | 46 | 47.4 |
| II | 1,000 | 17 | M | 13 | 2 | 15.4 | 2 | 15.4 | 4 | 30.8 | 4 | 30.8 |
| | | (breeders) | F | 37 | 6 | 16.2 | 1 | 2.7 | 6 | 16.2 | 9 | 24.3 |
| | | | M + F | 50 | 8 | 16.0 | 3 | 6.0 | 10 | 20.0 | 13 | 26.0 |
| | | Embryos | M | 37 | 6 | 16.2 | 0 | — | 6 | 16.2 | 9 | 24.3 |
| | | (offspring) | F | 44 | 3 | 6.8 | 1 | 2.3 | 4 | 9.1 | 4 | 9.1 |
| | | | M + F | 81 | 9 | 11.1 | 1 | 1.2 | 10 | 12.3 | 13 | 16.0 |
| III | 0[a] | 17 | M | 14 | 2 | 14.3 | 2 | 14.3 | 4 | 28.6 | 5 | 35.7 |
| | | (breeders) | F | 37 | 3 | 8.1 | 0 | — | 3 | 8.1 | 3 | 8.1 |
| | | | M + F | 51 | 5 | 9.8 | 2 | 3.9 | 7 | 13.7 | 8 | 15.7 |
| | | Embryos | M | 38 | 6 | 15.8 | 1 | 2.6 | 7 | 18.4 | 8 | 21.1 |
| | | (offspring) | F | 48 | 6 | 12.5 | 0 | — | 6 | 12.5 | 7 | 14.6 |
| | | | M + F | 86 | 12 | 14.0 | 1 | 1.2 | 13 | 15.1 | 15 | 17.4 |

[a] Drinking water alone.

**TABLE 13.** Results of Long-term Carcinogenicity Bioassays on Vinyl Acetate (VAM), Administered to Swiss Mice in Drinking Water Supplied ad Libitum (BT 52): Hepatocarcinomas

| Group No. | Concentration (ppm, v/v) | Animals | | | Animals Bearing Hepatocarcinomas | |
|---|---|---|---|---|---|---|
| | | Age at Start (weeks) | Sex | No. | No. | % |
| I | 5,000 | 17 (breeders) | M | 13 | 2 | 15.4 |
| | | | F | 37 | 0 | – |
| | | | M + F | 50 | 2 | 4.0 |
| | | Embryos (offspring) | M | 49 | 17 | 34.7 |
| | | | F | 48 | 2 | 4.2 |
| | | | M + F | 97 | 19 | 19.6 |
| II | 1,000 | 17 (breeders) | M | 13 | 4 | 30.7 |
| | | | F | 37 | 0 | – |
| | | | M + F | 50 | 4 | 8.0 |
| | | Embryos (offspring) | M | 37 | 8 | 21.6 |
| | | | F | 44 | 0 | – |
| | | | M + F | 81 | 8 | 9.9 |
| III | 0[a] | 17 (breeders) | M | 14 | 3 | 21.4 |
| | | | F | 37 | 0 | – |
| | | | M + F | 51 | 3 | 5.9 |
| | | Embryos (offspring) | M | 38 | 10 | 26.3 |
| | | | F | 48 | 1 | 2.1 |
| | | | M + F | 86 | 11 | 12.8 |

[a] Drinking water alone.

**TABLE 14.** Results of Long-term Carcinogenicity Bioassays on Vinyl Acetate (VAM), Administered to Swiss Mice in Drinking Water Supplied ad Libitum (BT 52): Leiomyomas, Leiomyosarcomas, and Adenocarcinomas of the Uterus

| Group No. | Concentration (ppm, v/v) | Animals | | | Animals Bearing Tumors | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Age at Start (weeks) | Sex | No. | Leiomyomas | | Leiomyosarcomas | | Adenocarcinomas | | Total Malignant Tumors | |
| | | | | | No. | % | No. | % | No. | % | No. | % |
| I | 5,000 | 17 (breeders) | F | 37 | 2 | 5.4 | 2 | 5.4 | 6 | 16.2 | 8 | 21.6 |
| | | Embryos (offspring) | F | 48 | 6 | 12.5 | 4 | 8.3 | 8 | 16.7 | 12 | 25.0 |
| II | 1,000 | 17 (breeders) | F | 37 | 0 | – | 0 | – | 2 | 5.4 | 2 | 5.4 |
| | | Embryos (offspring) | F | 44 | 3 | 6.8 | 2 | 4.5 | 6 | 13.6 | 8 | 18.2 |
| III | 0[a] | 17 (breeders) | F | 37 | 1 | 2.7 | 1 | 2.7 | 1 | 2.7 | 1 | 2.7 |
| | | Embryos (offspring) | F | 48 | 2 | 4.2 | 0 | – | 5 | 10.4 | 5 | 10.4 |

[a] Drinking water alone.

**TABLE 15.** Results of Long-term Carcinogenicity Bioassays on Vinyl Acetate (VAM), Administered to Swiss Mice in Drinking Water Supplied ad Libitum (BT 52): Mammary Cancers

| Group No. | Concentration (ppm, v/v) | Animals | | | Mammary Cancers | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | Animals Bearing Tumors | | | Tumors | |
| | | Age at Start (weeks) | Sex | No. | No. | % | | No. | Per 100 animals |
| I | 5,000 | 17 | M | 13 | 0 | – | | 0 | – |
| | | (breeders) | F | 37 | 6 | 16.2 | | 6 | 16.2 |
| | | | M + F | 50 | 6 | 12.0 | | 6 | 12.0 |
| | | Embryos | M | 49 | 0 | | – | 0 | – |
| | | (offspring) | F | 48 | 10 | | 20.8 | 10 | 20.8 |
| | | | M + F | 97 | 10 | | 10.3 | 10 | 10.3 |
| II | 1,000 | 17 | M | 13 | 0 | – | | 0 | – |
| | | (breeders) | F | 37 | 5 | 13.5 | | 5 | 13.5 |
| | | | M + F | 50 | 5 | 10.0 | | 5 | 10.0 |
| | | Embryos | M | 37 | 1 | | 2.7 | 1 | 2.7 |
| | | (offspring) | F | 44 | 7 | | 15.9 | 7 | 15.9 |
| | | | M + F | 81 | 8 | | 9.9 | 8 | 9.9 |
| III | 0[a] | 17 | M | 14 | 0 | – | | 0 | – |
| | | (breeders) | F | 37 | 6 | 16.2 | | 7 | 18.9 |
| | | | M + F | 51 | 6 | 11.8 | | 7 | 13.7 |
| | | Embryos | M | 38 | 0 | | – | 0 | – |
| | | (offspring) | F | 48 | 9 | | 18.8 | 10 | 20.8 |
| | | | M + F | 86 | 9 | | 10.5 | 10 | 11.6 |

[a] Drinking water alone.

**TABLE 16.** Results of Long-term Carcinogenicity Bioassays on Vinyl Acetate (VAM), Administered to Swiss Mice in Drinking Water Supplied ad Libitum (BT 52): Lymphomas and Leukemias

| Group No. | Concentration (ppm, v/v) | Animals | | | Animals Bearing Lymphomas and Leukemias | |
|---|---|---|---|---|---|---|
| | | Age at Start (weeks) | Sex | No. | No. | % |
| I | 5,000 | 17 (breeders) | M | 13 | 4 | 30.8 |
| | | | F | 37 | 18 | 48.6 |
| | | | M + F | 50 | 22 | 44.0 |
| | | Embryos (offspring) | M | 49 | 23 | 46.9 |
| | | | F | 48 | 33 | 68.8 |
| | | | M + F | 97 | 56 | 57.7 |
| II | 1,000 | 17 (breeders) | M | 13 | 2 | 15.4 |
| | | | F | 37 | 22 | 59.5 |
| | | | M + F | 50 | 24 | 48.0 |
| | | Embryos (offspring) | M | 37 | 17 | 45.9 |
| | | | F | 44 | 28 | 63.6 |
| | | | M + F | 81 | 45 | 55.6 |
| III | 0[a] | 17 (breeders) | M | 14 | 4 | 28.6 |
| | | | F | 37 | 18 | 48.6 |
| | | | M + F | 51 | 22 | 43.1 |
| | | Embryos (offspring) | M | 38 | 15 | 39.5 |
| | | | F | 48 | 27 | 56.3 |
| | | | M + F | 86 | 42 | 48.8 |

[a] Drinking water alone.

the present results, regulatory measures and preventive actions must be undertaken to prevent the carcinogenic risk of VAM, mainly among exposed workers and among consumers of the goods containing the monomer.

Of particular concern is the current use of VAM-based polymers as a component in contact with food and beverages and in the production of chewing gum, since the vinyl acetate monomer has been found to migrate from plastic materials into, for example, wine[18] and water,[19] (and therefore presumably into saliva and other biological fluids).

## SUMMARY

Vinyl acetate monomer (VAM) was administered in drinking water at doses of 5,000, 1,000, and 0 ppm (v/v), to Swiss mice, 17 weeks old (breeders) or 12-day embryos (offspring) at the start of the experiment. The treatment lasted 78 weeks, and the animals were kept under control until spontaneous death. VAM has been shown to cause an increase in: (1) total malignant tumors; (2) carcinomas of the Zymbal glands, oral cavity, tongue, esophagus, and forestomach; (3) stomach tumors; (4) lung tumors; and (5) uterine tumors. A slight increase of hepatomas has been observed among male mice offspring treated with the higher dose. On the basis of these data VAM must be considered a multipotential carcinogen.

## REFERENCES

1. International Agency for Research on Cancer. 1979. Monographs on the evaluation of the carcinogenic risk of chemicals to humans, Vol. 19. Some monomers, plastics and synthetic elastomers, and acrolein. IARC. Lyon.
2. International Agency for Research on Cancer. 1986. Monographs on the evaluation of the carcinogenic risk of chemicals to humans, Vol. 39. Some chemicals used in plastics and elastomers. IARC. Lyon.
3. International Agency for Research on Cancer. 1995. Monographs on the evaluation of the carcinogenic risk of chemicals to humans, Vol. 63. Dry cleaning, some chlorinated solvents and other industrial chemicals. IARC. Lyon.
4. United States Food and Drug Administration. 1984. U.S. Code Fed. Regul., *Title 21*, Parts 175.105, 175.300, 175.350, 176.170, 176.180, 177.1010, 177.1200, 177.1350, 177.1360, 177.1670, 177.2260, 177.2260, 177.2800, 178.3910: 133, 145, 160, 180, 189, 199, 211, 225, 255, 271, 289, 348.
5. Hazleton Laboratories Europe. 1979. Vinyl acetate. Unpublished reports Nos. 1910-51/8, 2511-51/11-14, 1835-51/3, 1884-51/3, 2286-51/5, 2303-51/5. Compilation of data. *In* Gesundheitsschädliche Arbeitsstoffe, Toxikologischarbeitsmedizische Begründungen von MAK-Werten. D. Henschler, Ed. Verlag Chemie. Weinheim, Germany.
6. Simon, P., V. G. Filser & H. M. Bolt. 1985. Metabolism and pharmacokinetics of vinyl acetate. Arch. Toxicol. **57:** 19-23.
7. Filov, V. A. 1959. The fate of complex esters of vinyl alcohol and fatty acid in the body. Gig. Tr. Prof. Zabol. **3:** 42-46.
8. International Agency for Research on Cancer. 1985. Monographs on the evaluation of the carcinogenic risk of chemicals to humans, Vol. 36. Allyl compounds, aldehydes, epoxides and peroxides. IARC. Lyon.
9. Soffritti, M., F. Belpoggi, A. Ciliberti *et al.* 1994. Long-term carcinogenicity bioassays of formaldehyde and acetaldehyde administered with drinking water: Results and implications. Presented at the International Conference on Drinking Waters, Other Beverages,

and Their Containers: A Present Problem of Public Health. Bologna, October 28, 1994. In press.
10. MALTONI, C. & G. LEFEMINE. 1974. Carcinogenicity bioassays of vinyl chloride. I. Research plan and early results. Environ. Res. **7:** 387-405.
11. MALTONI, C., G. LEFEMINE, P. CHIECO *et al.* 1974. Vinyl chloride carcinogenesis: Current results and perspectives. Med. Lav. **65:** 421-444.
12. MALTONI, C. & G. LEFEMINE. 1975. Carcinogenicity bioassays of vinyl chloride: Current results. Ann. N.Y. Acad. Sci. **246:** 195-218.
13. LIJINSKY, W. & M. D. REUBER. 1983. Chronic toxicity studies of vinyl acetate in Fischer rats. Toxicol. Appl. Pharmacol. **68:** 43-53.
14. BOGDANFFY, M. S., H. C. DREEF-VAN DER MEULEN, R. B. BEEMS *et al.* 1994. Chronic toxicity and oncogenicity inhalation study with vinyl acetate in the rat and mouse. Fundam. Appl. Toxicol. **23:** 215-229.
15. BOGDANFFY, M. S., T. R. TYLER, M. B. VINEGAR *et al.* 1994. Chronic toxicity and oncogenicity study with vinyl acetate in the rat: In utero exposure in drinking water. Fundam. Appl. Toxicol. **23:** 206-214.
16. WAXWEILER, R. J., A. H. SMITH, H. FALK *et al.* 1981. Excess lung cancer risk in a synthetic chemical plant. Environ. Health Perspect. **41:** 159-165.
17. OTT, M. G., M. J. TETA & H. L. GREENBERG. 1989. Lymphatic and hematopoietic tissue cancer in a chemical manufacturing environment. Am. J. Ind. Med. **16:** 631-643.
18. NOBLE, A. C., R. A. FLATH & R. R. FORREY. 1980. Wine headspace analysis. Reproducibility and application to varietal classification. J. Agric. Food Chem. **28:** 346-353.
19. MONTIEL, A. & S. RAUZY. 1983. Dosage des monomères et solvants légers dans les matériaux plastiques en contact avec l'eau et dans l'eau en contact avec ces matériaux. Rev. Fr. Sci. Eau **2:** 255-266.