

Table 1 - VAM: production^(a)

<i>Methods of production</i>
VAM is produced mainly by two processes:
• in one process, used since 1920, acetylene and acetic acid were reacted in the vapour phase over a catalyst bed ⁴ ;
• in the other process, largely used since the '70s, ethylene is reacted with acetic acid in the presence of oxygen ⁵ .
<i>World production</i>
2.5 million tons per year ⁶ .
<i>Geographic areas of production</i>
Japan, China, the United States, Germany, Russia, Brazil, Canada, France, Mexico, Poland, Romania, Spain, Thailand, the United Kingdom, Venezuela ⁷ .

^(a) From IARC¹

Table 2 - VAM: uses^(a)

• The only commercial use of VAM is in the production of polymers (polyvinyl acetate, polyvinyl alcohol, polyvinyl acetals) and copolymers (ethylene-vinyl acetate and polyvinyl-acetate chloride) ⁵ .
• Polyvinyl acetate is mainly used 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 ^{8,9} .
• Polyvinyl acetate is used as a component in the production of chewing-gum and the amount of polymer used varies from country to country: in the US it seems to be around 5% of the final product; in some European countries the average is higher.
• Polyvinyl alcohol is the most highly produced synthetic, water-soluble plastic in the world, used in sizing for textile warp and yarn, in laminating adhesives, photosensitive films and, as a binder and emulsifying agent, in cements ^{8,9} .
• Polyvinyl acetals are produced by the condensation of polyvinyl alcohol with an aldehyde. Commonly used aldehydes are formaldehyde, acetaldehyde and butyraldehyde. Polyvinyl formal, polyvinyl acetals and polyvinyl butyrals are mainly used in adhesives, paints, lacquers and films. Polyvinyl butyral is also used in sheet form as an interlayer in safety glasses and shatter-resistant acrylic protection in aircraft ⁸ .
• 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 ^{8,9} .
• Polyvinyl chloride-acetate copolymers, compounded with plasticizers, are used for cable and wire coverings, in chemical plants and in protective garments ⁹ .

^(a) From IARC¹

Sprague-Dawley and Wistar rats, was started at the Cancer Research Centre of the Ramazzini Foundation (CRC/RF).

The results of the experiment on Swiss mice, which have already been published², have shown that VAM produces an increase in: 1) total malignant tumours; 2) carcinomas of the Zymbal glands, oral cavity, tongue, oesophagus, and forestomach; 3) stomach tumours; 4) lung tumours; 5) uterine tumours; and 6) a slight increase of hepatomas among male mice offspring treated with the highest dose.

Table 3 - VAM: occurrence^(a)

<i>Natural sources</i>
VAM is not known to occur in nature.
<i>Workplaces</i>
Wherever VAM or its polymers are produced, used, and stocked.
<i>Air</i>
• In areas where several vinyl acetate manufactures or process facilities are located, a concentration of 0.25-2 mg/m ³ has been detected ¹⁰ .
• In areas near chemical waste disposal sites, a concentration of 0.5 µg/m ³ has been detected ¹¹ .
<i>Water</i>
• VAM has been detected at concentrations of 50 mg/l in waste water effluents from a polyvinyl acetate plant ¹² .
<i>Other</i>
• VAM was among the volatile chemicals released from food packaging during heating in microwave ovens. A concentration of 0.002-0.14 µg/cm ² has been detected ¹³ .
• VAM has also been detected in cigarette smoke, at concentrations of 400 ng/cigarette ¹⁴ .

^(a) From IARC¹

The results of the experiment on Sprague-Dawley rats, which also have already been published³, have shown that VAM produces an increase in: 1) total malignant tumours; 2) carcinomas of the oral cavity, lips and tongue; 3) cell dysplasias of the oesophagus; and 4) carcinomas of the forestomach.

The results of the experiment on Wistar rats are reported herein for the first time.

Materials and methods

VAM was administered by ingestion in drinking water, supplied *ad libitum*, on Wistar rats.

Details on the test compound and test animals are given in Table 5.

The experiment included breeders and offspring. The treatment of male and female breeders and offspring started when the female breeders were at the 12th day of pregnancy.

After weaning, at 4-5 weeks of age, the offspring was identified by ear punch and housed in groups of 5 in makrolon cages (41 x 25 x 15 cm) with stainless-steel wire tops; a shallow layer of white wood-shavings served as bedding. The animals were kept in one single room, at 23 ± 2°C and 50-60% relative humidity.

The plan of the experiment is shown in Table 6.

The conduct of the experiment is given in Table 7.

All animals were kept under control for their life span.

Every morning fresh water solutions of VAM at the required concentrations were prepared; the residual drinking water from the day before was removed, and the glass drinking bottles were washed and filled with fresh solution. Control animals received tap water alone.

Upon death, animals were submitted to systematic necropsy. Histopathology was routinely performed on the organs and tissues listed in Table 8.

Table 4 - VAM: data on carcinogenicity and other relevant correlated biological effects(1) Carcinogenicity studies(A) *Experimental animals*a) *Rat**- Inhalation*

- A group of 96 male and female Sprague-Dawley rats, 13 weeks of age, was exposed by inhalation for 4 hours per day, 5 days per week, for 52 weeks, to 2500 ppm (maximum tolerated concentration) of VAM. Early mortality was high: only 49 animals survived for 26 or more weeks. No tumours related to VAM were reported during 135 weeks¹⁵⁻¹⁷. Because of the poor survival of the animals, this study was not adequate for exposing the carcinogenic potential of the monomer.
- 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 tumours (benign and malignant) was found in animals of each sex¹⁸.

- Drinking water

- 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 in liver neoplastic nodules, in uterine adenocarcinomas and polyps, and in thyroid C-cell adenomas was observed¹⁹. 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.
- 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 started 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 F₀ 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 F₁ 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 tumour incidence was observed²⁰.
- Groups of 50 male and 50 female F344 rats received 10000, 2000, 400, and 0 ppm vinyl acetate (98% pure) for 104 weeks. Statistically significant increases in preneoplastic changes (e.g. squamous cell hyperplasia, basal cell activation) and squamous cell neoplasms were observed at several sites in the upper digestive tract, but only at 10000 ppm (unpublished data)²¹.

b) *Mouse**- Inhalation*

- Groups 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 tumour incidence was observed¹⁸.
- Groups of 50 male and 50 female BDF1 mice received 10000, 2000, 400, and 0 ppm vinyl acetate (98% pure) for 104 weeks. Statistically significant increases in preneoplastic changes (e.g. squamous cell hyperplasia, basal cell activation) and squamous cell neoplasms were observed at several sites in the upper digestive tract, but only at 10000 ppm (unpublished data)²¹.

(B) *Humans*

- In a cohort study aimed at identifying the specific exposure associated with an excess of lung cancer risk in a US synthetic chemical plant, 19 chemicals were studied: the subgroup with indifferently large-cell lung cancer had had slightly higher cumulative exposure to VAM²².
- A nested case-control study on a cohort of 29,139 men, employed in two US facilities, and died with lymphomas/leukemias, reported not significant results²³.

(2) Genetic effects:

VAM shows genotoxic effects both in human and rodent cells:

- *in vitro* VAM produces a dose-related, statistically significant increase of sister chromatid exchanges and chromosomal aberrations in human lymphocytes and whole blood, and an increase of sister chromatid exchanges in ovarian cells of the Chinese hamster⁴.

Table 5 - VAM: test compound and test animalsTest compound

(A) *Supplier:* an Italian chemical plant.

(B) *Purity:*

- VAM: >99%
- Benzene: 30-40 ppm
- Methyl and ethyl acetate: 50 ppm
- Crotonaldehyde: 6-16 ppm
- Acetaldehyde: 2-11 ppm
- Acetone: 330-500 ppm

Test animals

Male and female Wistar rats, 17-week-old breeders and 12 day embryos. This type of animal has been employed for various experiments at the Cancer Research Centre for nearly 30 years.

All organs and tissues were preserved in 70% ethyl alcohol, except for the bones which were fixed in 10% formalin and then decalcified with 10% formaldehyde and 20% formic acid in water solution. The normal specimens were trimmed, following Standard Operating Procedures (SOP) at the CRC/RF Laboratories: i. e. parenchymal organs were dissected through the hilus to expose the widest surface, and hollow organs were sectioned across the greatest diameter(s). Any pathological tissue was trimmed through the largest surface, including normal adjacent tissue. Trimmed specimens were processed as paraffin blocks, and 3-5 micron sections of every specimen were obtained. Sections were routinely stained with haematoxylin-eosin. Specific stainings were performed when needed. All slides were examined microscopically by the same group of pathologists; a senior pathologist reviewed all tumours and any other lesion of onco-

Table 6 - Long-term carcinogenicity bioassay on VAM administered to Wistar rats in drinking water supplied *ad libitum* for 104 weeks (Experiment BT 53). Plan of the experiment

Group No.	Concentration (ppm, v/v)	Animals		
		Sex	Age at start	No.
I	5,000	M	Breeders	13
		F	(17 weeks old)	37
		M+F		50
		M	Offspring	82
		F	(embryos)	95
		M+F		177
II	1,000	M	Breeders	13
		F	(17 weeks old)	37
		M+F		50
		M	Offspring	64
		F	(embryos)	73
		M+F		137
III	0 (control)	M	Breeders	14
		F	(17 weeks old)	37
		M+F		51
		M	Offspring	86
		F	(embryos)	69
		M+F		155

logical interest. All pathologists followed the same criteria of histopathological evaluation and classification. Multiple tumours of different type and site, or of different type in the same site, or of the same type in bilateral organs, or of the same type in the skin, in the subcutaneous tissue and in mammary glands, or at distant sites of diffuse tissue (i.e. bones, skeletal muscle, etc.), were plotted as single/independent tumours. Multiple tumours of the same type in the same tissue and organ (including those of the bilateral organs) were plotted only once.

The χ^2 test was used for the analysis of tumour incidence and the Cochran-Armitage test for the dose-response relationship. The results of the statistical evaluation are reported in the tables.

The experiment was conducted in conformity with the principles of Good Laboratory Practices (GLP) and the SOP of the CRC/RF.

Table 7 - VAM: conduct of the experiment

- The animals were exposed by ingestion, adding the compound to drinking water, supplied *ad libitum*, for 104 weeks, then they received tap water alone.
- All the animals were kept under observation until spontaneous death.
- The status and behaviour of the animals were examined 3 times daily.
- The animals were submitted to clinical examination for gross changes every 2 weeks.
- The animals were weighed once weekly for the first 13 weeks of the experiment, every 2 weeks until the treatment was stopped, and then every 8 weeks.
- Full necropsy was 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 during the last 30 years.
- Statistical analysis was performed using the χ^2 test, in order to evaluate the level of significance in tumour incidence differences between treated and control groups, and Cochran-Armitage test, to evaluate the dose-response relationship.

Results

Body weight

A slight increase in mean body weight was observed in male breeders of both treated groups, and there were no differences in mean body weight in female breeders (fig. 1). In the offspring treated at the higher dose, there was a slight decrease in mean body weight of the animals of both sexes, more evident in males (fig. 2).

Survival

In male breeders from 72 to 120 weeks of age, there was a decrease in survival of the higher dose treated animals (fig. 3). From the start of the treatment to 104 weeks of age there was a slight decrease in survival among untreated female breeders (fig. 4). In male offspring treated with the lower dose a slight decrease in survival was observed (fig. 5). No noteworthy differences were observed in female offspring (fig. 6).

Nononcological changes

No evident behavioural changes were observed in VAM-treated animals. No treatment-related nononcological pathological

Table 8 - VAM: histopathology

Histopathologic examination was performed on all tissues and organs taken at necropsy

- | | | |
|--|---|---|
| <ul style="list-style-type: none"> • subcutaneous lymph nodes (axillary and inguinal) • brain • pituitary gland • Zymbal glands • parotid glands • submaxillary glands • Harderian glands • nasal and oral cavities (5 sections of head) • tongue | <ul style="list-style-type: none"> • thymus and mediastinal lymph nodes • trachea • lung and mainstem bronchi • diaphragm • liver • spleen • pancreas • kidneys • adrenal glands • oesophagus | <ul style="list-style-type: none"> • stomach (fore and glandular) • intestine (four levels: duodenum, jejunum-ileum, colon, rectum) • urinary bladder • prostate • uterus • ovaries • testes • brown adipose tissue (interscapular fat pad) • mesenteric lymph nodes |
|--|---|---|

and any other organs and tissues with pathological lesions

Fig. 1 - Mean body weight in male (M) and female (F) breeder rats

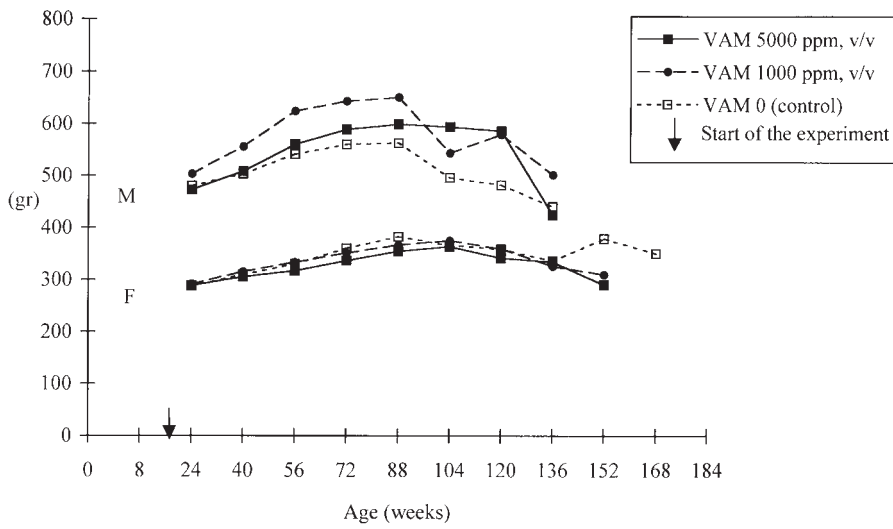


Fig. 2 - Mean body weight in male (M) and female (F) offspring rats

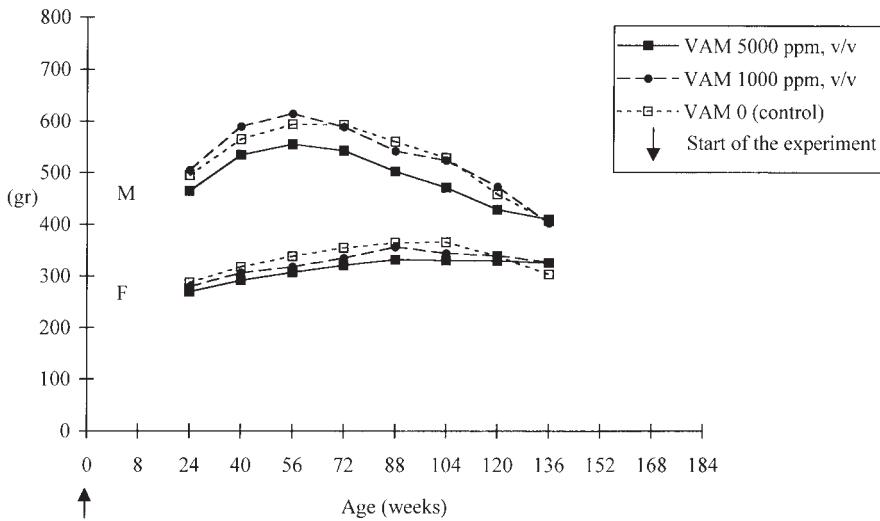
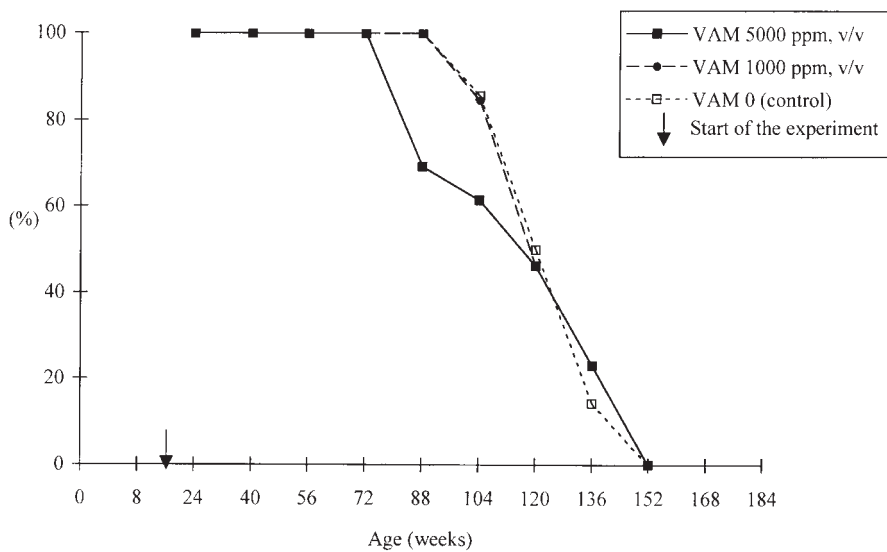


Fig. 3 - Survival in male breeder rats



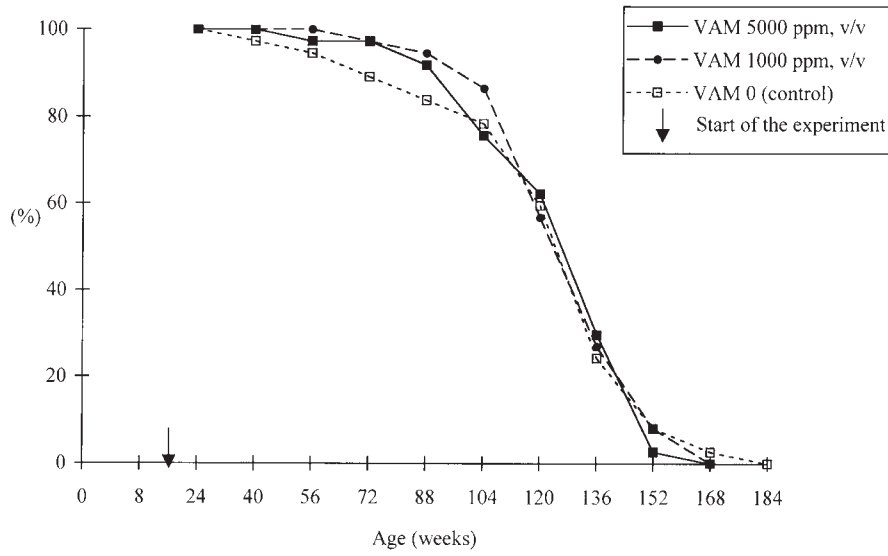


Fig. 4 - Survival in female breeder rats

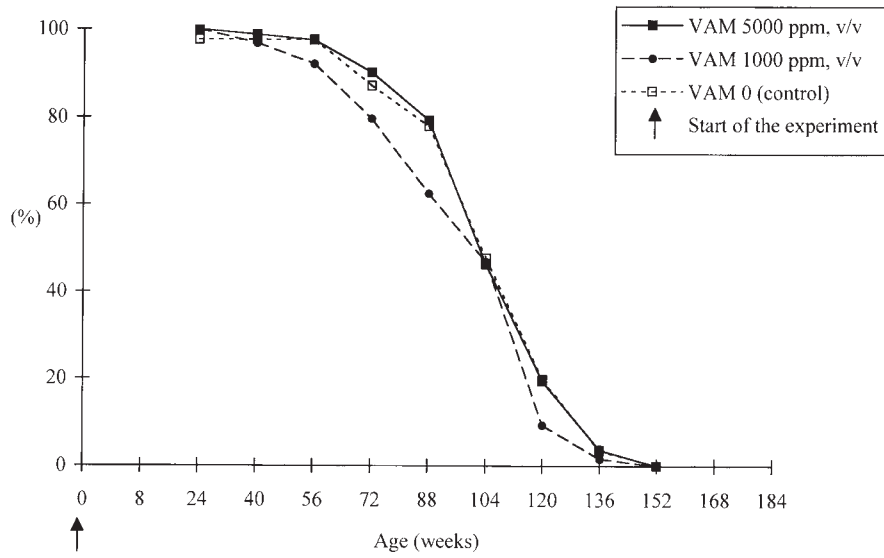


Fig. 5 - Survival in male offspring rats

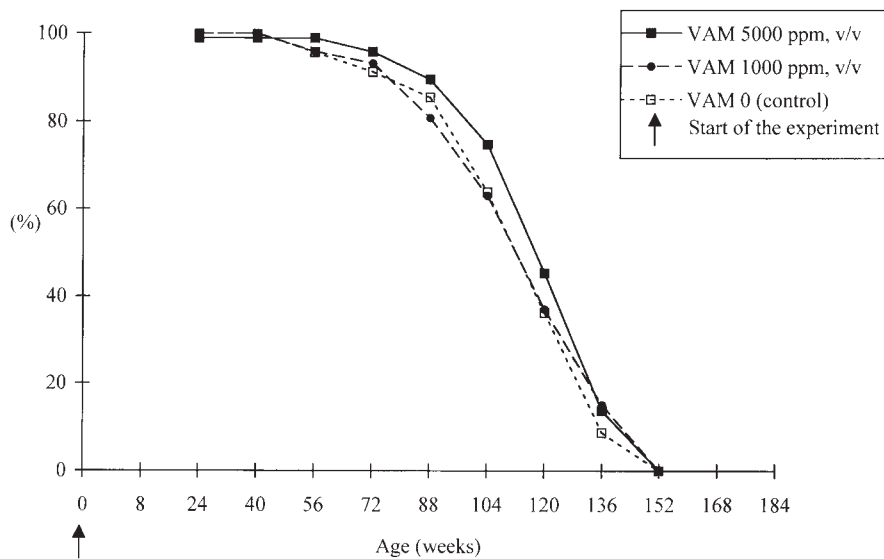


Fig. 6 - Survival in female offspring rats

Table 9 - Long-term carcinogenicity bioassay on VAM, administered with drinking water, supplied *ad libitum*, to male (M) and female (F) Wistar rats (Experiment BT 53). Number and percentage of male Wistar rats bearing various types of benign and malignant tumours^(a)

Site	Histotype	Groups											
		I: 5,000 ppm				II: 1,000 ppm				III: 0 (control)			
		Breeders		Offspring		Breeders		Offspring		Breeders		Offspring	
		No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Skin	Acanthoma	0	-	1	1.2	0	-	0	-	1	7.1	1	1.2
	Squamous cell carcinoma	0	-	1	1.2	1	7.7	0	-	0	-	1	1.2
Subcutaneous tissue	Fibroma	0	-	0	-	0	-	1	1.6	0	-	2	2.3
	Fibroangioma	0	-	0	-	0	-	0	-	0	-	1	1.2
	Lipoma	1	7.7	0	-	0	-	0	-	0	-	0	-
	Fibrosarcoma	0	-	0	-	1	7.7	0	-	0	-	0	-
	Liposarcoma	2	15.4	0	-	0	-	0	-	0	-	0	-
Interscapular fat pad	Liposarcoma	0	-	0	-	0	-	0	-	0	-	1	1.2
Mammary glands	Fibroma and fibroadenoma	0	-	2 (3)	2.4	1	7.7	3	4.7	1	7.1	5	5.8
	Lipoma	0	-	0	-	0	-	2	3.1	0	-	0	-
	Fibroangioma	0	-	0	-	0	-	1	1.6	0	-	1	1.2
	Adenocarcinoma	0	-	0	-	0	-	0	-	0	-	1	1.2
	Fibrosarcoma	0	-	0	-	0	-	0	-	1	7.1	0	-
	Liposarcoma	1	7.7	0	-	1	7.7	2	3.1	0	-	0	-
Harderian glands	Adenocarcinoma	0	-	1	1.2	0	-	0	-	0	-	0	-
Zymbal glands	Carcinoma	0	-	1	1.2	0	-	1	1.6	0	-	1	1.2
Ear ducts	Carcinoma	0	-	1	1.2	0	-	0	-	0	-	1	1.2
Nasal cavities	Carcinoma	0	-	1	1.2	0	-	0	-	0	-	0	-
	Olfactory neuroblastoma	0	-	0	-	0	-	1	1.6	0	-	0	-
Oral cavity and lips ^(b)	Acanthoma	1	7.7	0	-	0	-	0	-	0	-	0	-
	Carcinoma	3	23.1	12	14.6	1	7.7	1	1.6	1	7.1	3	3.5
Tongue ^(c)	Carcinoma	0	-	2	2.4	0	-	0	-	0	-	0	-
Pharynx	Carcinoma	0	-	3	3.7	0	-	0	-	0	-	0	-
Lung	Adenocarcinoma	0	-	0	-	0	-	0	-	0	-	1	1.2
Oesophagus ^(d)	Carcinoma	0	-	3	3.7	0	-	0	-	0	-	0	-
Stomach - Forestomach ^(e)	Acanthoma	0	-	1	1.2	0	-	0	-	0	-	0	-
	Carcinoma	1	7.7	4	4.9	0	-	0	-	0	-	0	-
- Glandular stomach	Leiomyosarcoma	0	-	0	-	0	-	1	1.6	0	-	0	-
Intestine	Adenocarcinoma	1	7.7	0	-	0	-	1	1.6	0	-	0	-
Liver	Cholangioma	0	-	1	1.2	0	-	1	1.6	0	-	0	-
	Hepatocarcinoma	0	-	0	-	0	-	0	-	0	-	2	2.3
	Cholangiocarcinoma	0	-	0	-	0	-	0	-	0	-	1	1.2
Pancreas	Exocrine adenoma	0	-	4	4.9	4	30.8	14	21.9	3	21.4	6	7.0
	Islet cell adenoma	2	15.4	2	2.4	0	-	1	1.6	1	7.1	9	10.5
	Islet cell carcinoma	0	-	1	1.2	3	23.1	0	-	0	-	0	-
Kidneys	Adenoma	0	-	0	-	0	-	0	-	0	-	1	1.2
	Fibroangioma	0	-	0	-	0	-	0	-	0	-	1	1.2
	Lipoma	0	-	0	-	0	-	0	-	0	-	1	1.2
	Nephroblastoma	0	-	0	-	0	-	0	-	0	-	1	1.2

(table 9 continued)

Table 9 cont.

Site	Histotype	Groups											
		I: 5,000 ppm				II: 1,000 ppm				III: 0 (control)			
		Breeders		Offspring		Breeders		Offspring		Breeders		Offspring	
		No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Prostate	Adenoma	0	-	1	1.2	0	-	0	-	0	-	0	-
	Adenocarcinoma	0	-	1	1.2	0	-	1	1.6	0	-	0	-
Seminal vesicles	Adenocarcinoma	0	-	0	-	0	-	0	-	1	7.1	0	-
Testes	Leydig cell tumour	3 (4)	23.1	7 (9)	8.5	1 (2)	7.7	4 (5)	6.3	3 (5)	21.4	11 (16)	12.8
Pituitary gland	Adenoma	3	23.1	8	9.8	7	53.8	8	12.5	8	57.1	15	17.4
Thyroid gland	Follicular carcinoma	0	-	0	-	0	-	0	-	0	-	1	1.2
	C-cell carcinoma	0	-	1	1.2	1	7.7	0	-	0	-	0	-
Adrenal glands	Cortical adenoma	0	-	0	-	0	-	0	-	0	-	1	1.2
	Pheochromocytoma	3 (4)	23.1	20 (26)	24.4	6 (8)	46.2	25 (36)	39.1	5 (6)	35.7	24 (36)	27.9
	Cortical adenocarcinoma	1	7.7	0	-	0	-	0	-	0	-	0	-
	Pheochromoblastoma	0	-	5	6.1	2 (3)	15.4	1	1.6	0	-	0	-
Central nervous system													
- Brain	Oligodendroglioma	0	-	1	1.2	0	-	2	3.1	0	-	0	-
- Meninges	Benign meningioma	0	-	0	-	0	-	0	-	1	7.1	1	1.2
Peripheral nervous system													
- Ganglia	Ganglioneuroma	0	-	0	-	0	-	1	1.6	0	-	0	-
Bones													
- Head	Osteosarcoma	0	-	2	2.4	0	-	0	-	0	-	0	-
- Other	Osteosarcoma	0	-	1	1.2	0	-	0	-	0	-	1	1.2
Thymus ^(a)	Benign thymoma	0	-	0	-	0	-	1	1.6	0	-	0	-
	Malignant thymoma	0	-	0	-	0	-	0	-	0	-	1	1.2
Spleen	Angiosarcoma	0	-	0	-	0	-	0	-	1	7.1	0	-
Subcutaneous lymph nodes	Fibroangioma	1	7.7	0	-	0	-	1	1.6	0	-	0	-
Mediastinal lymph nodes	Fibroangioma	0	-	0	-	0	-	1	1.6	0	-	0	-
Mesenteric lymph nodes	Fibroangioma	0	-	1	1.2	1	7.7	1	1.6	0	-	8	9.3
Haemolymphoreticular tissues ^{(a) (b)}	Lymphomas and leukaemias	1	7.7	8	9.8	1	7.7	7	10.9	2	14.3	5	5.8

^(a) Between brackets the number of tumours (one animal can bear more than one tumour)

^(b) See table 12

^(c) See table 13

^(d) See table 14

^(e) See table 15

^(f) In 96% of cases, the tumour itself is composed of a mixture in varying proportions of epithelial cells and lymphocytes. In the remaining 4% only epithelial cells are present. We consider that a tumour composed exclusively of lymphocytes should not be classified as a thymoma but as a lymphoma involving the thymus

^(g) Including thymus, spleen, subcutaneous, mediastinal and mesenteric lymph nodes

^(h) See table 18

changes were detected by gross inspection or histopathological examination.

Tumours

The occurrence of benign and malignant tumours among male

and female rats of treated and control groups is reported in Tables 9 and 10.

The incidence of total benign tumours was not affected by the treatment. An increase in total malignant tumours was observed in male and female breeders and offspring treated with both doses (Table 11).

Table 10 - Long-term carcinogenicity bioassay on VAM, administered with drinking water, supplied *ad libitum*, to male (M) and female (F) Wistar rats (Experiment BT 53). Number and percentage of female Wistar rats bearing various types of benign and malignant tumours^(a)

Site	Histotype	Groups												
		I: 5,000 ppm				II: 1,000 ppm				III: 0 (control)				
		Breeders		Offspring		Breeders		Offspring		Breeders		Offspring		
		No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	
Skin	Acanthoma	0	-	1	1.1	0	-	0	-	0	-	0	-	
	Squamous cell carcinoma	0	-	1	1.1	0	-	0	-	0	-	0	-	
Subcutaneous tissue	Lipoma	0	-	1	1.1	0	-	1	1.4	0	-	0	-	
	Fibrosarcoma	1	2.7	1	1.1	0	-	0	-	0	-	0	-	
Interscapular fat pad	Liposarcoma	0	-	1	1.1	0	-	0	-	0	-	0	-	
Mammary glands	Fibroma and fibroadenoma	12 (13)	32.4	40 (61)	42.1	19 (23)	51.4	27 (37)	37.0	22 (27)	59.5	38 (48)	55.1	
	Lipoma	0	-	0	-	0	-	2	2.7	1	2.7	0	-	
	Adenocarcinoma	5	13.5	8 (9)	8.4	2	5.4	6 (7)	8.2	4	10.8	5	7.2	
	Liposarcoma	0	-	0	-	0	-	0	-	1	2.7	0	-	
Zymbal glands	Acanthoma	0	-	0	-	0	-	0	-	2	5.4	0	-	
	Sebaceous adenoma	0	-	0	-	0	-	0	-	2	5.4	0	-	
	Carcinoma	0	-	1	1.1	1	2.7	2	2.7	0	-	0	-	
Ear ducts	Carcinoma	0	-	0	-	0	-	2	2.7	1	2.7	1	1.4	
Nasal cavities	Carcinoma	0	-	1	1.1	0	-	0	-	0	-	1	1.4	
	Olfactory neuroblastoma	0	-	2	2.1	0	-	0	-	0	-	0	-	
Oral cavity and lips ^(b)	Carcinoma	1	2.7	24	25.3	4	10.8	11	15.1	2	5.4	5	7.2	
Tongue ^(c)	Carcinoma	1	2.7	6	6.3	1	2.7	0	-	0	-	0	-	
Pharynx	Carcinoma	1	2.7	2	2.1	0	-	0	-	0	-	0	-	
Lung	Adenoma	0	-	1	1.1	0	-	0	-	0	-	0	-	
Oesophagus ^(d)	Acanthoma	0	-	1	1.1	0	-	0	-	0	-	0	-	
	Carcinoma	1	2.7	4	4.2	0	-	1	1.4	0	-	0	-	
Stomach	- Forestomach ^(e)	Acanthoma	2	5.4	4	4.2	1	2.7	0	-	0	-	1	1.4
		Leiomyoma	0	-	0	-	1	2.7	0	-	0	-	0	-
		Carcinoma	2	5.4	4	4.2	2	5.4	0	-	0	-	0	-
- Glandular stomach	Adenocarcinoma	0	-	0	-	0	-	0	-	1	2.7	0	-	
	Intestine	Adenomatous polyp	0	-	0	-	1	2.7	0	-	0	-	0	-
Salivary glands	Adenoma	1	2.7	1	1.1	0	-	0	-	2	5.4	1	1.4	
Liver	Angioma	0	-	0	-	0	-	0	-	0	-	1	1.4	
	Cholangioma	0	-	1	1.1	0	-	0	-	0	-	0	-	
	Hepatocarcinoma	0	-	0	-	0	-	1	1.4	0	-	1	1.4	
Pancreas	Exocrine adenoma	1	2.7	0	-	3	8.1	5	6.8	2	5.4	1	1.4	
	Islet cell adenoma	1	2.7	3	3.2	0	-	5	6.8	2	5.4	2	2.9	
	Islet cell carcinoma	1	2.7	2	2.1	0	-	0	-	0	-	0	-	
Kidneys	Adenoma	0	-	0	-	0	-	0	-	1	2.7	0	-	
	Adenocarcinoma	0	-	0	-	1	2.7	0	-	0	-	3	4.3	
	Nephroblastoma	0	-	0	-	0	-	0	-	0	-	1	1.4	
	Liposarcoma	0	-	1	1.1	0	-	0	-	0	-	0	-	
Bladder	Papilloma	0	-	1	1.1	0	-	0	-	0	-	0	-	
	Transitional cell carcinoma	0	-	1	1.1	0	-	0	-	0	-	0	-	
Ovaries	Cystadenoma	4 (6)	10.8	4 (5)	4.2	1	2.7	2 (3)	2.7	0	-	1	1.4	
	Granulosa cell tumour	0	-	2	2.1	2	5.4	2 (4)	2.7	1 (2)	2.7	0	-	
	Granulosa and theca cell tumour	0	-	1	1.1	0	-	0	-	0	-	0	-	
	Sertoli cell tumour	0	-	0	-	0	-	2 (4)	2.7	2	5.4	0	-	
	Adenocarcinoma	0	-	3 (4)	3.2	0	-	0	-	0	-	1	1.4	
	Granulosa cell malignant tumour	0	-	0	-	0	-	1	1.4	1	2.7	0	-	
	Sertoli cell malignant tumour	0	-	1 (2)	1.1	1	2.7	1 (2)	1.4	0	-	0	-	

(table 10 continued)

Table 10 cont.

Site	Histotype	Groups											
		I: 5,000 ppm				II: 1,000 ppm				III: 0 (control)			
		Breeders		Offspring		Breeders		Offspring		Breeders		Offspring	
No.	%	No.	%	No.	%	No.	%	No.	%	No.	%		
Uterus ^(d)	Polyp	9	24.3	23	24.2	9	24.3	20	27.4	10	27.0	15	21.7
	Fibroma	0	-	2	2.1	0	-	0	-	0	-	0	-
	Leiomyoma	0	-	0	-	0	-	1	1.4	0	-	1	1.4
	Fibroangioma	1	2.7	0	-	0	-	0	-	0	-	1	1.4
	Granular cell tumour (Abrikosoff's tumour)	0	-	0	-	0	-	0	-	0	-	1	1.4
	Squamous cell carcinoma	1	2.7	3	3.2	1	2.7	1	1.4	0	-	1	1.4
	Adenocarcinoma	5	13.5	19	20.0	3	8.1	5	6.8	2	5.4	4	5.8
	Fibrosarcoma	3	8.1	3	3.2	0	-	0	-	0	-	0	-
	Leiomyosarcoma	1	2.7	2	2.1	0	-	0	-	0	-	0	-
	Liposarcoma	0	-	0	-	0	-	0	-	0	-	1	1.4
	Angiosarcoma	2	5.4	0	-	0	-	2	2.7	1	2.7	4	5.8
	Malignant Schwannoma	0	-	0	-	0	-	2	2.7	0	-	1	1.4
Vagina	Granular cell tumour (Abrikosoff's tumour)	0	-	0	-	0	-	0	-	0	-	1	1.4
	Squamous cell carcinoma	0	-	0	-	1	2.7	0	-	0	-	0	-
	Fibrosarcoma	0	-	0	-	1	2.7	0	-	0	-	0	-
	Malignant Schwannoma	0	-	0	-	1	2.7	0	-	0	-	0	-
Uterus and vagina ^(d)	Malignant Schwannoma	0	-	4	4.2	5	13.5	2	2.7	1	2.7	2	2.9
Peritoneum	Mesothelioma	0	-	0	-	0	-	1	1.4	0	-	0	-
	Liposarcoma	0	-	0	-	0	-	1	1.4	0	-	0	-
Pituitary gland	Adenoma	18	48.6	48	50.5	20	54.1	30	41.1	20	54.1	34	49.3
Thyroid gland	Follicular adenoma	0	-	1	1.1	0	-	0	-	0	-	0	-
	C-cell adenoma	0	-	0	-	0	-	0	-	0	-	1	1.4
	Follicular carcinoma	1	2.7	1	1.1	0	-	0	-	0	-	0	-
	C-cell carcinoma	0	-	1	1.1	0	-	0	-	0	-	0	-
Adrenal glands	Cortical adenoma	1	2.7	1	1.1	0	-	1	1.4	0	-	0	-
	Pheochromocytoma	6	16.2	13 (15)	13.7	14 (18)	37.8	13 (15)	17.8	5	13.5	12 (16)	17.4
	Cortical adenocarcinoma	2 (3)	5.4	1	1.1	1	2.7	0	-	0	-	1	1.4
	Pheochromoblastoma	0	-	2	2.1	0	-	3 (4)	4.1	0	-	0	-
Central nervous system													
- Brain	Oligodendroglioma	0	-	1	1.1	0	-	0	-	0	-	2	2.9
- Meninges	Benign meningioma	0	-	1	1.1	1	2.7	1	1.4	1	2.7	1	1.4
Peripheral nervous system													
- Major peripheral nerves	Benign Schwannoma	1	2.7	0	-	0	-	0	-	0	-	0	-
	Malignant Schwannoma	0	-	1	1.1	0	-	0	-	0	-	1	1.4
- Ganglia	Ganglioneuroma	0	-	0	-	0	-	0	-	1	2.7	0	-
Bones													
- Head	Osteosarcoma	0	-	3	3.2	0	-	4	5.5	0	-	2	2.9
- Other	Osteosarcoma	0	-	1	1.1	0	-	0	-	1	2.7	1	1.4
Soft tissues	Liposarcoma	0	-	1	1.1	0	-	0	-	0	-	0	-
Thymus ^(e)	Malignant thymoma	1	2.7	7	7.4	7	18.9	1	1.4	2	5.4	5	7.2
Spleen	Fibroma	0	-	1	1.1	0	-	0	-	0	-	0	-
	Angioma and fibroangioma	0	-	0	-	1	2.7	0	-	1	2.7	1	1.4
Mediastinal lymph nodes	Fibroangioma	0	-	0	-	0	-	0	-	0	-	1	1.4
Mesenteric lymph nodes	Fibroangioma	1	2.7	1	1.1	2	5.4	0	-	0	-	0	-
Haemolympho-reticular tissues ^{(b) (c)}	Lymphomas and leukaemias	6	16.2	14	14.7	3	8.1	5	6.8	1	2.7	3	4.3

^(a) Between brackets the number of tumours (one animal can bear more than one tumour)

^(b) See table 12

^(c) See table 13

^(d) See table 14

^(e) See table 15

^(f) See table 17

^(g) In 96% of cases, the tumour itself is composed of a mixture in varying proportions of epithelial cells and lymphocytes. In the remaining 4%, only epithelial cells are present. We consider that a tumour composed exclusively of lymphocytes should not be classified as a thymoma but as a lymphoma involving the thymus

^(h) Including thymus, spleen, mediastinal and mesenteric lymph nodes

⁽ⁱ⁾ See table 18

Table 11 - Long-term carcinogenicity bioassay on VAM, administered with drinking water, supplied *ad libitum*, to male (M) and female (F) Wistar rats (Experiment BT 53). Total malignant tumours

Group No.	Concentration (ppm, v/v)	Animals			Malignant tumours			
		Age	Sex	No.	Tumour-bearing animals		Tumours	
					No.	%	No.	Per 100 animals
I	5,000	Breeders (17 weeks old)	M	13	8	61.5	10	76.9**
			F	37	20	54.1	36	97.3**
			M+F	50	28	56.0	46	92.0
		Offspring (Embryos)	M	82	36	43.9**	49	59.8**
			F	95	70	73.7**	130	136.8**
			M+F	177	106	59.9	179	101.1
II	1,000	Breeders (17 weeks old)	M	13	7	53.8	12	92.3**
			F	37	22	59.5	35	94.6**
			M+F	50	29	58.0	47	94.0
		Offspring (Embryos)	M	64	15	23.4	18	28.1
			F	73	33	45.2	55	75.3
			M+F	137	48	35.0	73	53.3
III	0 ^(a)	Breeders (17 weeks old)	M	14	5	35.7	6	42.9
			F	37	13	35.1	18	48.6
			M+F	51	18	35.3	24	47.1
		Offspring (Embryos)	M	86	17	19.8	21	24.4
			F	69	35	50.7	45	65.2
			M+F	155	52	33.5	66	42.6

^(a) Drinking water alone** Statistically significant (p<0.01) using χ^2 test

Statistically significant (p<0.01) using Cochrane-Armitage test for dose-response relationship

Table 12 - Long-term carcinogenicity bioassay on VAM, administered with drinking water, supplied *ad libitum* to male (M) and female (F) Wistar rats (Experiment BT 53). Oncological lesions of the oral cavity

Group No.	Concentration (ppm, v/v)	Animals			Animals with oncological lesions					
		Age	Sex	No.	Acanthomas		Squamous cell dysplasias		Squamous cell carcinomas	
					No.	%	No.	%	No.	%
I	5,000	Breeders (17 weeks old)	M	13	1	7.7	1	7.7	3	23.1
			F	37	0	-	2	5.4	1	2.7
			M+F	50	1	2.0	3	6.0	4	8.0
		Offspring (Embryos)	M	82	0	-	1	1.2	12	14.6*
			F	95	0	-	12	12.6*	24	25.3**
			M+F	177	0	-	13	7.3	36	20.3
II	1,000	Breeders (17 weeks old)	M	13	0	-	0	-	1	7.7
			F	37	0	-	0	-	4	10.8
			M+F	50	0	-	0	-	5	10.0
		Offspring (Embryos)	M	64	0	-	0	-	1	1.6
			F	73	0	-	0	-	11	15.1
			M+F	137	0	-	0	-	12	8.8
III	0 ^(a)	Breeders (17 weeks old)	M	14	0	-	0	-	1	7.1
			F	37	0	-	0	-	2	5.4
			M+F	51	0	-	0	-	3	5.9
		Offspring (Embryos)	M	86	0	-	0	-	3	3.5
			F	69	0	-	1	1.4	5	7.2
			M+F	155	0	-	1	0.6	8	5.2

^(a) Drinking water alone* Statistically significant (p<0.05) using χ^2 test** Statistically significant (p<0.01) using χ^2 test

Statistically significant (p<0.01) using Cochrane-Armitage test for dose-response relationship

Table 13 - Long-term carcinogenicity bioassay on VAM, administered with drinking water, supplied *ad libitum* to male (M) and female (F) Wistar rats (Experiment BT 53). Oncological lesions of the tongue

Group No.	Concentration (ppm, v/v)	Animals			Animals with oncological lesions						
		Age	Sex	No.	Acanthomas		Squamous cell dysplasias		Squamous cell carcinomas		
					No.	%	No.	%	No.	%	
I	5,000	Breeders (17 weeks old)	M	13	0	-	3	23.1	0	-	
			F	37	0	-	4	10.8	1	2.7	
			M+F	50	0	-	7	14.0	1	2.0	
		Offspring (Embryos)	M	82	0	-	1		1.2	2	2.4
			F	95	0	-	5		5.3	6	6.3
			M+F	177	0	-	6		3.4	8	4.5
II	1,000	Breeders (17 weeks old)	M	13	0	-	0	-	0	-	
			F	37	0	-	0	-	1	2.7	
			M+F	50	0	-	0	-	1	2.0	
		Offspring (Embryos)	M	64	0	-	1		1.6	0	-
			F	73	0	-	0		-	0	-
			M+F	137	0	-	1		0.7	0	-
III	0 ^(a)	Breeders (17 weeks old)	M	14	0	-	0	-	0	-	
			F	37	0	-	0	-	0	-	
			M+F	51	0	-	0	-	0	-	
		Offspring (Embryos)	M	86	0	-	0		-	0	-
			F	69	0	-	0		-	0	-
			M+F	155	0	-	0		-	0	-

^(a)Drinking water alone

VAM caused squamous cell carcinomas of the oral cavity in male breeders treated at the higher dose, female breeders treated with the lower dose, male and female offspring of the higher dose and female offspring of the lower dose group (Table 12).

The incidence of tongue squamous cell dysplasias proved to be increased among male and female breeders and offspring treated with the higher dose. There was a borderline increase in squamous cell carcinomas in female breeders of both treated groups, and an evident increase in male and female offspring treated at the higher dose (Table 13).

Squamous cell dysplasias of the oesophagus were increased among male and female breeders and offspring treated with the higher dose. Squamous cell carcinomas were increased in male and female offspring treated with the higher dose (Table 14).

A borderline increase of the incidence of squamous cell carcinomas of the forestomach was observed among male and female breeders and offspring treated with the higher dose, and in female breeders treated with the lower dose (Table 15).

When upper gastrointestinal tract squamous cell carcinomas plus their precursors were considered as a whole, a highly significant dose-related increase was observed in male and female breeders and offspring (Table 16).

The number of malignant tumours (sarcomas and carcinomas) of the uterus was found to have increased in breeders of both treated groups and in offspring treated with the higher dose (Table 17).

An increase of haemolymphoreticular neoplasias was observed in female breeders treated with both doses, and in male and female offspring of both treated groups (Table 18).

Conclusions

In the tested experimental conditions, VAM is shown to cause an increase in total malignant tumours and tumours at several body sites. Of particular significance is the increase in squamous cell carcinomas of the oral cavity, tongue, oesophagus and forestomach. The sites of these tumours were the same found in Swiss mice and Sprague-Dawley rats in the experiments performed in our laboratory following the same protocol. It must be also considered that the sites of these tumours were those most directly exposed to VAM, since the compound was administered by oral route.

The results of this experiment, together with those of the experiments on Swiss mice² and on Sprague-Dawley rats³, show that VAM is a multipotent carcinogen. On the basis of the whole evaluation of this compound, regulatory measures and preventive action must be undertaken to prevent the carcinogenic risk of VAM, mainly among workers exposed and consumers of goods containing the monomer.

Of particular concern is the current use of VAM-based polymers as compounds in contact with food and beverages, including the use of polyvinyl acetate in the production of chewing-gum. In fact, since VAM has been found to migrate from plastic materials into wine²⁴ and water²⁵, one cannot exclude the migration into saliva and other biological fluids.

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Table 14 - Long-term carcinogenicity bioassay on VAM, administered with drinking water, supplied *ad libitum* to male (M) and female (F) Wistar rats (Experiment BT 53). Oncological lesions of the oesophagus

Group No.	Concentration (ppm, v/v)	Animals			Animals with oncological lesions					
		Age	Sex	No.	Acanthomas		Squamous cell dysplasias		Squamous cell carcinomas	
					No.	%	No.	%	No.	%
I	5,000	Breeders (17 weeks old)	M	13	0	-	3	23.1	0	-
			F	37	0	-	6	16.2*	1	2.7
			M+F	50	0	-	9	18.0	1	2.0
		Offspring (Embryos)	M	82	0	-	10	12.2**	3	3.7
			F	95	1	1.1	29	30.5**	4	4.2
			M+F	177	1	0.6	39	22.0	7	4.0
II	1,000	Breeders (17 weeks old)	M	13	0	-	0	-	0	-
			F	37	0	-	0	-	0	-
			M+F	50	0	-	0	-	0	-
		Offspring (Embryos)	M	64	0	-	1	1.6	0	-
			F	73	0	-	0	-	1	1.4
			M+F	137	0	-	1	0.7	1	0.7
III	0 ^(a)	Breeders (17 weeks old)	M	14	0	-	0	-	0	-
			F	37	0	-	0	-	0	-
			M+F	51	0	-	0	-	0	-
		Offspring (Embryos)	M	86	0	-	0	-	0	-
			F	69	0	-	0	-	0	-
			M+F	155	0	-	0	-	0	-

^(a)Drinking water alone* Statistically significant (p<0.05) using χ^2 test**Statistically significant (p<0.01) using χ^2 test

Statistically significant (p<0.01) using Cochran-Armitage test for dose-response relationship

Table 15 - Long-term carcinogenicity bioassay on VAM, administered with drinking water, supplied *ad libitum* to male (M) and female (F) Wistar rats (Experiment BT 53). Oncological lesions of the forestomach

Group No.	Concentration (ppm, v/v)	Animals			Animals with oncological lesions					
		Age	Sex	No.	Acanthomas		Squamous cell dysplasias		Squamous cell carcinomas	
					No.	%	No.	%	No.	%
I	5,000	Breeders (17 weeks old)	M	13	0	-	0	-	1	7.7
			F	37	2	5.4	4	10.8	2	5.4
			M+F	50	2	4.0	4	8.0	3	6.0
		Offspring (Embryos)	M	82	1	1.2	6	7.3	4	4.9
			F	95	4	4.2	5	5.3	4	4.2
			M+F	177	5	2.8	11	6.2	8	4.5
II	1,000	Breeders (17 weeks old)	M	13	0	-	1	7.7	0	-
			F	37	1	2.7	2	5.4	2	5.4
			M+F	50	1	2.0	3	6.0	2	4.0
		Offspring (Embryos)	M	64	0	-	1	1.6	0	-
			F	73	0	-	2	2.7	0	-
			M+F	137	0	-	3	2.2	0	-
III	0 ^(a)	Breeders (17 weeks old)	M	14	0	-	0	-	0	-
			F	37	0	-	0	-	0	-
			M+F	51	0	-	0	-	0	-
		Offspring (Embryos)	M	86	0	-	1	1.2	0	-
			F	69	1	1.4	1	1.4	0	-
			M+F	155	1	0.6	2	1.3	0	-

^(a)Drinking water alone

Table 16 - Long-term carcinogenicity bioassay on VAM, administered with drinking water, supplied *ad libitum*, to male (M) and female (F) Wistar rats (Experiment BT 53). Upper gastrointestinal tract squamous cell carcinomas (SqCa) plus their precursors (SqDy)

Group No.	Concentration (ppm, v/v)	Animals			SqCa + SqDy No. per 100 animals	
		Age	Sex	No.		
I	5,000	Breeders (17 weeks old)	M	13	84.6**	
			F	37		56.8**
			M+F	50		
		Offspring (Embryos)	M	82	47.6**	
			F	95		93.7**
			M+F	177		
II	1,000	Breeders (17 weeks old)	M	13	15.4	
			F	37		24.3*
			M+F	50		
		Offspring (Embryos)	M	64	6.3	
			F	73		19.2
			M+F	137		
III	0 ^(a)	Breeders (17 weeks old)	M	14	7.1	
			F	37		5.4
			M+F	51		
		Offspring (Embryos)	M	86	4.7	
			F	69		10.1
			M+F	155		

^(a)Drinking water alone

* Statistically significant (p<0.05) using χ^2 test

** Statistically significant (p<0.01) using χ^2 test

Statistically significant (p<0.01) using Cochran-Armitage test for dose-response relationship

Table 17 - Long-term carcinogenicity bioassay on VAM, administered with drinking water, supplied *ad libitum*, to male (M) and female (F) Wistar rats (Experiment BT 53). Malignant tumours of the uterus

Group No.	Concentration (ppm, v/v)	Animals		Tumour-bearing animals				Total malignant tumours ^(c)	
		Age	No.	Carcinomas ^(a)		Sarcomas ^(b)		No.	Per 100 animals
				No.	%	No.	%		
I	5,000	Breeders (17 weeks old)	37	6	16.2	5	13.5	12	32.4 *
		Offspring (Embryos)	95	22	23.2**	9	9.5	31	32.6*
II	1,000	Breeders (17 weeks old)	37	4	10.8	5	13.5	9	24.3
		Offspring (Embryos)	73	6	8.2	6	8.2	12	16.4
III	0 ^(d)	Breeders (17 weeks old)	37	2	5.4	2	5.4	4	10.8
		Offspring (Embryos)	69	4	5.8	7	10.1	13	18.8

^(a)Squamous cell carcinoma and adenocarcinoma

^(b)Fibrosarcoma, leiomyosarcoma, liposarcoma, angiosarcoma and malignant Schwannoma

^(c)One animal can bear more than one tumour

^(d)Drinking water alone

* Statistically significant (p<0.05) using χ^2 test

** Statistically significant (p<0.01) using χ^2 test

Statistically significant (p<0.05) using Cochran-Armitage test for dose-response relationship

Table 18 - Long-term carcinogenicity bioassay on VAM, administered with drinking water, supplied *ad libitum*, to male (M) and female (F) Wistar rats (Experiment BT 53). Haemolymphoreticular neoplasias

Group No.	Concentration (ppm, v/v)	Age	Animals		Animals with haemolymphoreticular neoplasias	
			Sex	No.	No.	%
I	5,000	Breeders (17 weeks old)	M	13	1	7.7
			F	37	6	16.2
			M+F	50	7	14.0
		Offspring (Embryos)	M	82	8	9.8
			F	95	14	14.7
			M+F	177	22	12.4
II	1,000	Breeders (17 weeks old)	M	13	1	7.7
			F	37	3	8.1
			M+F	50	4	8.0
		Offspring (Embryos)	M	64	7	10.9
			F	73	5	6.8
			M+F	137	12	8.8
III	0 ^(a)	Breeders (17 weeks old)	M	14	2	14.3
			F	37	1	2.7
			M+F	51	3	5.9
		Offspring (Embryos)	M	86	5	5.8
			F	69	3	4.3
			M+F	155	8	5.2

^(a)Drinking water alone

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