# β-Butyrolactone

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. 1999/05OSH, 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 bekijkt zij of zo'n schatting mogelijk is voor β-butyrolacton. Zij heeft daarbij gebruik gemaakt van de methode die is beschreven in het rapport 'Berekening van het risico op kanker' (1995/06WGD) (Hea95).

De commissie is echter van mening dat wegens een gebrek aan voldoende gegevens het niet mogelijk is om het extra kankerrisico voor β-butyrolacton te berekenen.

# Executive summary

On request of the Minister of Social Affairs and Employment the Dutch Expert Committee on Occupational Standards (DECOS) 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 studies if such estimates can calculated for β-butyrolactone. It has used the method described in the report 'Calculating cancer risks due to occupational exposure to genotoxic carcinogens' (1995/06WGD) (Hea95).

The committee is of the opinion that due to a lack of sufficient data, it is not possible to estimate the additional lifetime cancer risk for β-butyrolactone.

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-OCRV's by the committee for β-butyrolactone. 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

# β-Butyrolactone

## 2.1 Introduction

β-Butyrolactone has been classified as a genotoxic carcinogen by DECOS (DEC95).

This evaluation of the carcinogenic effects of β-butyrolactone has been based on the review by IARC (IARC76). Where relevant, the original publications have been reviewed and evaluated as will be indicated in the text. In addition, literature has been retrieved from the online data bases Chemical Abstracts, Toxline, and Medline, covering the period 1967 to December 1995/January 1996.

## 2.2 Identity and physical and chemical properties*

| | | |
|---|---|---|
| Chemical name | : | b-butyrolactone |
| CAS registry number | : | 3068-88-0 |
| CAS name | : | 4-methyl-2-oxetanone |
| EINECS number | : | 221-330-4 |
| Synonyms | : | 3-hydroxybuturic acid lactone; 3-hydroxybutanoic acid, b-lactone; 3-hydroxybutyric acid, b-lactone; b-hydroxybutyric acid lactone; b-methylpropiolactone |
| Description | : | oily liquid with acetone-like odour |
| Molecular formula | : | $C_4H_6O_2$ |
| Structure | : | |

| | | |
|---|---|---|
| Molecular weight | : | 86.1 |
| Boiling point | : | 110-118 ºC (24 kPa); 71-73 ºC (3.9 kPa); 50-54 ºC (1.3 kPa) |
| Relative density (20ºC/20ºC) | : | 1.0555 |
| Solubility in water | : | miscible with water (15.3% w/w, 18 ºC) |
| Solubility in organic solvents | : | miscible with most organic solvents |
| Conversion factors (20ºC, 101.3 kPa) | : | 1 ppm = 3.59 mg/m$^3$<br>1 mg/m$^3$ = 0.28 ppm[a] |

[a] calculated using the equation: 1 ppm = M/24 mg/m$^3$ (M = molecular weight)

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

The carcinogenicity of β-butyrolactone has been evaluated by IARC (IARC76). No additional data were found. There were no epidemiological studies on the incidence of cancer in man due to exposure to β-butyrolactone. The animal carcinogenicity studies are summarized in table 1 (annex D).

There were no carcinogenicity inhalation studies available. Oral or subcutaneous treatment of rats (only female animals were treated) with 100 mg β-butyrolactone per

* data from IARC76; Ric92

animal once weekly induced squamous cell carcinomas of the forestomach and local subcutaneous sarcomas, respectively. No tumours were found following weekly subcutaneous injections of 1 mg β-butyrolactone per rat (Duu66).

In mice (only females used), dermal and subcutaneous application caused local tumours (Duu66). When 0.1 mg β-butyrolactone per mouse (n=50) was injected subcutaneously once weekly, for life-span, local anaplastic sarcomas and local fibrosarcomas were found in 2/50 and 2/50 animals, respectively. When given 10 mg/mouse, local fibrosarcomas, local squamous cell carcinomas, and local adenocarcinomas were induced in 15/30, 2/30, and 1/30 animals, respectively. No such tumours were seen in vehicle- and not-treated control animals.

These studies clearly demonstrated the carcinogenic properties of β-butyrolactone. However, since only local tumours were induced following routes of administration irrelevant in view of the scope of this evaluation, i.e., the establishment of an inhalation health-based occupational cancer risk value, these studies are considered inappropriate for this purpose. Therefore, the committee is of the opinion that due to a lack of sufficient data, it is not possible to estimate the additional cancer risk for β-butyrolactone.

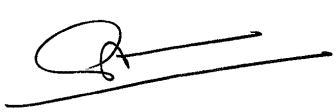
## 2.4 Existing occupational exposure limits

No occupational exposure limits are listed for β-butyrolactone in The Netherlands, Denmark, Germany, Sweden, the UK, the EU or the USA (ACG99; Arb96; DFG99; HSE99; Hun97; ISZW99). In Sweden, β-butyrolactone has been classified as a Class B carcinogen (NBO93).

## 2.5 Toxicity profile of β-butyrolactone

Only very few data on the toxicity of β-butyrolactone were found. No mortality occurred in rats exposed to concentrated (not specified) vapours for eight hours. The oral $LD_{50}$ in rats and the dermal $LD_{50}$ in rabbits were reported to be 17.2 g/kg bw and >20 ml/kg bw, respectively. When applied to the clipped belly of rabbits, β-butyrolactone scored grade 3 for skin irritation on a 10-grade scale; when instilled into the eyes of rabbits the irritation score was grade 5 (Smy69).

The Hague, 20 December 1999,
for the committee



dr ASAM van der Burght,
scientific secretary

Prof. dr GJ Mulder,
chairman

# 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.

Duu66 Van Duuren BL, Langseth L, Orris L, *et al*. Carcinogenicity of epoxides, lactones, and peroxy compounds. IV. Tumor reponse in epithelial and connective tissue in mice and rats. J Natl Cancer Inst 1966; 37: 825-38.

Duu67 Van Duuren BL, Langseth L, Orris L, *et al*. Carcinogenicity of epoxides, lactones, and peroxy compounds. V. Subcutaneous injection in rats. J Natl Cancer Inst 1967; 39: 1213-16.

DEC95 Dutch Expert Committee on Occupational Standards. Scientific documents on the Dutch list of occupational Carcinogens (II). The Hague, The Netherlands: Sdu Servicecentrum Uitgeverijen, 1995; rep no RA 2/95

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.

IARC76 International Agency for Research on Cancer (IARC). -Butyrolactone. In: Cadmium, nickel, some epoxides, miscellaneous industrial chemicals and general consideration on volatile anaesthetics. Lyon, France: IARC, 1976: 225-9 (IARC monographs on the evaluation of carcinogenic risk of chemicals to man; Vol 11).

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: 74 (Ordinance AFS 1993/9).

Ric92 Richardson ML, Gangolli S, ed. B301. β-Butyrolactone. In: The dictionary of substances and their effects. Cambridge, UK: Royal Sociaty of Chemistry, 1992: 871-2 (Vol 1).

Smy69 Smyth HF Jr, Carpenter CP, Weil CS, *et al*. Range-finding toxicity data: list VII. Am Ind Hyg Assoc J 1969; 30: 470-6.

# 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. No organizations and persons have commented on the draft document.

Annex **D**

# Animal studies

*Table 1* Carcinogenicity studies with β-butyrolactone (data from IARC76, unless otherwise indicated).

| authors (ref) | species/route | experimental | findings, tumours | remark |
|---|---|---|---|---|
| Van Duuren *et al* (Duu66) | rat (Eastern Sprague-Dawley female; n=5) gavage | 0, 100 mg/animal (»286 mg/kg bw[a]) once/w, until death/sacrifice | squamous cell carcinomas of forestomach in 3/5 vs 0/5 in both vehicle and not-treated control groups<br>isolated liver metastasis in one animal at sacrifice at d 385; no other tumours found in treated animals | vehicle: tricaprylin<br>median survival time:<br>treated group: 426 d, vehicle controls: 525 d, not-treated controls: duration of test:<br>treated group: 492 d, vehicle controls: 587 d, not-treated controls: 563 d) |
| incidence per mg/kg bw/d (see 2.3): [3/5-0/5] : [286 x 492/1000 x 492/1000 x 24/24 x 1/7] = 6.1 x $10^{-2}$ | | | | |
| Van Duuren *et al* (Duu66) | rat (Eastern Sprague-Dawley female; n=50) subcutaneous | 0, 1 mg/animal ( 3 mg/kg bw[a]) once/week, until death/sacrifice | no tumours in treated group | vehicle: tricaprylin<br>median survival time: >559 d; duration of test: 559 d (control groups: similar) |
| Van Duuren *et al* (Duu67) | rat (Eastern Sprague-Dawley female; n=20) subcutaneous | 0, 100 mg/animal (286 mg/kg bw[a]) once/week, until death/sarcifice | local subcutaneous sarcomas in 9/20 vs 0/20 in both non-treated and vehicle control groups | vehicle: tricarpylin<br>median survival time: treated group: 283 d, vehicle controls (2 gr): 483, 537 d, not-treated controls: 537; duration of test: treated group: 533 d, vehicle controls: 554, 555 d; not-treated controls: 559 d |

Continuation *table 1*

| authors (ref) | species/route | experimental | findings, tumours | remark |
|---|---|---|---|---|
| incidence per mg/kg bw/d (see 2.3): [9/20 - 0/20] : [286 x 533/1000 x 533/1000 x 24/24 x 1/7] = 3.9 x $10^{-2}$ | | | | |
| Van Duuren *et al* (Duu66) | mouse (Swiss ICR/Ha; female; low dose: n=50, high dose: n=30) subcutaneous | 0, 0.1, 10 mg/animal (4, 400 mg/kg bw[b]) once/week | *low dose*: local anaplastic sarcomas in 2/50, local fibro-sarcomas in 2/50; *high dose*: local fibrosarcomas in 15/30, local squamous cell carcinomas in 2/30, local adenomacarcenomas in 1/30; no tumours in control groups | vehicle: tricaprylin median survival time: low dose group: 483 d, high dose group: 265 d, vehicle controls (3 gr): 368-535 d, not-treated controls (2 gr): 415, 431 d; duration of test: low dose: 595 d; high dose: 490 d; vehicle controls: 532-581 d; not-treated control: 519, 599d |
| Swern *et al*, 1970 (IARC76) | mouse (Swiss Webster CFW; female; n=16) subcutaneous | 0, 0.2 mg(/animal ?) 3 times/w, 4 w | local sarcomas in 1/16; no tumours in vehicle control group observed at 18 mo | vehicle: tricarpylin 15/16 treated animals were alive at 12 mo |
| Van Duuren *et al*, 1965 (IARC76) | mouse (Swiss ICR/Ha; female; n=30) dermal | 0, 0.1 ml of a 10% solution, 3 times/w, until death/sacrifice | skin carcinomas in 21/30, skin papillomas in 4/30; no tumours in vehicle control group | vehicle: benzene first tumour appeared after 346 d; median survival time: 466 d (controls: 498 d) |
| Van Duuren *et al*, 1967 (IARC76) | mouse (Swiss ICR/Ha; female; n=30-40) dermal | 0, 0.1 ml in 10 % benzene, 0.1 ml in 10% acetone | benzene group: skin papillomas in 20/30, of these 16 developed skin carcinomas; acetone group: skin papillomas in 1/40 at d 439, progressing to a carcinoma by d 504; no data on controls | vehicle: benzene, acetone median survival time: benzene group: 439 d, acetone group: 452 d; duration of test: 598 d |

[a] assuming a bw of 350 g

[b] assuming a bw of 25 g

incidence per mg/kg bw/d (see Section 2.3):
low dose: [4/50 - 0/50] : [4 x 595/750 x 595/750 x 24/24 x 1/7] = 2.2 x $10^{-1}$
high dose: [18/30 - 0/50] : [400 x 490/750 x 490/750 x 24/24 x 1/7] = 2.5 x $10^{-2}$