Vinylbromide

Health based calculated occupational cancer risk values

Aanbiedingsbrief

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Health based calculated occupational cancer risk values

Dutch Expert Committee on Occupational Standards,
a committee of the Health Council of the Netherlands

to

the Minister and State Secretary of Social Affairs and Employment

No. 1999/15OSH, The Hague, 20 December 1999

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Contents

Samenvatting

Op verzoek van de Minister van Sociale Zaken en Werkgelegenheid schat de Commissie WGD van de Gezondheidsraad het extra kankerrisico bij beroepsmatige blootstelling aan stoffen die door de Europese Unie of door de Commissie WGD als genotoxisch kankerverwekkend zijn aangemerkt. In dit rapport maakt zij zo'n schatting voor vinylbromide. Zij heeft daarbij gebruik gemaakt van de methode die is beschreven in het rapport 'Berekening van het risico op kanker' (1995/06WGD) (Hea95).

Naar schatting van de commissie is de extra kans op kanker voor vinylbromide:

- 4×10^{-5} bij 40 jaar beroepsmatige blootstelling aan 0.012 mg/m^3
- 4×10^{-3} bij 40 jaar beroepsmatige blootstelling aan 1.2 mg/m^3

Executive summary

On request of the Minister of Social Affairs and Employment the Dutch Expert Committee on Occupational Standards (DECOS), a committee of the Health Council of the Netherlands, estimates the additional lifetime cancer risk associated with occupational exposure to substances that have been classified by the European Union or the DECOS as genotoxic carcinogen. In this report the committee presents such estimates for vinylbromide. It has used the method described in the report 'Calculating cancer risks due to occupational exposure to genotoxic carcinogens' (1995/06WGD) (Hea95).

The committee estimated that the additional lifetime cancer risk for vinylbromide amounts to:

- 4×10^{-5} for 40 years of occupational exposure to 0.012 mg/m^3
- 4×10^{-3} for 40 years of occupational exposure to 1.2 mg/m^3

Chapter 1

Scope

1.1 Background

In the Netherlands, occupational exposure limits for chemical substances are set using a three-step procedure. In the first step, a scientific evaluation of the data on the toxicity of the substance is made by the Dutch Expert Committee on Occupational Standards (DECOS), a committee of the Health Council of the Netherlands, on request of the Minister of Social Affairs and Employment (annex A). This evaluation should lead to a health-based recommended exposure limit for the concentration of the substance in air. Such an exposure limit cannot be derived if the toxic action cannot be evaluated using a threshold model, as is the case for substances with genotoxic carcinogenic properties.

In this case an exposure-response relationship is recommended for use in regulatory standard setting, ie. the calculation of so-called health-based calculated occupational cancer risk values (HBC-OCRVs). The committee calculates HBC-OCRVs for compounds which are classified as genotoxic carcinogens by the European Union or by the present committee.

For the establishment of the HBC-OCRV's the committee generally uses a linear extrapolation method, as described in the committee's report 'Calculating cancer risk due to occupational exposure to genotoxic carcinogens' (1995/06WGD). The linear model to calculate occupational cancer risk is used as a default method, unless scientific data would indicate that using this model is not appropriate.

In the next phase of the three-step procedure, the Social and Economic Council advises the Minister of Social Affairs and Employment on the feasibility of using the

HBC-OCRVs as regulatory occupational exposure limits. In the final step of the procedure the Minister sets the official occupational exposure limits.

1.2 Committee and procedure

The present document contains the derivation of HBC-OCRVs for vinylbromide by the committee. The members of the committee are listed in Annex B. The first draft of this report was prepared by H Stouten and MI Willems, from the TNO Nutrition and Food Research Institute in Zeist, by contract with the Ministry of Social Affairs and Employment.

Chapter 2

Vinylbromide

2.1 Introduction

Vinylbromide has been classified as a genotoxic carcinogen by the Dutch Expert Committee on Occupational Standards (DECOS95).

This evaluation of the carcinogenicity and other toxic effects of vinylbromide has been based on reviews by IARC (IARC86), and the American Conference of Governmental Industrial Hygienists (ACGIH; ACG91). In addition, literature was retrieved from the online data bases Medline, Toxline, and Chemical Abstracts, covering the period 1966 to December 1995/January 1996. Where relevant, the original publications were reviewed and evaluated as indicated in the text.

2.2 Identity and physical and chemical properties*

Chemical name	:	vinylbromide
CAS registry number	:	593-60-20
EEC number	:	602-024-00-2
EINECS number	:	209-800-6
Synonyms	:	bromoethene, bromoethylene
Description	:	gas under normal atmospheric conditions, under pressure a colourless liquid; has a characteristic pungent odour
Molecular formula	:	C_2H_3Br
Structure	:	$CH_2 = CHBr$
Molecular weight	:	106.96
Boiling point (100 kPa)	:	15.8 ºC
Melting point	:	- 139.5 ºC
Relative vapour density (air=1)	:	3.7
Vapour pressure (20 ºC)	:	137.7 kPa
Specific gravity	:	1.4933 at 20 ºC (liquid)
Solubility in water	:	insoluble at 20 ºC
Solubility in organic solvents	:	soluble in ethanol, ether, acetone, benzene, chloroform
Conversion factors	:	1 ppm = 4.4 mg/m^3 air (25 ºC, 101.3 kPa) 1 mg/m^3 = 0.227 ppm
EC labeling	:	R: 12; S: (2-)9-16-13
EC classification	:	F; R 12

2.3 Carcinogenicity studies and selection of study suitable for risk estimation in the occupational situation

The carcinogenicity of vinylbromide has been evaluated by IARC (IARC86), and ACGIH (ACG91). Vinylbromide was tested in female mice by skin application and by subcutaneous injection, and in rats by inhalation exposure. In the inhalation study in rats, there was a dose-related increase in the incidence of liver angiosarcomas and Zymbal gland carcinomas; an increased incidence of neoplastic liver nodules and hepatocellular carcinoma was also noted. In the limited studies in mice by skin application and sc injection, no local tumours were observed (IARC86).

* data from Tor94, IARC86, CEG93

Based on the results of the rat inhalation study, IARC concluded that there was sufficient evidence for the carcinogenicity to experimental animals. No data on humans were available. IARC has classified vinylbromide as a group 2A carcinogen, probably carcinogenic to humans (IARC86; IARC87).

Table 1 (annex D) summarizes the carcinogenicity studies in experimental animals. The long-term rat study (Ben82) was selected for calculation of the carcinogenic activity of vinylbromide. The chronic toxicity and carcinogenicity of vinylbromide was evaluated in rats exposed to nominal vapour concentrations of 10, 50, 250, or 1250 ppm for 24 months (Ben82). The actual concentrations amounted to 0, 9.7, 52, 247 and 1235 ppm i.e. 0, 43, 229, 1087 and 5434 mg/m^3. Interim sacrifices were performed at 6 (n = 5), 12 (n = 10), and 18 months (n = 10), and rats were examined for microscopic abnormalities. The control group consisted of 144 male and 144 female rats; each of the exposure groups consisted of 120 male and 120 female rats. At 43 mg/m^3, 17 (7 and 10) angiosarcomas were found in male and female rats.

Angiosarcomas, primarily in the liver, but also occasionally in lung, spleen, nasal cavity and mesentery, were induced in both male and female rats in all dose groups. The rate of metastasis of these angiosarcomas was high. An increase in the number of Zymbal's gland neoplasms was found in both male and female rats at 50, 250, and 1250 ppm. An increased incidence of primary hepatocellular neoplasms was seen in males exposed to 250 ppm and in females exposed to 10, 50 and 250 ppm. The actual numbers of animals with angiosarcomas in the liver and Zymbal's gland neoplasms are given in Table 1. The higher number of angiosarcomas in males exposed to 250 ppm and in females exposed to 50 or 250 ppm than in animals exposed to 1250 ppm may be due to the early termination, at 72 weeks, of animals exposed to 1250 ppm. From the results of this study it is obvious that the most sensitive indicator of vinylbromide carcinogenicity in rats is the induction of hepatic angiosarcomas. It should be noted that the article of Benya *et al*. does not give either the total number of tumour-bearing animals or the number of animals with angiosarcomas (Ben82). The committee realises that this may lead to an underestimation of the carcinogenic activity, since it is clear from the article of Benya *et al*. that, besides animals with liver angiosarcomas, also animals with primary angiosarcoms in other organs and animals with other types of treatment-related tumours were found. In addition, the final incidence numbers were not corrected for animals sacrificed at the scheduled interim kills.

2.4 Carcinogenic activity in experimental animals, lifetime low-dose exposure

To calculate the carcinogenic activity expressed as the incidence per mg vinylbromide per m^3, the lowest concentration (43 mg/m^3) resulting in the induction of angiosarcomas in the liver of both male and female rats was used as starting point (Ben82). The

committee is of the opinion that the available data do not indicate that the use of the linear model is not appropriate.

The incidence of tumour bearing animals per mg/kg bw/day (lifespan conditions, assuming a linear dose-response relationship), $I_{concentration}$, is calculated as follows:

$$I^*_{concentration} = \frac{I_e - I_c}{C \times (X_{po}/L) \times (X_{pe}/L) \times \text{exposure hours per day}/24 \times \text{exposure days per week}/7} =$$

$$\frac{(17/240 - 1/288)}{(43\ mg/m^3) \times (730^d/1000^d) \times (730^d/1000^d) \times 6/24 \times 5/7} = 1.6*10^{-2}\ [mg/m^3]^{-1}**$$

2.5 Health risk to humans, lifetime low-dose exposure

To estimate the additional lifetime risk of cancer in humans under lifespan conditions on the basis of results in animal experiments, it is assumed that no difference exists between experimental animals and man with respect to toxicokinetics, mechanism of tumour induction, target, susceptibility etc, unless specific information is available which justifies a different approach. Furthermore, it is assumed that the average man lives 75 years, weighs 70 kg, and is exposed 24 hours per day 7 days per week, 52 weeks per year for lifetime.

2.6 Health risk to workers, calculation of the HBC-OCRV

To estimate the additional lifetime risk of cancer in humans under workplace conditions, it is assumed that the average man lives 75 years, is exposed 8 hours per day during 5 days per week, 48 weeks per year, for 40 years, and inhales 10 m^3 air per 8-hour-working day.

Using as starting point the estimated incidence of 1.6 x 10^{-2} per mg/m^3, the additional lifetime cancer risk per mg/m^3 under occupational conditions (=HBC-OCRV) amounts to:

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* $I_{concentration}$ = the carcinogenic activity attributable to the exposure to the substance per unit daily dose under lifespan conditions, assuming a linear dose response relationship, usually expressed per mg/m^3 or per mg/kg bw/day.
I_e and I_c = incidence of tumour bearing animals or tumours in exposed and control animals, respectively,
X_{po} = exposure period, X_{pe} = experimental period
L = standard lifespan for the animals in question (L rat is assumed to be 1000 days)

** The final incidence numbers were not corrected for animals sacrified at the scheduled interim kills

$$\text{HBC-OCRV} = 1.6 \times 10^{-2} x \frac{40y}{75y} x \frac{48w}{52w} x \frac{5d}{7d} x \frac{10m^3}{18m^3} = 3.2 \times 10^{-3} [mg/m^3]^{-1}$$

Based on the HBC-OCRV the additional lifetime cancer risk amounts to:

- 4×10^{-5} for 40 years of exposure to 0.012 mg/m^3
- 4×10^{-3} for 40 years of exposure to 1.2 mg/m^3

2.7 Existing occupational exposure limits

Table 1 summarizes the occupational exposure limits established by regulatory authorities of The Netherlands and by the USA-ACGIH. None of the other consulted listings appeared to contain occupational exposure limits for vinylbromide (DFG96, HSE96, NBO93). The ACGIH limit value amounts to 2,2 mg/m^3 and is about a factor 2 higher than the exposure concentration estimated to be associated with an additional cancer risk of 4×10^{-3}.

Table 1 Occupational exposure limits for vinylbromide.

country	level		time relation	ref.
	ppm	mg/m^3		
The Netherlands[a]	-	-	8-h TWA	ISZW99
Germany DFG MAK-kom	-	-		DFG99
Great Brittain HSE	-	-		HSE99
Sweden				NBO93
Denmark[b]	5	20	8-h TWA	Arb96
USA				ACG99
ACGIH[c]	0.5	2.2	8-h TWA	
OSHA	-	-		
NIOSH[d]	-	-		
European Union SCOEL	-	-		Hun97

[a] Included in 'list of carcinogenic chemicals' (Appendix 2)

[b] substance appears in the List of substances considered to be carcinogenic

[c] A2: suspected human carcinogen

[d] X: carcinogen defined with no further categorization

2.8 Toxicity profile of vinylbromide

The toxicity of vinylbromide has been reviewed by the IARC (IARC86), and the ACGIH (ACG91).

Acute toxicity. The reported oral LD_{50} of a 50% solution of vinylbromide in corn oil is 500 mg/kg in male rats. No LC_{50}-value is given, 100,000 ppm is reported to be lethal in 15 min, 50,000 ppm killed rats after 7 hours of exposure, at 25,000 ppm no deaths were found after 7 hours. Vinylbromide is a potent, acute hepatotoxin in rodents (ACG91). Liquid vinylbromide is slightly to moderately irritating to the eyes, but is non-irritating to intact or abraded rabbit skin (ACG91).

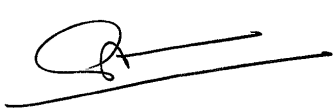
Repeated-dose toxicity. Twenty repeated seven-hour exposures of male rats to 10,000 ppm (44,000 mg/m^3) of vinylbromide resulted in an observable decrease in activity during the exposures and a significant decrease in body weight gain. However, no significant gross or microscopic pathological changes were detected in the major organs and tissues (Ben82; ACG91). In a subsequent 6-month inhalation study the only significant compound-related effect in the treated animals (rats, rabbits, and monkeys) was an increase in serum bromide levels following exposure to atmospheres containing 250 or 500 ppm (1100, 2200 mg/m^3) of vinylbromide (Ben82; ACG91). The combined chronic toxicity/carcinogenicity study reported by Benya *et al*. (Ben82, see Table 1) did not allow the establishment of a NOAEL. At the lowest concentration examined (9.7 ppm or 43 mg/m^3) a number of non-neoplastic effects were found (Ben82).

Vinylbromide is mutagenic in standard short-term tests with *Salmonella typimurium* and *Tradescantia* in the presence of mammalian exogenous metabolic activation.

No reproduction and/or other teratogenicity studies were available.

Based on the data as described above, it is concluded that a health-based occupational exposure limit for vinylbromide derived from data other than data on genotoxicity/carcinogenicity is expected to be close to the concentration level (1.2 mg/m^3) associated with the referential lifetime cancer risk level of 4×10^{-3}.

The Hague, 20 December 1999,
for the committee



dr ASAM van der Burght,
scientific secretary

Prof. dr GJ Mulder,
chairman

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ACG99 American Conference of Governmental Industrial Hygienists (ACGIH). 1999. TLVs® and BEIs®. Guide to Occupational Exposure Values, Cincinnati OH, USA: ACGIH, 1999: 126.

Arb96 Arbejdstilsynet. Exposure Limit value for substances and materials. Copenhagen, Danmark: Arbejdstilsynet, 1996:10.

Ben82 Benya ThJ, Busey WM, Dorato MA, *et al*. Inhalation carcinogenicity bioassay of vinylbromide in rats. Toxicol Appl Pharmacol 1982; 64: 367-79.

Bol79 Bolt HM, Laib RJ, Stöckle G. Formation of pre-neoplastic hepatocellular foci by vinylbromide in newborn rats (letter to the editor). Arch Toxicol 1979; 43: 83-4.

CEG93 Commissie van de Europese Gemeenschappen (CEG). In: Bijlage bij Richtlijn 93/72/EEG van de Commissie van 1 september tot negentiende aanpassing aan de vooruitgang van de techniek van Richtlijn 67/543/EEG van de Raad betreffende de aanpassing van de wettelijke en bestuursrechtelijke bepalingen inzake de indeling, de verpakking en het kenmerken van gevaarlijke stoffen (vervolg). Maastricht, The Netherlands: Ellis Publications, 1993: 683 (Publicatieblad van de Europese Gemeenschappen L258A, deel 1).

DECOS95 Scientific documentation on the Dutch list of occupational Carcinogens (I). Dutch Expert Committee on Occupational Standards; 1995; RA 1/95.

DFG99 Deutsche Forschungsgemeinschaft (DFG): Senatskommission zur Prüfung gesundheitsschädlicher Arbeitsstoffe. MAK- und BAT-Werte-Liste 1999. MAK- und BAT-Werteliste 1999. Maximale Arbeitsplatzkonzentrationen und biologische Arbeitsstofftoleranzwerte. Weinheim, (Mitteilung 35).

Hea95 Health Council of the Netherlands, Dutch Expert Committee on Occupational Standards (DECOS). Calculating cancer risks, The Hague, The Netherlands. 1995; pub no 1995/06 WGD.

HSE99 Health and Safety Executive (HSE). Occupational exposure limits 1999. Sudbury (Suffolk), UK: HSE Books, 1999; Guidance note EH 40/96.

Hun97 Hunter WJ, Aresini G, Haigh R *et al*. Occupational exposure limits for chemicals in de European Union. Occup. Environ. Med, 1997; 54:217-22.

IARC86 International Agency for Research on Cancer (IARC). Vinylbromide. In: Some chemicals used in plastics and elastomers. Lyon, France: IARC, 1986: 133-45 (IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans; Vol 39).

IARC87 International Agency for Research on Cancer (IARC). In: Overall evaluations of carcinogenicity: an updating of IARC monographs volumes 1 to 42. Lyon, France: IARC, 1987: 73 (IARC monographs on the evaluation of carcinogenic risks to humans; Suppl 7) .

ISZW99 Inspectiedienst van het Ministerie van Sociale Zaken en Werkgelegenheid (I-SZW). De nationale MAC-lijst 1999. The Hague, The Netherlands: Sdu Servicecentrum Uitgeverijen, 1999.

NBO93 National Board of Occupational Safety and Health (NBOSH). Occupational exposure limits. Solna, Sweden: NBOSH, 1993; Ordinance AFS 1993/9.

Tor94 Torkelson TR . Vinylbromide, Monobromoethylene, Bromoethane [CAS # 593-60-2]: CH_2 = CHBr. In: Clayton GD, Clayton FE, eds. Toxicology. 4th ed. New York, USA: John Wiley & Sons, Inc, 1994: 4178-81 (Patty's industrial hygiene and toxicology; Vol II, Part E)

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A	Request for advice
B	The committee
C	Comments on the public draft
D	Animal studies

Annexes

Annex **A**

Request for advice

In a letter dated October 11, 1993, ref DGA/G/TOS/93/07732A, to, the State Secretary of Welfare, Health and Cultural Affairs, the Minister of Social Affairs and Employment wrote:

Some time ago a policy proposal has been formulated, as part of the simplification of the governmental advisory structure, to improve the integration of the development of recommendations for health based occupation standards and the development of comparable standards for the general population. A consequence of this policy proposal is the initiative to transfer the activities of the Dutch Expert Committee on Occupational Standards (DECOS) to the Health Council. DECOS has been established by ministerial decree of 2 June 1976. Its primary task is to recommend health based occupational exposure limits as the first step in the process of establishing Maximal Accepted Concentrations (MAC-values) for substances at the work place.

In an addendum, the Minister detailed his request to the Health Council as follows:

The Health Council should advice the Minister of Social Affairs and Employment on the hygienic aspects of his policy to protect workers against exposure to chemicals. Primarily, the Council should report on health based recommended exposure limits as a basis for (regulatory) exposure limits for air quality at the work place. This implies:

- A scientific evaluation of all relevant data on the health effects of exposure to substances using a criteria-document that will be made available to the Health Council as part of a specific request for advice. If possible this evaluation should lead to a health based recommended exposure limit, or, in

the case of genotoxic carcinogens, a ‘exposure versus tumour incidence range’ and a calculated concentration in air corresponding with reference tumour incidences of 10^{-4} and 10^{-6} per year.

- The evaluation of documents review the basis of occupational exposure limits that have been recently established in other countries.
- Recommending classifications for substances as part of the occupational hygiene policy of the government. In any case this regards the list of carcinogenic substances, for which the classification criteria of the Directive of the European Communities of 27 June 1967 (67/548/EEG) are used.
- Reporting on other subjects that will be specified at a later date.

In his letter of 14 December 1993, ref U 6102/WP/MK/459, to the Minister of Social Affairs and Employment the President of the Health Council agreed to establish DECOS as a Committee of the Health Council. The membership of the Committee is given in annex B.

Annex **B**

The Committee

- GJ Mulder, *chairman*
  professor of toxicology; Leiden University, Leiden
- RB Beems
  toxicologic pathologist; National Institute of Public Health and the Environment, Bilthoven
- PJ Borm
  toxicologist; Heinrich Heine Universität Düsseldorf (Germany)
- JJAM Brokamp, *advisor*
  Social and Economic Council, The Hague
- VJ Feron,
  professor of toxicology; TNO Nutrition and Food Research Institute, Zeist
- DJJ Heederik
  epidemiologist; Wageningen University, Wageningen
- LCMP Hontelez, *advisor*
  Ministry of Social Affairs and Employment, The Hague
- G de Jong
  occupational physician; Shell International Petroleum Maatschappij, The Hague
- J Molier-Bloot
  occupational physician; BMD Akers bv, Amsterdam
- IM Rietjens
  professor in Biochemical toxicology; Wageningen University, Wageningen.

- H Roelfzema, *advisor*
  Ministry of Health, Welfare and Sport, Den Haag
- T Smid
  occupational hygienist; KLM Health Safety & Environment, Schiphol and professor of working conditions, Free University, Amsterdam
- GMH Swaen
  epidemiologist; Maastricht University, Maastricht
- HG Verschuuren
  toxicologist; DOW Europe, Horgen (Switzerland)
- AAE Wibowo
  toxicologist; Coronel Institute, Amsterdam
- F de Wit
  occupational physician; Labour Inspectorate, Arnhem
- CA Bouwman, *scientific secretary*
  Health Council of the Netherlands, Den Haag
- ASAM van der Burght, *scientific secretary*
  Health Council of the Netherlands, Den Haag

The first draft of the present advisory report was prepared by H Stouten and M Willems, from the Department of Occupational Toxicology of the TNO Nutrition and Food Research Institute, by contract with the Ministry of Social Affairs and Employment.

Secretarial assistance: E Vandenbussche-Parméus.
Lay-out: J van Kan.

Annex **C**

Comments on the public draft

A draft of the present report was released in 1999 for public review. The following organizations and persons have commented on the draft document:

- mr P Ridgeway, Health and Safety Executive, United Kingdom
- mr A Aalto, Tampere, Finland

Annex **D**

Animal studies

See next page.

Table 1 Carcinogenicity studies with vinyl bromide.

authors	species	exposure characteristics	findings	remarks
Benya *et al* (Ben82)	rats (Sprague-Dawley) control group: 144 males and 144 females test groups: 120 males, 120 females per group	*inhalation exposure* 0, 9.7, 52, 247, 1235 ppm i.e. 0, 43, 229, 1087, 5434 mg/m^3 X_{po}: 6 hrs/day, 5 days per week for 2 years X_{pe} = 2 years	*liver, angiosarcoma* males: 0/144, 7/120, 36/120, 61/120, 43/120 females: 1/144, 10/120, 50/120, 61/120, 41/120 *ear, Zymbal gland, sqamous cell carcinoma* males: 2/142, 1/99, 1/112, 13/114, 35/116 females: 0/139, 0/99, 3/113, 2/119, 11/114	concentration-related mortality was apparent at 52 ppm and higher. Because of the high mortality animals of the 1235 ppm group were sacrificed at 72 weeks
Van Duuren 1977 cited in IARC 86	mouse (ICR/HA Swiss) control group (untre-ated): 160 females, test group: 30 females	*dermal application* 15 mg/0.1 ml acetone X_{po} 3 times per week for 60 weeks X_{pe} 420 days	no skin tumours observed either in test or in untreated control animals	the IARC working group noted that sites other than the skin were not examined, and that the test material was volatile
Van Duuren 1977 cited in IARC86	mouse (ICR/HA Swiss) test group: 30 females; vehicle control group: 30 females; untreated control group: 60 females	*subcutaneous ad-ministration* X_{po}: 25 mg/0.05 ml trioctanoin once weekly for 48 weeks X_{pe}: 420 days	no local tumours seen either in treated or in control mice	examination of animals was limited to injection site

Xpo = exposure period, Xpe = experimental period