Procarbazine hydrochloride

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. 1999/14OSH, 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 procarbazine hydrochloride. Zij heeft daarbij gebruik gemaakt van de methode die is beschreven in het rapport 'Berekening van het risico op kanker' (1995/06WGD) (Dec95a).

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

- 4×10^{-5} bij 40 jaar beroepsmatige blootstelling aan 0.002 mg/m^3
- 4×10^{-3} bij 40 jaar beroepsmatige blootstelling aan 0.2 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 procarbazine hydrochloride. It has used the method described in the report 'Calculating cancer risks due to occupational exposure to genotoxic carcinogens' (1995/06WGD) (Dec95a).

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

- 4×10^{-5} for 40 years of occupational exposure to 0.002 mg/m^3
- 4×10^{-3} for 40 years of occupational exposure to 0.2 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 procarbazine hydrochloride by the committee. The members of the committee are listed in Annex B. The first draft of this report was prepared by MI Willems, from the TNO Nutrition and Food Research Institute in Zeist, by contract with the Ministry of Social Affairs and Employment.

Chapter 2

Procarbazine hydrochloride

2.1 Introduction

The carcinogenicity of procarbazine hydrochloride (CAS no. 366-70-1) has been evaluated by IARC (IARC81, IARC87) and the DECOS committee (DEC95b). The latter committee concluded that there was inadequate evidence that procarbazine hydrochloride is carcinogenic to humans. There was sufficient evidence for the carcinogenicity in animals. Procarbazine hydrochloride is a genotoxic carcinogen (DEC95b).

The compound is used as an antineoplastic agent. This evaluation of the carcinogenicity was based on reviews by IARC (IARC81, IARC87). In addition, literature was retrieved from online databases Medline, Toxline and Chemical Abstracts, covering the period 1966 to January 1996.

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

No epidemiological data have been found with respect to exposure to procarbazine alone. An increased risk of cancer has been linked to combination chemotherapy, which often includes procarbazine, but there was no qualitative nor quantitative information on procarbazine as a single aetiological agent.

Animal data are summarized in Table 1 (Annex D).

There are no long-term carcinogenicity inhalation studies. Exposure by various routes resulted in tumour formation in various species of monkeys (Ada82; IARC81). However, data on monkeys are from experiments with individual animals using different doses, exposure times, etc, and are therefore not suitable for risk calculations.

The oral studies do not meet the study selection criteria. Although the ip route is generally not considered to be relevant with respect to evaluate health risk from occupational exposure, the ip studies using mice performed by NCI (NCI78) are nevertheless selected because they show compound-related induction of systemic tumours, some of which were found following oral administration as well. In addition, these studies were most appropriate with respect to exposure and observation period and dose-response relationship.

In the NCI study, the total incidences of mice with a mixture of malignant tumours are 8/30 (male) and 19/23 (female) after exposure to 6 mg/kg bw/day.

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

To calculate the carcinogenic activity expressed as the incidence per mg procarbazine per kg bw per day, the total number of animals (males plus females) with malignant tumours is used; In addition, data from untreated and matched vehicle controls are combined (NCI78).

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 test substance/kg bw/day (lifespan conditions, assuming a linear dose response relationship), I_{dose}, is calculated as follows:

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

$$= \frac{27/53 - 2/53}{6 \text{ mg/kg bw/d} \times (52 \times 7^d/750^d) \times (85 \times 7/750^d) \times 24/24 \times 3/7} = 4.8 \times 10^{-1} \text{ [mg/kg bw/d]}^{-1}$$

* I_{dose} = is 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 per m^3 or as mg per kg body weight per day.
C is the concentration to which the animals are exposed, expressed as mg/m^3 or as mg/kg bw/day.
I_e and I_c = incidence of tumour bearing animals or tumours in exposed and control animals, respectively,
Xpo = exposure period, Xpe = experimental period
L = standard lifespan for the animals in question (L rat is assumed to be 1000 days)

2.4 Health risk to humans

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, weights 70 kg and is exposed 24 hours per day 7 days/week, 52 weeks per year for lifetime.

2.5 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, five days a week, 48 weeks a year, for 40 years, and inhales 10 m^3 air per 8 hour-working day. Using as starting point the estimated incidence I_{dose} of 0.48 per mg/kg bw/day the additional lifetime cancer risk per mg/m^3 under occupational conditions, the HBC-OCRV, amounts to:

$$\text{HBC-OCRV} = 0.48 x \frac{40y}{75y} x \frac{48w}{52w} x \frac{5d}{7d} x \frac{10m^3}{70kg} = 2.4 \text{ x } 10^{-2} [mg/m^3]^{-1}$$

Based on the HBC-OCRV of 2.4 x 10^{-2} per mg/m^3 the reference additional lifetime cancer risk amounts to:

- 4 x 10^{-5} for 40 years of exposure to 0.002 mg/m^3
- 4 x 10^{-3} for 40 years of exposure to 0.2 mg/m^3

2.6 Existing occupational exposure limits

No occupational exposure limits of procarbazine (hydrochloride) have been established in other countries.

2.7 Toxicity profile of procarbazine

There are no data on the toxicity (including irritation of mucous membranes or respiratory tract) resulting from occupational exposure.

The therapeutic (oral) doses range between 1 to 6 mg/kg/d, and frequently cause more or less acute effects such as leukopenia, thrombocytopenia, nausea, vomiting,

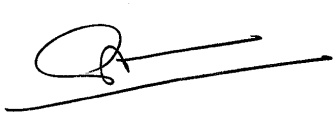
while in a latter stage myelosuppression may occur. Less frequently gastrointestinal, neurological, or dermatological manifestations may be seen (Goodman Gilman *et al*, 1985 (Goo85)). Daily oral intake of 250-300 mg, for 2-3 weeks, caused a dose-related reversible depression of peripheralleucocyte and platelet count (IARC81).

Teratogenicity and embryomortality are reported in animal (rat) experiments (IARC81) at doses higher than those inducing tumours.

Conclusion

Due to a lack of toxicity data the concentration levels associated with the referential cancer risk levels cannot be compared with a tentatively estimated health-based occupational exposure limit derived from data other than those on genotoxicity/carcinogenicity.

The Hague, 20 December 1999,
for the committee



dr ASAM van der Burght,
scientific secretary

Prof. dr GJ Mulder,
chairman

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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 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 1998 for public review. The following organizations and persons have commented on the draft document:

- WF ten Berge, DSM, Heerlen

Annex **D**

Animal studies

See next pages.

Table 1 Carcinogenicity studies with procarbazine hydrochloride.

authors	species[a]	exposure characteristics[b]	dose	exposure and experimental period	findings	remark
Heuson, Heimann (Heu66)	rat (Sprague-Dawley; female; n=10)	oral (gavage)	50, 100, 150 mg 50 mg	Xpo = 1 d; Xpe: ? Xpo = 3 d (d 0, d 3, d 6); Xpe : ?	in all animals of all exposure groups mammary tumours (mainly carcinomas)	no negative controls; no survival times reported
Kelly *et al*. (Kel68)	rat (Osborne-Mendel; female; n = ?	oral (gavage?)	50, 100 mg/kg; once weekly; 500, 1000 mg/kg	Xpo = 10 w; Xpe > 11 w Xpo = 1 d; Xpe > 11 w	high dose: in 17/18 mammary adenocarcinomas low dose: in 17/19 mammary adenocarcinomas high dose: in 1/1 mammary adenocarcinomas low dose: 9/9 mammary adenocarcinomas	no data on controls, no other tumours observed in exposed rats
	rat (Fischer 344/N; female)	oral (gavage?)	100 mg/kg, once weekly; 250 mg/kg, once weekly;	Xpo = 10 w; Xpe > 11 w Xpo = 4 w; Xpe > 11 w	in 8/15 mammary tumours (adenocarcinomas and/or fibromas) in 9/19 mammary tumours	no data on controls; other tumours observed, but not specified per dose group
	rat (Fischer 344/N; male and female)	oral (gavage?)	500, 1000 mg/kg;	Xpo = 1 d; Xpe > 11 w	high dose: female: in 1/5 mammary tumours; *male*: in 0/9 mammary tumours low dose: female: in 4/5 mammary tumours; *male*: in 0/9 mammary tumours	
Bacci *et al*. (Bac84)	rat (Osborne-Mendel; 24 male, 27 female)	oral (gavage)	3 mg	Xpo = 100 d; Xpe = 54.5w (av, male), Xpe = 47.1w (av, female).	*male*: total tumour-bearing animals: 17/24 (total number of tumours: 32, 44% lung, 16% mammary gland, 16% mediastinum) *female*: total number of tumour-bearing animals: 25/27 (total number of tumours: 44, 47% mammary gland, 23% lung, 14% thoracic wall) *controls*: male: number of tumour-bearing animals: 4/24; female: number of tumour-bearing animals: 9/27 controls: 24 male, 27 female	controls: 24 male, 27 female
Kelly *et al*. (Kel64)	mouse (CD2F1; male and female)	oral (gavage)	258 mg/kg, once weekly; 470-675 mg/kg; 1000-1800 mg/kg;	Xpo= 8 w; Xpe=15-22w Xpo= 1 d; Xpe=10-14w or 25 w Xpo=1 d; Xpe=10-14w or 22-25 w	in 7/7 lung tumours, in 3/7 leukaemias no leukaemias; lung tumours in 8/9 (Xpe=10-14 w) and in 9/9 (Xpe= 25 w) no leukaemias; lung tumours in3/4 (Xpe=10-14 w) and in 5/5 (Xpe=22-25 w) controls: no leukaemias; lung tumours in 2/100 (Xpe=38 w) and 2/111 (Xpe=55 w)	number of controls not indicated; number of animals exposed per sex per group not indicated, results of male and female combined (no difference in results); single doses not specified.
	mouse (non-inbred albino male and female)	oral (gavage)	300 mg/kg, once weekly;	Xpo= 8 w, Xpe= 6-11 w or 12-16 w	Lung tumours in 9/14 and leukaemias in 2/14 (Xpe=6-11 w) lung tumours in 21/21, leukaemias in 17/21 (Xpe=12-16 w) controls: lung tumours, leukaemias in 0/70 (Xpe= 6-11 w). lung tumours in 29/144, leukaemias in 1/144 (Xpe=12-16 w).	

Table 1 Continued.

authors	species[a]	exposure characteristics[b]	dose	exposure and experimental period	findings	remark
Kelly *et al*. (Kel69)	mouse (BALB/c x DBA/2)F1 (CDG1); female; n=30)	oral (gavage)	10.3 (w1), 5.2 (w2-3), 2.6 (w4-8) mg, once weekly;	Xpo= 8 w; Xpe=28-33w	pulmonary tumours in 8/8, leukaemia in 5/8 controls: pulmonary tumours in 1/10, leukaemia in 0/10	controls: number not indicated
	mouse (id; male; n=25)		300 mg/kg, once weekly	Xpo= 8 w; Xpe= ?;	8 x 300 mg/kg: pulmonary tumours in 9/11, leukaemia in 10/11	
	mouse (id; male; n=25)		300 mg/kg (w1-4), 200 mg/kg (w5-8);	Xpo= 8 w; Xpe=?	4 x 300, 4 x 200 mg/kg: pulmonary tumours in 7/10, leukaemias in 4/10, kidney cystadenomas in 2/10 controls: lung tumours in 1/23, leukaemias in 0/23, kidney cystadenomas in 1/23	dose lowered because of toxicity
Bacci *et al*. (Bac82)	mouse (BALB/c/ Cb/Se; male and female; n=25)	oral (gavage)	0.5 mg, daily;	Xpo=120 d; Xpe=30 w	multiple lung tumours in 23/25 male and 22/25 female controls: single lung neoplasias in 6/25 male and 3/25 female	controls: n=25 male, 25 female
Kelly *et al.* (Kel68)	rat (Osborne-Mendel; ?)	ip	50 mg/kg, once weekly;	Xpo= 10 w; Xpe > 11 w	in 19/20 mammary adenocarcinomas	no data on controls; no other tumour observed in exposed rats
			500 mg/kg, one injection	Xpo= 1 d; Xpe > 11 w	in 4/7 mammary adenocarcinomas	no data on controls; other tumours observed, but not specified per dose group
	rat (Fischer 344/N; female)		50 mg/kg, once weekly;	Xpo= 10 w; Xpe > 11 w	in 3/15 mammary adenocarcinomas	
Deckers *et al*. (Dec74)	rat (R strain; female; n=10)	ip	15 mg, twice monthly;	Xpo= 7.5 mo; Xpe > 301 d	in 8/10 mammary tumours, in 3/10 uterus tumours, in 2/10 ear duct tumours controls: no tumours	controls: no data on number
Weis-burger *et al*. (Wei75)	rat (Sprague-Dawley derived Charles River CD; male and female; n=25)	ip	30, 60 mg/kg, 3 x weekly;	Xpo= 6 mo; Xpe= 18 mo	*male*: breast carcinomas in 18/47 ($p<0.001$), lymphomas in 11/47 ($p<0.001$), leukaemia in 14/47 ($p<0.001$) *female*: breast carcinomas in 20/37 ($p<0.001$), lymphomas in 4/37 ($p=0.003$), leukaemias in 13/37 ($p<0.001$) *controls:* male: breast carcinomas in 2/179, lymphomas in 0/179, leukaemias in 2/179; female: breast carcinomas in 13/181, lymphoma in 1/181, leukaemia in 0/181	controls: 179 male, 181 female; obviously results of dose groups combined

Table 1 Continued.

authors	species[a]	exposure characteristics[b]	dose	exposure and experimental period	findings	remark
NCI (NCI78)	rat (Sprague-Dawley; low dose: 34 male 35 female, high dose: 36 male 35 female)	ip	15, 30 mg/kg, 3 x weekly;	Xpo= 26 w; Xpe= 31 (high dose female), 43 (high dose male), 53 (low dose female), 60 w (low dose male)	*high dose: male*: total malignant tumour-bearing animals 30/33; in 9/33 lymphomas; in 3/33 leukaemias (ns); in 7/33 mammary gland adenocarcinomas; in 9/33 olfactory neuroblastomas; *female:* total malignant tumour-bearing animals 30/31; in 20/30 lymphomas; in 25/31 mammary gland adenocarcinomas; in 2/31 olfactory neuroblastomas (ns); no leukaemias. *low dose: male*: total malignant tumour-bearing animals 19/30; in 3/31 lymphomas; no leukaemias; in 1/31 mammary gland adenocarcinomas (ns); in 12/27 olfactory neuroblastomas; *female*: total malignant tumour-bearing animals 27/30; no lynphomas; no leukaemias; in 16/31 mammary gland adenocarcinomas; in 17/28 olfactory neuroblastomas *controls: male*: total malignant tumour-bearing animals 2/10; in 1/10 (matched) and 1/39 (pooled) lymphomas; *female*: no tumours in matched controls; in 2/38 pooled controls mammary gland adenocarcinomas	controls: matched vehicle: n=10 per sex; untreated: n=10 per sex; pooled vehicle: n=40 per sex early termination due to mortality
Kelly *et al* (Kel64)	mouse (CD2F1); male and female; ?)	ip	200-400 mg/kg, once weekly;	Xpo= 8 w; Xpe= 6-9 w, 10-12 w, or 13-21 w	pulmonary tumours in 1/11, 4/10 and 21/21, respectively. at Xpe = 13-21 w: leukaemias in 11/21	number of controls not indicated; number of animals exposed per group per sex not indicated, results of male and female combined; single doses not specified
			200-450 mg/kg, once weekly;	Xpo= 4 w; Xpe=10-12 w or 13-21 w	pulmonary tumours in 3/9, 29/32, respectively at Xpe= 13-21 w: leukaemias in 3/32	
			300-450 mg/kg, one injection,	Xpe= 14 w or 25 w	pulmonary tumours in 3/10, 10/10 respectively.	
			740-827 mg/kg, one injection,	Xpe= 17 w	pulmonary tumours in 6/6 controls (all experiments): pulmonary tumours in 2/100 and 2/111; no leukaemias	
	mouse (non-inbred albino; male and female)		300 mg/kg, one injection,	Xpe= 6-11 w, 12-16 w	pulmonary tumours in 3/9, 12/12, respectively controls: pulmonary tumours in 0/70 and 29/144	
Kelly *et al*. (Kel69)	mouse (BALB/c x DBA/2)F1 (CDF1); male; n=30)	ip	5.2 (w 1-3), 2.6 (w 4-8) mg, once weekly;	Xpo= 8 w; Xpe=28-33 w	pulmonary tumours in 17/21, leukaemias in 10/21 controls: pulmonary tumours in 1/9, no leukaemias	controls: number not indicated

Table 1 Continued.

authors	species[a]	exposure characteristics[b]	dose	exposure and experimental period	findings	remark
Weisburger *et al.* (Wei75)	mouse (Swiss-Webster-derived; male and female; n=25)	ip	12, 25 mg/kg, 3 x weekly;	Xpo= 6 mo; Xpe= 18 mo	*male:* lung tumours in 15/33 ($p<0.001$); *female:* lung tumours in 23/34 ($p<0.001$), lymphomas in 9/34 ($p<0.001$), renal tumours in 3/34 ($p=0.006$), uterine tumours in 8/34 ($p<0.001$) *controls*: male: lung tumours in 10/101; female: lung tumours in 21/153, lymphomas in 2/153, uterine tumours in 3/153, no renal tumours	controls: 101 male, 153 female obviously results of dose groups combined
NCI (NCI78)	mouse (B6C3F1; male and female; n=35 per sex per dose 15 untreate and 15 vehicle controls sex)	ip	6, 12 mg/kg, 3 x weekly;	Xpo= 52 w; Xpe= 67 (high dose), 85 w (low dose)	*high dose: male*: total malignant tumour-bearing animals 16/31; in 9/29 olfactory neuroblastomas; in 10/31 lung adenomas; in 4/31 lymphomas/leukaemias; *female*: total malignant tumour-bearing animals 20/26; in 11/25 olfactory neuroblastomas; in 6/26 lung adenomas; in 2/26 lymphomas (ns); in 8/25 uterine adenocarcinomas *low dose: male*: total malignant tumour-bearing animals 8/30; no olfactory neuroblastomas; in 10/30 lung adenomas; in 4/30 lymphomas/leukaemias; *female*: total malignant tumour-bearing animals 19/23; no olfactory neuroblastomas; in 1/23 lung adenomas (ns); in 8/23 lymphomas; in 14/23 uterine adenocarcinomas *controls:* no tumours in male vehicle (12 tested) and female vehicle (14 tested) and untreated controls; male: total malignant tumour-bearing untreated 2/15, and no tumours in untreated female controls (12 tested)	controls: addition of the two different controlgroups and sexes makes a total number of 53 tested controls. Early termination due to mortality
Schmähl Osswald (Sch70)	rat (BR46; male; n=48)	iv	24 mg/kg, once weekly;	Xpo= 52 w; Xpe= ?	total malignant tumour-bearing animals: 14/34 total malignant tumour-bearing controls: 4/65	controls: n=89 100-d-old rats used

[a] The number between parentheses represents the number of animals exposed per group per sex.

[b] Xpo= exposure period; Xpe= experimental/observation period.