Carbadox

Health based calculated occupational cancer risk values

Aanbiedingsbrief

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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. 1999/06OSH, 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 carbadox. 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 carbadox:

- 4×10^{-5} bij 40 jaar beroepsmatige blootstelling aan 0.003 mg/m^3
- 4×10^{-3} bij 40 jaar beroepsmatige blootstelling aan 0.3 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 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 carbadox. 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 cancer risk for carbadox amounts to:

- 4×10^{-5} for 40 years of occupational exposure to 0.003 mg/m^3.
- 4×10^{-3} for 40 years of occupational exposure to 0.3 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 by the committee for carbadox. 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

Carbadox

2.1 Introduction

Carbadox has been classified as a genotoxic carcinogen by the European Union (ISZW99).

The evaluation of the carcinogenicity and other toxic effects of carbadox has been based on the review by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) (JEC91). In addition, literature was retrieved from the online data bases Medline, Toxline, and Chemical Abstracts, covering the period 1966 to December 1995/January 1996.

2.2 Identity and physical and chemical properties*

Chemical name	:	carbadox
CAS registry number	:	6804-07-5
CAS name	:	(2-quinoxalinylmethylene)hydrazinecarboxilic acid methyl ester N,N^1-dioxide; 3-(2-quinoxalinylmethylene)carbazic acid methyl ester N,N^1 dioxide
EEC number	:	613-050-00-9
EINECS number	:	229-879-0
Synonyms	:	methyl 3-(2-quinoxalinylmethylene)carbazate N^1,N^4-dioxide; 2-formylquinoxaline-1,4-dioxide carbomethoxyhydrazone
Description	:	minute yellow crystals
Molecular formula	:	$C_{11}H_{10}N_4O_4$
Structure	:	

Molecular weight	:	262.23
Melting point	:	240ºC
Solubility in water	:	Practically insoluble
EEC labeling	:	R: 45-11-22
		S: 53-45
EEC classification	:	F; R 11/Carc cat 2; R 45/Xn; R 22

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

There were no reports found on the potential carcinogenicity of carbadox in humans.

The animal carcinogenicity studies are summarized in Table 1 (Annex D). No inhalation studies are available. The carcinogenicity studies of carbadox are restricted to studies in rats. After administration of carbadox in the diet, a dose-dependent increase of the incidence of both benign and malignant tumours in the liver was observed.

* data from Bud89, CEG93

Because the incidences of malignant hepatic tumours were higher in Wistar rats than in Charles River CD rats, the committee selected the study of Sýkora (Sýk84) for the calculation of the potential risk of cancer at the workplace. The incidence of malignant hepatomas in male and female rats was 3/10 and 2/10 respectively, at 50 ppm.

2.4 Carcinogenic activity in experimental animals, life-time low-dose exposure

To calculate the carcinogenic activity expressed as the incidence per mg carbadox per kg bw per day, the observed number of rats (male and female) showing a treatment related induction of malignant hepatomas, at the lowest dose, is used. At a dose level of 50 ppm, a significant increase in malignant hepatomas was observed. The dose of 50 ppm* corresponds to 2.4 mg/kg bw/day for male rats and to 3.0 mg/kg bw/day for female rats (average 2.7 mg/kg bw/day). 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_{dose}, is calculated as follows:

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

$$= \frac{5/20 - 0/20}{2.7 \text{ mg/kg bw/day} \times (78 \times 7^d/1000^d) \times (78 \times 7^d/1000^d) \times 24/24 \times 7/7} = 0.31[mg/kg/day]^{-1}$$

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

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* the average intake for male and female rats, calculated from data on body weight and feed intake presented by Sýk84

** 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 per mg/kg bw/day
Ie and *Ic* are the tumour incidences in exposed and control animals, respectively
C is the concentration to which the animals are exposed, usually expressed in mg/m^3
X_{po} and X_{pe} are the exposure and experimental periods, respectively
L is the standard lifespan for animal species in question

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 per 8-hour-working day. Using as starting point the estimated incidence of 0.31 per mg/kg bw per day, the additional lifetime cancer risk per mg/m^3 under occupational conditions (= HBC-OCRV) amounts to:

HBC-OCRV = 0.31 x 40/75 x 5/7 x 48/52 x 10/70 = 1.6 x 10^{-2} $[mg/m^3]^{-1}$

Based on the HBC-OCRV of 1.6 x 10^{-2} the additional lifetime cancer risks amount to

- 4 x 10^{-5} for 40 years of exposure to 0.003 mg/m^3
- 4 x 10^{-3} for 40 years of exposure to 0.3 mg/m^3.

2.7 Existing occupational exposure limits

No occupational exposure limits are listed for carbadox in The Netherlands, Germany, Denmark, Sweden, the EU, the UK, or the USA. In the UK, carbadox is listed as carcinogen for the purpose of the COSHH regulations 1999 (ACG99, Arb96, DFG99, HSE99, Hun97, NBO93, HSE99, ISZW99).

2.8 Toxicity profile of carbadox*

No data were found on the toxicity of carbadox to humans following occupational exposure.

No data on irritation were presented. Oral LD_{50} of 2810, >2810, and 850 mg/kg bw have been reported for male mice, female mice and male rats, respectively. Following ip injection, the LD_{50} was 1050 and 810 mg/kg bw for mice and rats, respectively.
Short-term oral studies have been performed in rats and dogs. In rats (n=2-3/sex/group), administration of 50 and 100 mg/kg bw/d for 30 days caused a dose-dependent decrease in body weight gain and food consumption. All other parameters (complete blood count, cholesterol, urinalysis) were normal. In dogs (n=1/sex/group) fed doses of 25 or 50 mg/kg bw/d which were later reduced to 10 and 15 mg/kg bw/d due to emesis (dosing schedule: 6 d/w, 3 weeks), weight loss, and elevated serum glutamic-pyruvic

* data from JEC91

transaminase levels were seen. In monkeys orally dosed with 5, 10, and 20 mg/kg bw/d, 5 d/w, for 2 years, no adverse effects were observed.

In a three generation reproduction study with two litters per generation in which rats were fed diets containing 1, 2.5, and 10 mg/kg bw/d, no effects were reported to occur in the first two generations. In all groups of the third generation, pregnancy rate was reduced. Cannibalism occurred in all treated groups of the third generation (incidence: 30-44%) as well as in the second litter of the control group (19%), producing a reduction (not dose-related) in lactation index in the treated groups of the third generation (59-79% vs 93-98% in controls).

A health-based occupational exposure limit for carbadox derived from the data presented in this section would in all likelihood be expected to be higher than the concentration level associated with the upper referential cancer risk level.

The Hague, 20 December 1999,
for the committee

dr ASAM van der Burght,
scientific secretary

References

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.

Bud89 Budavari S, ed. The Merck index. An encyclopedia of chemicals, drugs, and biologicals. 11th ed. Rahway NJ, USA: Merck & Co, 1989: 269.

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: 1265 (Publicatieblad van de Europese Gemeenschappen L258A, deel II).

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.

JEC91 Joint FAO/HO Expert Committee on Food Additives (JECFA). Carbadox. In: Toxicological evaluation of certain veterinary drug residues in food. Geneva, Switzerland: WHO, 1991: 141-73 (WHO Food Additives Series 27).

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.

Sýk84 Sýkora I, Vortel V. Orientaèní kancerogenní studie cyadoxu a cabadoxu na krysách. Biol Chem Vet 1984; 20: 21-6.

Sýk86 Sýkora I, Vortel V. Postnatálni karcinogenní studie cyadoxu a carbadoxu. Biol Chem Vet 1986; 22: 53-62 ("Postnatal study of the carcinogenicity of cyadox and carbadox"; English translation submitted to the EC Working Group "Dangerous Substances" by the UK delegation; by courtesy of Dr H. Roelfzema, Ministery of Public Health, Welfare, and Sports, Rijswijk, The Netherlands).

Sýk93 Sýkora I, Vortel V. Comparability of results of postnatal and long-term tests for carcinogenicity. Neoplasma 1993; 40: 321-7.

A Request for advice

B The committee

C Commens in 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 Nutritionand 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 relased in 1999 for public review. The Following organisations 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

Table 1 Carcinogenicity studies with carbadox, oral experiments.

authors	species	experimental	findings, tumours	remark
Stebbins, Coleman, 1967 (JEC91)	rat (Charles River CD; male/female; n= 10/sex/ group) diet	0, 5, 10, 25, 50, 100 mg/kg bw/d 112 w	*50 and 100 mg/kg bw groups*: no tumour incidences reported *25 mg/kg bw group*: multiple hepatic nodules in 13/13 rats; hepatic benign nodular hyperplasia in 10/13; malignant transformation based on metastatic foci (lung, kidney, lymph node) in remaining 3/13 *10 mg/kg bw group*: hepatic benign nodular hyperplasia in 11/13 *5 mg/kg bw group*: hepatic benign nodular hyperplasia in 5/13 controls: no hepatic benign nodular hyperplasia it was stated that a treatment-related increase in total tumours was reported (not specified)	unpublished study; data reviewed and presented by JECFA (JEC91) interim sacrifice at wk 14 (n=3/sex/group) *50, 100 mg/kg bw groups*: no animals survived beyond the 14 wk sacrifice; *25 mg/kg bw group*: 1 female died at wk 51, remaining 13 rats sacrified by wk 73 due to palpable abdominal masses; *10 mg/kg bw group*: 1 rat died at wk 67, remaining 13 rats sacrified between wk 64 and wk 112; *5 mg/kg bw group*: 1 male died at wk 20, remaining 13 rats sacrified between wk 61 and 112; controls: 1 male sacrified at wk 33, 1 male died at wk 93, remaining rats sacrified between wk 80 and 112 nodular hyperplasia was suggested to be associated with hepatic injury; dose levels concluded to be too high to be tolerated by the animals

Continuation *Table 1*

authors	species	experimental	findings, tumours	remark
Sigler, 1969 (JEC91)	rat (Charles River CD; male/female; n=20/sex/ group) diet	0, 1, 2.5 mg/kg bw/d 106 w	*2.5 mg/kg bw group*: hepatic benign nodular hyperplasia in 7/27; (not specified) increase in total mammary tumours *1 mg/kg bw group*: hepatic benign nodular hyperplasia in 1/29 controls: hepatic benign nodular hyperplasia in 3/29	unpublished study; data reviewed and presented by JECFA (JEC91) follow-up study to determine a chronic dose which is tolerated by rats (see above) interim sacrifice at wk 54 (n=5/sex/group) survival remaining animals: 43%, 45% vs 38% in controls
King, 1976 (JEC91)	rat (Charles River CD; male/female; n=14/sex/ group) diet	0, 25 mg/kg bw/d 10 months	hepatocellular carcinoma in 2/18	unpublished study; data reviewed and presented by JECFA (JEC91) study designed to compare the carcinogenic activity of carbadox and desoxycarbadox (metabolite)
Sýkora, Vortel (Sýk84)	rat (Wistar/ Han/Ko; male/female; n= 10/sex/ group) diet	0, 50, 100, 300 ppm (male:» 2.4, 5.0, 20 mg/kg bw/d; female: » 3.0, 6.7, 35 mg/kg bw/d[a] 18 mo	treatment-related tumours: *malignant hepatomas*: male: 3/10, 8/10, 10/10 vs 0/10; female: 2/10, 6/10, 10/10 vs 0/10; *meso-theliomas of testis*: 0/10, 1/10, 3/10 vs 0/10	study reported in Czech; tables also in English significantly reduced survival rate in high dose group; significantly reduced bw in high dose males and mid and high dose females
Sýkora, Vortel (Sýk86; Sýk93)	rat (Wistar/ Han/Ko; male/female; n= 2-18/sex/ group) ip, diet	ip: 0, 0.27-10.8 mg/animal during the first 8, 10, 15, or 20 days of life oral: 0, 300 ppm from d 22-25 to the end of experiment at 1y	ip (groups combined, n=38): tumour incidence: 2 malignant hepatomas, 12 other tumours (not specified) ip + diet (groups combined, n=53): 52 malignant hepatomas, 33 other tumours (not specified) diet only (n=8): 8 malignant hepatomas, 2 other tumours not-treated controls (n=35): no malignant hepatomas, 9 others	high mortality in groups given relatively high ip dosis over a short period ip, oral, and combinated treatment resulted in body weight effects (decrease)

[a] calculated from data on body weight and feed intake presented by Sýk84