European Chemicals Bureau

Institute for Health and Consumer Protection

European Chemicals Bureau

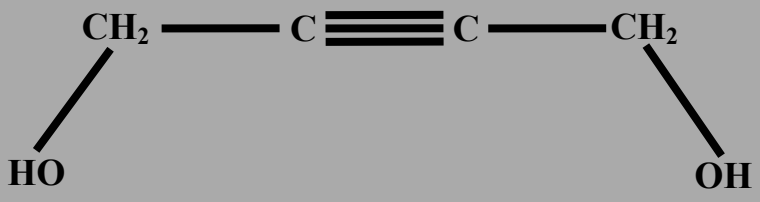
Existing Substances

European Union Risk Assessment Report

CAS No: 110-65-6

EINECS No: 203-788-6

but-2-yne-1,4-diol



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RISK ASSESSMENT

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RISK ASSESSMENT

Final Report, 2005

Germany

The risk assessment of but-2-yne-1,4-diol has been prepared by Germany on behalf of the European Union.

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Final report:	**2005**

Foreword

We are pleased to present this Risk Assessment Report which is the result of in-depth work carried out by experts in one Member State, working in co-operation with their counterparts in the other Member States, the Commission Services, Industry and public interest groups.

The Risk Assessment was carried out in accordance with Council Regulation (EEC) 793/93[1] on the evaluation and control of the risks of "existing" substances. "Existing" substances are chemical substances in use within the European Community before September 1981 and listed in the European Inventory of Existing Commercial Chemical Substances. Regulation 793/93 provides a systematic framework for the evaluation of the risks to human health and the environment of these substances if they are produced or imported into the Community in volumes above 10 tonnes per year.

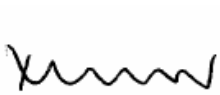
There are four overall stages in the Regulation for reducing the risks: data collection, priority setting, risk assessment and risk reduction. Data provided by Industry are used by Member States and the Commission services to determine the priority of the substances which need to be assessed. For each substance on a priority list, a Member State volunteers to act as "Rapporteur", undertaking the in-depth Risk Assessment and recommending a strategy to limit the risks of exposure to the substance, if necessary.

The methods for carrying out an in-depth Risk Assessment at Community level are laid down in Commission Regulation (EC) 1488/94[2], which is supported by a technical guidance document[3]. Normally, the "Rapporteur" and individual companies producing, importing and/or using the chemicals work closely together to develop a draft Risk Assessment Report, which is then presented at a Meeting of Member State technical experts for endorsement. The Risk Assessment Report is then peer-reviewed by the Scientific Committee on Health and Environmental Risks (SCHER) which gives its opinion to the European Commission on the quality of the risk assessment.

If a Risk Assessment Report concludes that measures to reduce the risks of exposure to the substances are needed, beyond any measures which may already be in place, the next step in the process is for the "Rapporteur" to develop a proposal for a strategy to limit those risks.

The Risk Assessment Report is also presented to the Organisation for Economic Co-operation and Development as a contribution to the Chapter 19, Agenda 21 goals for evaluating chemicals, agreed at the United Nations Conference on Environment and Development, held in Rio de Janeiro in 1992.

This Risk Assessment improves our knowledge about the risks to human health and the environment from exposure to chemicals. We hope you will agree that the results of this in-depth study and intensive co-operation will make a worthwhile contribution to the Community objective of reducing the overall risks from exposure to chemicals



Roland Schenkel
Acting Director-General
DG Joint Research Centre

Catherine Day
Director-General
DG Environment

[1] O.J. No L [illegible]

[2] O.J. No L 161, 29/06/1994 p. 0003 – 0011

[3] Technical Guidance Document, Part I – V, ISBN 92-827-801 [1234]

0 OVERALL RESULTS OF THE RISK ASSESSMENT

CAS No: 110-65-6
EINECS No: 203-788-6
IUPAC Name: But-2-yne-1,4-diol

Environment

Conclusion (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

Conclusion (ii) is reached for the environment because the risk assessment shows that no risks are expected for all environmental compartments regarded.

Human Health

Human health (toxicity)

Workers

Conclusion (iii) There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account.

Regarding respiratory tract irritation, risk reduction measures are considered to be necessary for those exposure scenarios in which butynediol is handled as a solid substance (Scenario 2: production and further processing; Scenario 3b: preparation of formulations, without LEV). Concern is expressed for repeated inhalation exposure (both scenarios) and for acute inhalation exposure (only Scenario 2).

In addition to its substantial irritation potential (skin, eye, respiratory tract) butynediol has been proved to be a weak skin sensitiser. Concern has been derived for the exposure scenarios with butynediol itself and preparations with a butynediol concentration of greater than 1%.

For butynediol, occupational exposure limits are not reported. Within the context of Council Regulation 793/93 toxicological data have been generated that do allow the establishment of a health-based occupational exposure level.

Consumers

Conclusion (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

Humans exposed via the environment

Conclusion (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

Human health (risks from physico-chemical properties)

Conclusion (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

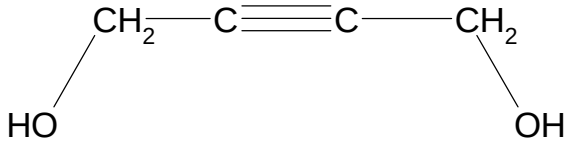
CONTENTS

TABLES

1 GENERAL SUBSTANCE INFORMATION

1.1 IDENTIFICATION OF THE SUBSTANCE

CAS No: 110-65-6
EINECS No: 203-788-6
IUPAC Name: But-2-yne-1,4-diol
Synonyms: 1,4–Butynediol, 1,4–Dihydroxy–2–butyne, 2–Butyne–1,4–diol, 2–Butynediol, Bis(hydroxymethyl)acetylene, But–2–in–1,4–diol, Butindiol, Butynediol
Empirical formula: $C_4H_6O_2$
Molecular weight: 86.09 g/mol
Structural formula:



1.2 PURITY/IMPURITIES, ADDITIVES

Purity: 98.5 - 99.5%
Impurities: < 0.5% water
1% butane-1,4-diol
Additives: no additives

1.3 PHYSICO-CHEMICAL PROPERTIES

Butynediol is a yellow scaly solid at room temperature and normal pressure. Data on the physical and chemical properties are given in **Table 1.1**.

Table 1.1 Physico-chemical properties

Parameter	Value	Reference
Melting point	58°C	Graefje (1992) Kirk-Othmer (1991)
Boiling point	> 200°C (238°C) decomposition relatively slowly between 160 and 200°C, violent above 200°C)	Graefje (1992) GAF-Huels (1994)
Relative density	1.114 at 20°C	Kirk-Othmer (1991)
Vapour pressure	0.17 Pa at 20°C	GAF-Huels (1994), Beilstein (1974), Kirk-Othmer (1991)
Surface tension	58.9 mN/m at 30.8°C (50% aqueous solution)	BASF, Diol-department (1994a)
Partition coefficient	logPow -0.73 at 25°C (OECD 107)	BASF (1988)
Water solubility	ca. 750 g/l solution at 20°C 20 g/l solvent at 0°C 3740 g/l solvent at 25°C	GAF-Huels (1994) Kirk-Othmer (1991)
Flash point	not determined	solid
Auto flammability	no self ignition up to the decomposition	Graefje (1992)
Flammability	not highly flammable (Annex V, 67/548/EEC)	BASF SIK (1994b)
Ignition temperature		
Explosive properties	not explosive	structural reasons
Oxidising properties	no oxidising properties	structural reasons

Boiling point

The boiling point submitted by one producer (GAF-Huels, 1994) was given as 238°C. In the literature a decomposition of the substance is noted above 160°C. The decomposition process starts relatively slowly between 160 and 200°C, and becomes violent above 200°C.

Vapour pressure

The vapour pressure was estimated according to Clausius-Clapeyron using values between 88.3 and 238 degrees (GAF-Huels (1994), Beilstein (1974), Kirk-Othmer (1991) without regarding the crystallisation of butynediol. The problem in such cases is the uncertainty of an estimation of values over a very large temperature range.

Water solubility

The solubility is given as value of 750 g/l solution at 20°C, which was used for the calculations. The value of 3,740 g/l solvent at 25°C converted into g/solution is comparable to the first mentioned value.

1.4 CLASSIFICATION

Classification according to Annex I of Directive 67/548/EEC.

Classification

T; R 23/25	Toxic by inhalation and if swallowed
C; R 34	Causes burns
Xn: R 48/22	Harmful: danger of serious damage to health by prolonged exposure if swallowed
Xn; R 21	Harmful in contact with skin
Xi; R 43	May cause sensitisation by skin contact

Specific Concentration limits

C ≥ 50%:	T , C; R 21-23/25-34-48/22-43
25% ≤ C < 50%:	T; R 21-23/25-36/38-48/22-43
10% ≤ C < 25%:	Xn; R 20/22-48/22-43
3% ≤ C < 10%:	Xn; R 20/22-43
1% ≤ C < 3%:	Xi; R 43

Labelling

C; T

R: 21-23/25-34-43-48/22

S: (1/2)-25-26-36/37/39-45-46

According to the data presented below and the criteria of Directive 67/548/EEC, butynediol has not to be classified as dangerous to the environment.

2 GENERAL INFORMATION ON EXPOSURE

2.1 PRODUCTION

According to the IUCLID data provided, butynediol is produced at two different sites in Europe. The cumulative production volume derived from the upper value of the indicated ranges amounts to 200,000 tonnes/annum.

From further information provided by the lead company, it is known, that the actual cumulative production volume was 185,000 tonnes in 1993 with no significant changes within the following three years.

The maximum volume produced at a single site is 100,000 tonnes/annum. Butynediol is not imported to the EU. Less than 300 tonnes of the substance were exported outside the EU in 1993.

2.1.1 Production method

Butynediol is produced by Reppe synthesis. The reaction of acetylene and formaldehyde is carried out in closed systems at 80 - 100°C using an aqueous formaldehyde solution (30-50%) and a partial pressure of acetylene of 1 - 6 · 10^5 Pa (Hüls AG, 1995; Graefje, 1992).

$$2\ CH_2O + HC{\equiv}CH \rightarrow HO\text{-}CH_2\text{-}C{\equiv}C\text{-}CH_2\text{-}OH$$

From the information provided by the lead company it is known, that the production process is conducted continuously in cascades of three to five reactors.

The catalyst usually consists of 3-6% bismuth(III) oxide and 10-20% copper(II) oxide, mostly on silica as a carrier material. During the process, copper(II) oxide is converted to copper(I) acetylide, catalysing the further reaction by complexation of acetylene. Bismuth oxide inhibits the formation of water-insoluble polymers, the “cuprenes“, from the oligomeric acetylene complexes (Greafje, 1992).

The crude product contains 33 - 55% butynediol, 1 - 2% propargyl alcohol, 0.4 - 1% of unreacted formaldehyde and 1 - 2% heavy by-products (BASF AG, 1995).

2.2 USE

According to the producers, hydrogenation in aqueous solution to butanediol and butenediol is the main application area. Butanediol and butenediol are used as intermediates in the chemical industry.

Less than 2% of the production volume of butynediol are not processed at the production sites but used as an external intermediate for the production of flame retardants or as a corrosion inhibitor and pickling agent in metal surface treatment (Graefje, 1992, BASF AG, 1994a, Hüls AG, 1994).

Besides this, butynediol is reported to serve as an intermediate for the synthesis of polyols, insecticides, pharmaceuticals and auxiliaries for the paint and textile industry.

Further direct uses have been identified from the information available in the product registers (see below). Butynediol is understood to be a component in cleaning solutions to remove scale by means of acids, in acid pickles and in organic paint removers.

The following consumer products may contain butynediol (see also Section 4.1.1.1):

- Cleansing agents for sanitary installations (conc. < 2%)
- Car cleansing products (conc. < 1%)
- Building facade cleansers (conc. <3%)
- Disinfectants for sanitary installations (0.33 - 2%)
- Pipe descaling agents (0.15 - 1%)
- Descaling agents (0.2 - 1%)

The content of butynediol in different products is presented in the Danish Product Register from January 1995 (no production in Denmark):

Table 2.1 Information from the Danish Product Register (January 1995)

Content of butynediol in the product	Number of products	Approximate quantity [t/a]
0 - 1%	53	2
1 - 10%	11	1
10 - 80%	< 3	
80 - 100%	< 3	
not determined	< 3	

The most frequent product types are cleaning agents, conserving agents and metal surface treatment agents. A total amount of 3 tonnes has been registered in 1995.

In the Norwegian Product Register from 1994, 10 products containing a total quantity of 1 tonne are registered.

In the Swedish Product Register 33 products containing a total quantity of 5 tonnes butynediol are identified. The most frequent product types are metal surface treatment agents, but there are also cleaning agents and high pressure cleaning agents for the food product and beverage industry.

The quantitative breakdown of the use pattern of butynediol is estimated and compiled in **Table 2.2**.

Table 2.2 Quantitative breakdown of the use pattern

Type of use	Approximately % in this application	Maximum amount in this application [tonnes/annum]
hydrogenation to butanediol	< 95	175,000
hydrogenation to butenediol	< 5	9,000
sales (co manufacturers and/or industrial users)	< 2	3,700
export	-	300

The corresponding main, industrial and use categories and the mass balance for the European market are presented in **Table 2.3**.

Table 2.3 Main, industrial and use categories and the mass balance for the European market

main category (MC)	industrial category (IC)	use category (UC)	mass balance [%]
non-dispersive use (1b), intermediate stored on-side	chemical industry (3)	intermediate (33)	> 98
non-dispersive use (1c), intermediate stored off-side	chemical industry (3)	intermediate (33)	< 2
non-dispersive use (3), industrial point sources	metal processing industry (8)	corrosion inhibitor (14)	< 2
non-dispersive use (3), industrial point sources	metal processing industry (8)	solvent (48)	< 2
wide dispersive use (4), diffuse releases	public domain (6)	cleaning agent (9)	< 2

3 ENVIRONMENT

3.1 ENVIRONMENTAL EXPOSURE

3.1.1 General discussion

3.1.1.1 Release into the environment

Releases of butynediol into the environment are to be expected during production and processing with wastewater and, to less extent, exhaust gases.

Further releases are to be expected through the use in metal surface treatment and of cleaning agents.

Direct releases to the soil compartment via sludge application may only occur from municipal sewage treatment plants (STP), because at both production sites the sewage sludge is incinerated.

Residual butynediol-contents in the final products can not be quantified but are expected to be not significant. According to the producers, butanediol contain generally less than 0.0001% of butynediol and the residual content in butenediol is less than 0.05%.

3.1.1.2 Degradation

3.1.1.2.1 Hydrolysis

There are no data available about hydrolysis of butynediol. From the molecular structure of the compound it can be concluded that hydrolysis is not a relevant degradation process.

3.1.1.2.2 Biodegradation

The following results on biodegradation are available:

- Ready biodegradability: A Modified Screening Test (EG 84/449/EWG C.3, identical with OECD 301 E) with activated sludge from a municipal source indicates complete degradation. Based on DOC measurement 100% degradation was observed after 5 days, 94% after 14 days and 90% after 19 days (Hüls AG, 1984a). Accuracy of the DOC measurement seems to be the reason for the apparent increase in DOC.
- Simulation Test: In a Coupled Units Test (OECD 303 A) 96% degradation after 35 days could be found (Hüls AG, 1984b). The documentation of the test conditions is not sufficient; there is no information on working-in time and sludge concentration available. The results of the test do not allow differentiating between biodegradation and other elimination processes and no mass balance can be deduced from the test.

- Inherent biodegradability: In a Zahn-Wellens-Test (mainly identical with Modified Zahn-Wellens-Test OECD 302 B) with industrial sludge 87% degradation after 15 days could be obtained in a closed as well as in an open system (BASF AG, 1977).

Butynediol can therefore be considered as readily biodegradable in the aquatic compartment. The results from the Coupled Units Test do not justify the use of the degradation rate quantitatively to estimate the degree of removal in the STP but can only be regarded as support for ready biodegradation.

As it is proposed in the Technical Guidance Documents (TGD, EC 1994) for readily biodegradable substances, a biodegradation rate in STP of 1 h^{-1} is assumed. Results from biodegradation simulation tests in surface water and soil are not available and have to be estimated based on the above described tests and the partition behaviour of butynediol. According to the input data and formulas given in Chapter 3, part 2.3.6 of the TGD (EC 1994); the following rate-constants are obtained, as presented in **Table 3.1**.

Table 3.1 Estimation of biodegradation rate constants in the different compartments

compartment / medium	biodegradation rate
activated sludge (STP)	$k_{STP} = 1\ h^{-1}$
surface water	$k_{SW} = 0.047\ d^{-1}$
sediment	$k_{sed} = \underline{0.002}\ d^{-1}$
soil	$k_{soil} = \underline{0.023}\ d^{-1}$

3.1.1.2.3 Photo oxidation

In the atmosphere, butynediol will react with the photochemically produced hydroxyl radicals. Based upon atmospheric concentrations of $5 \cdot 10^5$ OH/cm^3, the atmospheric half-life of butyne-diol has been estimated to be 11 hours (Atkinson, 1988).

From the spectroscopical data available for butynediol, direct photolysis is not to be expected.

3.1.1.3 Distribution

The Henry's law constant (calculated from the respective PC-data as presented in Section 1) of $H = 2 \cdot 10^{-5}$ $Pa.m^3/mol$ at 20°C indicates, that volatilisation of butynediol from water is low.

The adsorption and desorption behaviour of butynediol was not investigated. According to the TGD (EC, 1994), the Koc can be estimated from the experimentally determined logPow of -0.73. Using the equation for alcoholes ($\log Koc = 0.39 \log K_{ow} + 0.5$), a Koc of 1.64 l/kg is calculated.

From this value, the partition coefficients in the different compartments can be estimated using the respective default organic carbon contents as proposed in Table 3 of Chapter 3 of the TGD (EC, 1994). For the calculation of the partition coefficient K_{p_sludge} an organic carbon content of 37% in activated sludge is assumed (Struijs et al., 1991).

Table 3.2 Partition coefficient between different compartments

compartment	partition coefficient
soil-water	K_{p_soil} = 0.03 l/kg
sediment - water	K_{p_sed} = 0.08 l/kg
suspended matter - water	K_{p_susp} = 0.16 l/kg
activated sludge - water	K_{p_sludge} = 0.61 l/kg

Using the fugacity model of Mackay (level 1), the theoretical distribution at equilibrium can be estimated. More than 99.9% of the total amount of butynediol is expected to be distributed to the aquatic compartment.

Based on the physical chemical properties of butynediol, the hydrosphere is the target compartment.

3.1.1.3.1 Elimination in STP

Based on the above cited physical chemical properties (log H = -4.7; log Pow = -0.73), as well as the biodegradation rate of 1 h^{-1} in STP, the elimination through biodegradation and distribution can be estimated with the model SIMPLETREAT 3.0 (version February 97):

Table 3.3 Estimation of elimination

% to air	0
% to water	12.7
% to sludge	0
% degraded	87.3
% removal	87.3

3.1.1.4 Accumulation

There are no experimental results on bioaccumulation available. The measured log Pow of -0.73 does not indicate a potential for bioaccumulation though.

The estimated Koc-value of 1.64 l/kg also indicates no potential for geoaccumulation. Butynediol is thus expected to be mobile in soil and may leach by seepage to the groundwater. Groundwater contamination however may be counteracted by biodegradation in soil.

3.1.2 Aquatic compartment

Unless further details are available, the maximum production volumes from the indicated ranges are used for the estimation of the local PECs.

A total production volume of 185,000 tonnes/annum is assumed, taking into account the actual production volumes provided by the two companies.

3.1.2.1 Estimation of $Clocal_{water}$ / Generic approach: production and processing

In the Technical Guidance Document (EC, 1994), a generic (i.e. non site-specific) exposure scenario for the release into surface water of intermediates during production and processing is proposed. This scenario is described in the Emission Scenario Document (ESD) IC - 3 - "chemicals used in synthesis; intermediates" and reflects a realistic worst-case situation. Default emission factors of 0.3% for production and 0.7% for processing and a default flow rate of the receiving river of 60 m^3/second are proposed.

Using the highest single production quantity of 100,000 tonnes/annum and an elimination rate of 87.3% in STP, a $Clocal_{water}$ of approximately 80 µg/l is calculated.

3.1.2.2 Estimation of $Clocal_{water}$ / Site-specific approach: production and processing

Using the available specific data for the two production sites, more precise estimations can be performed. In the **Table 3.4** the results and underlying site-specific data are mentioned. The site specific flow rates of the receiving rivers used for the calculations represent the low flow situation (10 percentile) according to the TGD (EC, 1994).

Table 3.4 $Clocal_{water}$ for butynediol production based on site-specific information

site	$Clocal_{water}$ [µg/l]	specific data
A	6.5	specific production and processing volumes; default releases; specific flow rate of receiving river; specific flow rate of STP
	0.32	actual release estimated on the basis of effluent measurements*; specific flow rate of receiving river
B	196	specific production and processing volumes; default releases; specific flow rate of receiving river; specific flow rate of STP
	0.22	actual release estimated on the basis of effluent measurements**; specific flow rate of receiving river

* The detection limit of 50 µg/l of effluent measurements during 15 days was not exceeded and only reached once. In the test protocol it was mentioned, that due to the alcaline conditions of sample preparation hydrolytic reactions may have occurred, but the company confirmed, that this was adequately addressed by calibration of the method.

The measured value was used for a site specific calculation because it is not believed that butynediol concentration is underestimated significantly under the applied analytical conditions. For the calculation, the effluent concentration was set at 50 µg/l.

However, in comparison generic releases have also been calculated for this company, because of the spot-check character of the measurements.

** Effluent measurements had been performed over a sampling period of 3 weeks. The samples were methylated with dimethyl sulfate at 90°C and the quantitative determination was carried out using head space gas chromatography. The butynediol concentration did not exceed the detection limit in none of the 21 individual samples. For the method used a detection limit of 5 µg/l is stated by the company. Therefore, the effluent concentration was set at 5 µg/l for the calculation of the $Clocal_{water}$.

For comparison purpose the generic releases have also been calculated for this company, because of the spot-check character of the measurements.

3.1.2.3 Estimation of $Clocal_{water}$ / Generic approach: processing by non producers

A maximum amount of 3,700 tonnes/annum is sold to co-manufacturers. As the number of co-manufacturers is not known, as a worst-case scenario it is assumed for the PEC-estimation that the total amount is processed at one external processing site.

The estimation is performed according to the Emission Scenario Document (ESD) IC - 3 - "chemicals used in synthesis; intermediates" using a default release of 0.7% for processing, an elimination rate of 87.3% and a default flow rate of the receiving river of 60 m^3/second. This relative high dilution in surface water seems reasonable, because it balances the worst-case assumption of only one external processing site.

A concentration $Clocal_{water}$ of 2.1 µg/l is calculated.

3.1.2.4 Estimation of $Clocal_{water}$ / Generic approach: use

Metal Surface Treatment

As butynediol is used for metal surface treatment in electrodeposition, the releases into wastewater from this application have to be estimated.

According to the producer, bath concentrations of 1-5 g butynediol/l are used for corrosion inhibition and about 0.3 g/l for bright plating.

For the calculation of the local concentration in surface water, the following assumptions are made:

A bath concentration of 5 g/l is used. It is known, that butynediol is consumed during the process due to the oxidising / reductive conditions for electrodeposition. However, it has to be assumed that the bath concentration is maintained during the process by adding fresh butynediol. From time to time, the whole bath has to be renewed.

Cascade rinsing techniques are applied resulting in an internal dilution factor of 1,000-10,000 for the discharged rinsing water (Hartinger, 1991). For the calculation the lower value of 1,000 is used as a realistic worst case for internal dilution. Subsequent external dilution of 1:10 is considered, because it has to be assumed that the wastewater is purified in a municipal treatment plant and therefore is diluted by domestic sewage.

Considering the elimination rate of 87.3% in STP and a final dilution in the receiving surface water of 1:10, a concentration $Clocal_{water}$ of 6.3 µg/l is estimated.

3.1.2.5 Monitoring data

No data on measured aquatic concentrations are available.

3.1.2.6 Sediment

As neither monitoring data on concentrations of butynediol in sediment nor experimental results with benthic organisms are available and there is no evidence for relevant adsorption

of butynediol onto sediment, there is no need for performing a risk assessment for this compartment.

3.1.3 Atmosphere

3.1.3.1 Estimation of $Clocal_{air}$ / Generic approach: production and processing

No Emission Scenario Document for the release into the atmosphere of intermediates during production and processing is available at the moment. The emissions can therefore be estimated with the emission tables presented in Appendix I of the Technical Guidance Document (EC, 1994).

On the other hand, both producers stated, that at the production sites no relevant emissions (< 25 kg per year) into the atmosphere occur and that this information is in accordance with their official emission declaration for the local authorities.

Therefore, a local exposure assessment of the atmosphere may only be necessary for external processing. A maximum amount of 3,700 tonnes/annum is sold to co-manufacturers. As no further details are available, for a worst-case estimation it is assumed that the total amount is processed at one external processing site.

Based on the default release factor of 0.00001 proposed in Table A3.3 of Appendix I of the TGD (EC, 1994), a total release amount of 37 kg/annum is estimated and used for the calculation of $Clocal_{air}$:

$$\mathbf{Clocal_{air} = 3.43 \cdot 10^{-5}\ mg/m^3} \qquad \mathbf{Clocal_{air\text{-}ann} = 2.82 \cdot 10^{-5}\ mg/m^3}$$

$$\mathbf{DEPtotal = 6.2 \cdot 10^{-5}\ mg \cdot m^{-2} \cdot d^{-1}}$$

3.1.4 Terrestrial compartment

Direct releases of butynediol to the soil compartment are not expected. Exposure of soil may only occur through atmospheric deposition of local releases to the atmosphere from point sources. The input through sludge application on agricultural soil is considered negligible, as butynediol does not partition to a significant extent to the sewage sludge in STP. Furthermore, at both production sites the sewage sludge is incinerated.

Using the worst-case deposition rate of $\mathbf{DEPtotal = 6.2 \cdot 10^{-5}\ mg \cdot m^{-2} \cdot d^{-1}}$ calculated above for an external processing site, the equilibrium soil concentrations in the vicinity of that site is calculated according to the Technical Guidance Document (EC, 1994):

$\mathbf{Clocal_{soil}}$**:**	$\mathbf{1.52 \cdot 10^{-5}}$ **mg/kg**	$\mathbf{Clocal_{soil\_porew}}$**:**	$\mathbf{1.04 \cdot 10^{-4}}$ **mg/l**
$\mathbf{Clocal_{agr.soil}}$**:**	$\mathbf{1.52 \cdot 10^{-5}}$ **mg/kg**	$\mathbf{Clocal_{agr.soil\_porew}}$**:**	$\mathbf{1.04 \cdot 10^{-4}}$ **mg/l**
$\mathbf{Clocal_{grassland}}$**:**	$\mathbf{1.68 \cdot 10^{-5}}$ **mg/kg**	$\mathbf{Clocal_{grassland\_porew}}$**:**	$\mathbf{1.15 \cdot 10^{-4}}$ **mg/l**

3.1.5 Secondary poisoning

As butynediol does not present indications of a bioaccumulation potential, a risk characterisation for secondary poisoning is not required.

3.1.6 Regional concentrations

For the estimation of the regional background concentrations, all releases, from diffuse as well as point sources are taken into account. The total release volume is used in the continental model and 10% thereof in the defined EU-standard regional model.

Point releases to the aquatic compartment

Based on the actual release data provided by the producers (see Section 3.1.2.2) and the default release for external processing, the total release amounts are summed up in the following table. The releases through the industrial use of butynediol are taken into account below (diffuse releases).

Table 3.5 Point releases to the aquatic compartment

point source	release [tonnes/annum]
site A	6.2
site B	0.1
external processing site	3.3
total	9.6

Point releases to air

A maximum total release to air from the two production sites of 0.05 tonnes/annum are considered according to the respective emission declarations (see Section 3.1.3). For external processing and formulation default releases of 0.037 tonnes/annum are estimated. Therefore, a total release amount of 0.087 tonnes/annum to the atmosphere is used as an input for the model calculation.

Point releases to soil

No direct point releases to soil were identified.

Diffuse releases

Diffuse releases from residual butynediol in the final products are neglected.

At maximum 3,700 tonnes/annum are available to industrial users (see Section 2). A fraction of this amount serves as an intermediate for the production of flame retardants, but the actual tonnage is not known. Therefore, in a worst-case approach it is assumed, that the total volume of 3,700 tonnes/annum is available to end users.

The main application area is metal surface treatment, but according to the information provided by the Danish and Swedish product registers, other applications (i.e. cleaning agents) are reported. For the estimation of the diffuse releases it is assumed, that 90% of the total is used for metal surface treatment and 10% as cleaning agents.

As the aquatic compartment is the target compartment of butynediol, it is assumed that all releases occur into wastewater. A connection rate of 70% to biological wastewater treatment plants is presupposed.

Table 3.6 Diffuse releases

application area	application volume [tonnes/annum]	estimated discharge into wastewater [tonnes/annum]	release via STP effluent [tonnes/annum]	direct release [tonnes/annum]
metal surface treatment	3,330	330 (90% oxidation/ reduction during process*)	29.2	99
cleaning agents	370	300 (80% discharge)	26.6	90
total	3,700	630	55.8	189

* According to the information provided by industry, about 90% of the substance is consumed during the process due to the oxidising / reductive conditions for electrodeposition. For the determination of the local exposure concentration it has to be assumed that the bath concentration is maintained during the process by adding fresh butynediol. However, on a regional scale for the estimation of the total release amount the consumption rate has to be considered.

In **Table 3.7**, all releases used as an input for the estimation of the regional and continental background concentrations are summed up:

Table 3.7 Releases used as input for the estimation of the regional and continental concentrations

	continental [tonnes/annum]	regional [tonnes/annum]
Air	0.087	0.0087
water (STP effluents)	9.6 + 55.8	0.96 + 5.58
Wastewater	515	51.5
water (direct)	189	18.9
Soil	-	-

The calculations are performed with the EUSES-model and the following results are obtained:

- **$PEC_{continentalaquatic}$ = 0.04 µg/l**
  $PEC_{continental_{soil}}$ = $2 \cdot 10^{-8}$ mg/kg ww
  $PEC_{continental_{air}}$ = $3 \cdot 10^{-13}$ mg/m³

- **$PEC_{regionalaquatic}$ = 0.28 µg/l**
  $PEC_{regional_{soil}}$ = $1.8 \cdot 10^{-7}$ mg/kg ww
  $PEC_{regional_{air}}$ = $2.6 \cdot 10^{-12}$ mg/m³

3.2 EFFECTS ASSESSMENT: HAZARD IDENTIFICATION AND DOSE (CONCENTRATION) - RESPONSE (EFFECT) SSESSMENT

3.2.1 Aquatic compartment (incl. sediment)

3.2.1.1 Available effect data

Only a few acute tests with aquatic organisms are relevant for the effects assessment for butynediol. The results are presented below:

Vertebrates

Fish

Leuciscus idus melanotus

(DIN 38 412, static, nominal concentration, BASF 1988a)	96-hour LC50 > 46.4 < 100g/l
	96-hour NOEC = 21.5 mg/l

Leuciscus idus melanotus

(DIN 38412, static, nominal concentration, Hüls 1988)	48-hour LC50 = 82 mg/l

Pimephales promelas

(effective concentration, 99% purity, Geiger et al. 1988)	96-hour LC50 = 53.6 mg/l

Amphibia

(effect: larval toxicity, semi-static, renewal after daily feeding, 95% purity, Dawson et al. 1990)	96-hour LC50 = 5.5 mg/l
(effect: FETAX, embryonal toxicity static, 95% purity, Dawson et al. 1990)	96-hour LC50 = 5102 mg/l
(effect: FETAX, malformation of embryos, static, 95% purity, Dawson et al. 1990)	96-hour EC50 = 495 mg/l

Invertebrates:

Daphnia magna Straus	24-hour EC50 = 43.5mg/l
(effect: immobilisation; static, nominal concentration, 99.5 % purity, BASF 1987)	48-hour EC50 = 26.8mg/l

Plants

Scenedesmus subspicatus

(effect: cell growth; nominal concentrations, BASF 1987)	72-hourEC20 = 236.0 mg/l
	72-hour EC50 = 483.7mg/l
	96-hour EC20 = 218.5mg/l
	96-hour EC50 = 433.1mg/l

The method used to obtain the test results on *Leuciscus idus.* (BASF AG, 1988a) closely follows the Guideline DIN 38 412.

From the selected test concentrations (10, 21.5, 46.4 and 100 mg/l) only at the highest two lethal effects were observed. After 96 hours the mortality was 5% at 46.4 mg/l and 100% at 100 mg/l and therefore the LC50 is between > 46.4 and < 100 mg/l.

The No Observed Effect Concentration was 21.5 mg/l.

The results obtained in a second test under similar conditions (Hüls AG, 1988) are in the same range of concentration with a 48-hour LC50 of 82 mg/l (95% confidence limit: 71-94).

In another acute fish study with *Pimephales promelas* a 96-hour LC50 of 53.6 mg/l (95% confidence limit: 49.3-58.3) was obtained by Geiger et al. (1988). During the test mortality and sublethal effects were investigated. No equilibrium loss was observed prior to death. The test concentration was measured by Gas-Liquid-Chromatography with a recovery rate of 99%.

The comparative developmental toxicity on embryos and larvae of *Xenopus laevis* was investigated by Dawson et al. (1990). The Frog Embryo Teratogenesis Assay (FETAX) was chosen to evaluate the teratogenic potential, since it has application in both aquatic toxicology and teratology. The test was static in design. Mid-to-late blastula stage embryos with removed jelly coat were exposed to graded concentration for 96 hours.

At 24, 48 and 72 hours of exposure, dead animals were removed. At 96 hours, surviving embryos were fixed and the number of surviving and malformed surviving embryos were determined.

An embryo malformation endpoint (EmEC50) of 495 mg/l after 96 hours and a lethality endpoint (EmLC50) of 5,102 mg/l after 96 hours were determined, and the Mortality/Malformation Index (MMI = EmLC50/EmEC50) was calculated as a measure of relative teratogenic potential. Butynediol was scored with a strong teratogenic potential of 10.3. Gross malformation included skeletal, gut, eye and head abnormalities and edema.

In addition to the 96-hour embryo test to determine the teratogenic potential, previously unexposed, healthy-appearing 5-day old tadpoles were exposed for 96 hours and a tadpole lethality endpoint (Td5LC50) of 15.5 mg/l was determined. An embryo-to-tadpole toxicity ratio (E/T = EmLC50/Td5LC50) was calculated to 329.2. Thus butynediol was 330 times more toxic (lethal) in the 5-day old tadpole test than in the embryo test.

Since alcohol dehydrogenase activity is not present in *Xenopus* embryos before the fourth day of development, the difference in toxicity between embryos and tadpole may presumably be

due to enzyme-mediated reactivity of the compound. The E/T ratio may also reflect uptake differences between embryos and tadpoles, since the latter have more advanced gill system. This might allow toxicant to enter the tadpole and reach the site of action, producing greater toxicity.

For *Daphnia magna* acute toxicity was investigated in a static test according to US EPA Guideline EG-1 (BASF AG, 1987). The EC50 for immobilisation was 26.8 mg/l (nominal concentration) after 48 hours. At 100 mg/l all daphnids were immobile after 48 hours.

In a test similar to OECD Guidelines with *Scenedesmus subspicatus* after 96 hours an EC50 of 433 mg/l and an EC20 of 218 mg/l were derived for the reduction of biomass measured fluorometrically (BASF AG, 1987)

Microorganism

Bacteria

Pseudomonas putida	17-hour EC10 = 1,993 mg/l
(effect: growth inhibition, nominal concentrations, BASF 1987)	17-hour EC50 = 3,935 mg/l

Protozoa

Tetrahymena pyriformis	48-hour IG50 = 1,343 mg/l

(effect: population density inhibition, static, nominal concentration, ≥95% purity, Schultz et al., 1993)

In a test with *Pseudomonas putida* according to Bringmann and Kuehn after 17 hours an EC50 of 3,935 mg/l and an EC10 of 1993 were obtained for cell multiplication inhibition measured at 436 nm (BASF AG., 1987).

The population growth impairment testing was done in the *Tetrahymena pyriformis* batch system (Schultz et al,. 1993). This is a two-day assay using population density measured spectrophotometrically at 540 nm as the endpoint. An IG50 of 1,343 mg/l after 48 hours was obtained.

In addition, some further test results are available from literature, but they are too poorly documented and could not be checked for validity due to missing information on test conditions.

3.2.1.2 Determination of $PNEC_{aqua}$

Only results from acute toxicity tests with species from 3 trophic levels are available. The most sensitive organism from standard tests is *Daphnia magna* (96-hour EC50 = 26.8 mg/l). In non-standard tests the lowest acute toxicity is recorded for *Xenopus laevis* (96-hour LC50 = 15.5 mg/l, larval toxicity).

For the calculation of the PNEC the lowest LC50 of 15.5 mg/l obtained with *Xenopus laevis* is used although the test was not conducted with adult animals, because the value is sufficiently supported by the effect concentration observed with *Daphnia magna*.

As there are no long-term test results available, the assessment factor is set at F = 1,000. The fact that test with *Xenopus* was not conducted with adult animals is no justification to decrease the assessment factor.

Therefore: $PNEC_{aqua}$ = 15.5 mg/l / 1,000 = 15.5 µg/l.

3.2.1.3 Determination of $PNEC_{microorganisms}$

According to the procedure described in the TGD (EC, 1994) for assessing the toxicity of a substance to microorganisms to identify adverse effects in STP`s, an assessment factor in the range of 1 to 100 is applied for tests on microorganisms with different sensitivity and different endpoints.

For butynediol, no NOEC-value for microorganisms is available, but an EC10-value of 1,990 mg/l is reported for *Pseudomonas putida.*

In addition, a test result with *Tetrahymena pyriformis,* protozoa found in STPs, seems to be relevant for the assessment, although this species does not influence the degradation processes itself, but nevertheless is needed for the proper function of a STP.

According to the endpoints and sensitivities of the test systems the following assessment factors have to be applied:

Pseudomonas putida	EC10 = 1,990 mg/l	F = 1	PNEC = 1,990 mg/l
Tetrahymena pyriformis	EC50 = 1,343 mg/l	F = 10	PNEC = 134 mg/l

The data basis for determining a PNEC for microorganisms is poor. Therefore, following the precautionary principle, as a worst-case approach a $PNEC_{microorganisms}$ of 134 mg/l is used.

3.2.1.4 Sediment

As neither monitoring data on concentrations of butynediol in sediment nor experimental results with benthic organisms are available and as there is no evidence for relevant adsorption of butynediol onto sediment, there is no need for performing a risk assessment for this compartment.

3.2.2 Atmosphere

No experimental data are available that could be used for a quantitative effect assessment for this compartment.

3.2.3 Terrestrial compartment

Valid experimental data on effects of butynediol to terrestrial organisms are not available.
In an indicative risk assessment for the soil compartment, the aquatic PNEC will be used and compared to the concentration in soil pore water:

$$PNEC_{soil,\ porewater} = 15.5\ \mu g/l$$

In addition, there are indications that butynediol inhibits the nitrification of NH_4-N in soil. From the results with two different types of soil it is possible to deduce an EC50-value between 50 and 100 mg/kg (McCarty and Bremner 1986). An assessment factor of 1,000 is applied to determine the $PNEC_{soil}$ for the inhibition of nitrification:

$$PNEC_{soil} = 50\ \mu g/kg\ dw$$

3.2.4 Secondary poisoning

As butynediol does not present indications of a bioaccumulation potential, an effect assessment for secondary poisoning is not required.

3.3 RISK CHARACTERISATION

3.3.1 Aquatic compartment

3.3.1.1 Wastewater treatment plants

Because of the significant differences in responsibilities, functional control measures and data quality the possible risk to microorganisms is evaluated separately for municipal and industrial wastewater treatment plants.

The effluent concentration calculated for metal surface treatment is used for the risk assessment for municipal STPs. The assessment for industrial treatment plants is carried out with the worst-case effluent concentration calculated on the basis of default releases and additionally with the concentration derived on the basis of effluent measurements.

Therefore:	$PEC_{microorganisms} = 0.06$ mg/l	for municipal STPs
	$PEC_{microorganisms} = 4.5$ mg/l	for industrial STPs (generic release)
	$PEC_{microorganisms} = 0.05$ mg/l	for industrial STPs (specific data)

With a $PNEC_{microorganisms}$ of 134 mg/l, for all considered scenarios the PEC/PNEC ratio is below one and therefore a risk to microorganisms in STPs is not expected.

3.3.1.2 Surface waters

In the **Table 3.8** the comparison between PEC and PNEC (15.5 µg/l) for all relevant exposure scenarios are presented.

Table 3.8 Risk characterisation for the aquatic compartment

Scenario	$Clocal_{water}$ + $PEC_{regional}$ [µg/l]	PEC/PNEC
production and processing:		
site A (effluent measurement)	0.3 + 0.3 = 0.6	0.04
site A (default release)	6.5 + 0.3 = 6.8	0.4
site B (effluent measurement)	0.2 + 0.3 = 0.5	0.03
site B (default release)	196 + 0.3 = 196	13
processing by non-producers	2.1 + 0.3 = 2.4	0.2
metal surface treatment	6.3 + 0.3 = 6.6	0.4

A PEC/PNEC - ratio greater than one is only estimated on the basis of default releases for one production site. However, recently performed effluent measurements indicate actual releases far below the default assumptions so that no risk is identified for the aquatic environment. There is therefore no need for further testing and/or gathering of exposure information.

3.3.1.3 Sediment

As neither monitoring data on concentrations of butynediol in sediment nor experimental results with benthic organisms are available and as there is no evidence for relevant adsorption of butynediol onto sediment, there is no need for performing a risk assessment for this compartment.

3.3.2 Atmosphere

Due to the short atmospheric lifetime ($t_{1/2}$ = 11 hours), abiotic effects upon the atmosphere, like global warming and ozone depletion are not expected from butynediol.

In a Commission Proposal on the limitation of emissions of volatile organic compounds (VOC) (EC, 1996), only substances with a vapour pressure above 10 Pa at 20°C meet the criteria to be regarded a VOC. As the vapour pressure of butynediol is 0.17 Pa at 20°C and therefore significantly below this trigger value, the contribution to photochemical smog production can be assumed to be very low.

3.3.3 Terrestrial compartment

A generic exposure scenario representing a worst-case situation in the vicinity of an external processing site was used for the PEC calculation. Due to atmospheric deposition of butynediol a maximum concentration in soil porewater of $PEClocal_{soil,\ porewater}$ = 0.1 µg/l was estimated. The regional background concentration is considered negligible. As no adequate experimental effect data with terrestrial organisms are available, an indicative risk assessment is performed using the aquatic PNEC:

$$PEC/PNEC = 0.1\ \mu g/l / 15.5\ \mu g/l = 0.007$$

For the inhibition of nitrification a $PNEC_{soil}$ of 50 µg/kg dw can be estimated. The calculated local PEC_{soil} of 0.015 µg/kg ww is divided by a conversion factor of 0.7 to obtain the

concentration in soil per kg dry weight, i.e. $PEClocal_{soil}$ = 0.02 µg/kg, to be compared with the PNEC:

$$PEC/PNEC = 0.02\ \mu g/kg / 50\ \mu g/kg = 0.0004$$

As PEC/PNEC < 1 for both cases, a risk for the soil compartment is not identified.

3.3.4 Secondary poisoning

As butynediol does not present indications of a bioaccumulation potential, a risk characterisation for secondary poisoning is not required.

4 HUMAN HEALTH

4.1 HUMAN HEALTH (TOXICITY)

4.1.1 Exposure assessment

4.1.1.1 General discussion

Butynediol (approximately 98%) is mainly used as an internal chemical intermediate to produce butanediol and butenediol. The remainder (approximately 2%) is used as flakes and aqueous solution (32 - 34%) in further processing to polyols, auxiliaries for the paint industry and flameproofing agents as well as in the production of formulations. The most frequent product types are metal surface treatment and acidic cleaning solutions in which butynediol is used as an additive.

For workers the inhalation and dermal routes of exposure are likely to occur.

According to the Swedish product register and based on information from the BfR database of product compositions (Federal Institute for Risk Assessment, BfR) butynediol serves as a component of consumer products for the following uses

- cleansing agents and disinfectants for sanitary installations (conc. < 2%),
- car cleansing products (conc. < 1%),
- descaling agents for tiles (conc. < 1%).

There is no information on uses through spray products available.

4.1.1.2 Occupational exposure

Industrial activities involving butynediol present opportunities for exposure. Exposure ranges depend on the particular operation and the risk reduction measures in use.

Occupational exposure limit values (OEL) are not known.

The following scenarios are regarded to be relevant for occupational exposure:

- Scenario 1, 2: Production of butynediol and further processing as an intermediate (Section 4.1.1.2.1)
- Scenario 3, 4: Preparation of formulations, e.g. pickling, descaling solutions (Section 4.1.1.2.2)
- Scenario 5-8: Use of acid pickling and Ni-plating baths in the electroplating industry (Section 4.1.1.2.3)
- Scenario 9: Use in organic paint removers (Section 4.1.1.2.4)
- Scenario 10, 12: Use in acidic solutions for the removal of scale (Section 4.1.1.2.5)
- Scenario 11, 13: Use in acidic solutions for the removal of rust (Section 4.1.1.2.6)

Further applications of butynediol are possible, e. g. as car cleaning agent and sanitary disinfectants. Since these use patterns are very seldom, the corresponding exposure situations are judged to be of minor relevance for butynediol.

The assessment of inhalative exposure is mainly based on model estimates (according to the EASE model) and comparison by analogy. If possible, the EASE estimate for the pure substance is corrected in consideration of the percentage of butynediol in the formulation. Since no information on dermal exposure is available, the EASE model is used for assessing dermal exposure. Within the framework of the assessment of dermal exposure, the corrosivity of pure butynediol and of formulations containing more than 50% of the substance is taken as a indication of low dermal exposure and a low contact level is chosen (EASE model: incidental). This procedure is also applied in case of formulations like e.g. acidic cleaning solutions which are assumed to act as corrosive because of corrosive properties of other ingredients.

4.1.1.2.1 Production and further processing as a chemical intermediate within the large-scale chemical industry (Scenario 1 and 2)

Butynediol is produced to a crude concentrated solution (up to 50%), an aqueous solution (32-24%) and to ready-for-use flakes in the large-scale chemical industry.

Butynediol is synthesised via the Reppe reaction. The reaction of acetylene and formaldehyde is carried out at 80-100°C using an aqueous formaldehyde solution (30-50%) and a partial pressure of acetylene of 1-6 · 10^5 Pa (Hüls AG, 1995; Graefje, 1992). From the information provided by the lead company it is known, that the production process is conducted continuously in cascades of three to five reactors.

The final product is a crude concentrated solution (up to 50%). This in turn is internally transported via permanently installed piping for the further processing of diols (butanediol, butenediol). Further internal processing to polyols and auxiliaries for the paint industry is discontinuous. According to information provided by the manufacturer, to some extent flakes are added by means of "filling booths". Further production of flame retardants is carried out externally: Since no detailed information is available the use of either the diluted solution (32-34%) or the flakes must be taken into consideration.

Part of the concentrated solution – corresponding to 2% of the total production volume - is made into a more diluted solution (32-34%) and into ready-for-use flakes in a subsequent process. According to information provided by one manufacturer, the flakes contain particles, amounting to approximately 1% by weight, which are smaller than 1 mm. The flakes are filled automatically into 20 kg paper sacks (PE inside) and 65 kg steel drums.

Exposure associated with transporting the chemical could result from loading, unloading and drumming operations. For the large-scale chemical industry high standards of control at the workplace are assumed to be practiced even if the containment is breached, e.g. during filling, cleaning, maintenance, repair works and taking of samples. Inhalative exposure is normally reduced by technical equipment (e.g. special designed filling stations, local exhaust ventilation LEV).

For inhalative exposure at the workplace dust must be taken into consideration during the handling of the flakes. In contrast inhalative exposure to vapour of the butynediol solutions is assessed to be very low on account of the physico-chemical properties of the substance (solid, vapour pressure of 0.2 Pa at 20°C, extrapolated). Inhalative exposure to dusts is to be assumed during filling work involving the substance in flake form and during cleaning and maintenance. The available data only permit an individual assessment here for the filling of the starting boilers (see “Inhalative exposure / workplace measurements”).

Based on legal classification and labelling pure butynediol and its concentrated solutions (≥ 50%) are judged as corrosive. Presupposed that this effect is perceptible over the whole concentration range, in these cases daily repeated dermal exposure is assumed to be avoided by using personal protective equipment (gloves and eye protection). During activities like drumming, cleaning and maintenance potential exposure is assumed only by single contacts.

Based on the above given description, the exposure assessment for the production and further processing of butynediol is subdivided into two scenarios: Scenario 1 related to the handling of diluted solution of about 34% butynediol and Scenario 2 related to exposure to dust during the handling of butynediol in flake form.

Inhalative exposure

Workplace measurements

Workplace measurements are submitted by one producer. Air concentrations of between 0.04 and 1.1 mg/m^3 (1995, n = 6, total dust) have been determined in the production area during the drumming of the product in flake form. The geometric mean amounts to 0.3 mg/m^3.

Meanwhile filling processes have changed and the technical measures are improved (changing the local exhaust ventilation system and the crystallisation process). New workplace measurements show significant lower results (1998, highest value of 8 hours TWA: 0.02 mg/m^3).

Further workplace measurements (1995, n = 4, total dust) have been conducted during filling activities of the flakes for the further discontinuous processing to polyols and auxiliaries for the paint industry. The measurement results are located below the detection limit (0.035 mg/m³).

For cleaning and maintenance the production equipment is rinsed with water before or immediately after opening.

For the purpose of measuring butynediol concentration in workplace air a method is used which allows the simultaneous determination of the total dust concentration (glass fibre filter) and of the concentration in the gas phase (activated charcoal). The filter and the activated charcoal are subsequently eluted with methylene chloride/methanol and determined gas-chromatographically (flame ionisation detector, detection limit 0.035 mg/m^3). Due to the measurement method and the sampling strategy applied, the measurement results (see above) are regarded as valid.

1 of 2 producers (number of user unknown) submitted measurement results which cover drumming and cleaning activities. The measurement results for drumming (see above) show that exposure below approximately 1 mg/m^3 could be achieved for sure, if high requirements are made on the technical equipment. Therefore the workplace measurements of 1998 could not be assumed to be representative. Based on the available measurement results and the reasons discussed above, 1.0 mg/m^3 estimated from the first measurements is regarded to represent a reasonable worst-case situation for all activities during production and further processing in the chemical industry.

The drumming of the flakes is assessed to be continuously (confidential information). Cleaning and maintenance take place several times per year or only one time depending on the production conditions and lasting several minutes or 4 days to 3 weeks.

According to the information provided by one manufacturer at one production site, a total of 319 workers handle the substance. Approximately 119 workers are involved for about 50% of the working shift. There is no information on the other 200.

Model estimation (EASE for Windows 2.0, Aug. 1997)

The estimation of the level of inhalative exposure performed in accordance with the EASE model (EASE for Windows 2.0, Aug. 1997) produces the following results:

Exposure by inhalation to dust during drumming of butynediol flakes and it's further processing as a chemical intermediate:

- Input parameters: T = 20°C, closed system, significant breaching, low dust techniques, (flakes), LEV present
- Exposure level: 0 - 1 mg/m^3

Gmehling-Weidlich

Exposure to vapour for the handling of solutions is estimated to be very low due to the low vapour pressure of the substance (see **Table 4.1**). For the purpose of assessing the risks a more quantitative estimation of the exposure to vapour is helpful. Therefore, an attempt is made to quantify inhalative exposure to vapour for the handling of solutions (e.g. filling, drumming) containing 30-34% butynediol. Taking into account the vapour pressure of the pure substance (0.2 Pa), based on Raoult`s law, the partial vapour pressure of butynediol amounts to 0.01 Pa and the saturation concentration is about 1 ppm. For activities like drumming a deterministic exposure prediction model (Weidlich, Gmehling, 1986) that was validated by independent measurement results can be taken to estimate exposure. Based on this model inhalative exposure is estimated to be 100 times below that saturation concentration of 1 ppm so that an exposure level of 0.01 ppm (0.038 mg/m³) results. For this scenario regarding exposure to vapour, the exposure level is assumed to be in the same order of magnitude or below the assessed level.

Conclusions

Inhalative exposure has to be assessed for the production and the further processing of butynediol as a chemical intermediate in the large-scale chemical industry (Scenario 1 and 2).

The measurement results show that exposure to dust below approximately 1 mg/m^3 could be achieved for sure, if high requirements are made on the technical equipment. Based on the measurement results of one company before the technical measures are improved and considering the good agreement within the EASE estimates, 1.0 mg/m^3 is regarded to represent a reasonable worst-case situation for all activities connected with handling of the flakes during production and further processing in the chemical industry (Scenario 2).

For the assessment of health risks from daily inhalative exposure to vapour and dust during production and further processing an 8-hour time weighed average concentration (8-hour TWA) for Scenario 1 (to vapour resulting from handling butynediol solutions) of "very low" (0.01 ppm, 0.038 mg/m³) should be used because of the physico-chemical

properties of the substance (solid, vapour pressure of 0.2 Pa at 20°C, extrapolated) and for Scenario 2 (to dust resulting from handling butynediol flakes) 1.0 mg/m^3.

These levels should be taken as an 8-hour time weighed average representing the reasonable worst-case situation.

Dermal exposure

When producing butynediol and further processing as a chemical intermediate dermal exposure could occur during activities like drumming, sampling, cleaning, maintenance and repair work.

On the basis of legal classification and labelling pure butynediol and its concentrated solutions (≥ 50%) are judged as corrosive. Presupposed that this effect is perceptible over the whole concentration range, daily repeated dermal exposure is assumed to be avoided by using personal protective equipment (gloves and eye protection). Furthermore, it is assumed that the workers will not change their behaviour depending on the dilution of the substance. Therefore wearing PPE is also considered during handling the more diluted non corrosive solution. According to information provided by a manufacturer (exposure information), in the case of butynediol, suitable gloves tested according to EN 374 are worn. As a rule, for the use of suitable gloves, low levels of daily dermal exposure are to be expected. However, in spite of this, dermal exposure may occur due to e. g.:

- unintended contamination during the handling of used gloves,
- limited protection of suitable gloves at real working conditions (e. g. mechanical stress),
- time of use exceeding the permeation time of the gloves with regard to the substance.

Since no measurement results are available, an attempt is made to quantify dermal exposure for the above mentioned situations in application of the EASE model, keeping in mind that the model does not provide an appropriate scenario for this situation. Taking into account that dermal contact may occur only by single contacts, however, this situation could be described by the scenario:

- Input parameters: Non dispersive use, direct handling, incidental
- Level of exposure: 0-0.1 mg/cm²/day (pure substance, flakes) 0-0.03 mg/cm²/day (solution, 34% butynediol)

The consideration of an exposed area of 420 cm² (area corresponds to the surface area of the palms of both hands) leads to exposure levels of 0-42 mg/person/cm², and 0-13 mg /person /cm² for handling the diluted solution.

Conclusions

For assessing the health risks from daily dermal exposure to the diluted solution in the area of production and further processing (Scenario 1), an exposure level of 0-13 mg/person/day should be taken. For assessing the health risks from daily dermal exposure to the flakes in the area of production and further processing (Scenario 2), an exposure level of 0-42 mg/person/day should be taken.

This exposure assessment is based on the information that pure butynediol and its concentrated solutions (≥ 50%) are judged as corrosive and that the workers will not change their behaviour depending on the dilution of the substance.

Exposure to the eyes is largely avoided by using eye protection.

4.1.1.2.2 Preparation of formulations, e.g. galvanic bath, pickling and descaling solutions and organic paint remover (Scenario 3 and 4)

In addition to its use as an internal and external chemical intermediate butynediol is predominantly used as a brightening agent in galvanic baths (particularly in the case of nickel deposition) and as a pickling degreaser for the pre-treatment of metals before galvanic processes. Butynediol is also used as an additive in cleaning solutions for the removal of scale (boiler scale, milk scale, fruit scale, beer scale), in pickles for the removal of rust as well as in organic paint removers.

Formulations in liquid form are manufactured (e.g. by electroplating supply houses) by mixing the various raw materials together. The powder ingredients have to be dissolved in advance. User companies such as electroplating shops may employ these industrially manufactured solutions and formulations or they may produce appropriate solutions by themselves. In the production of these formulations butynediol may be used in the form of an aqueous solution (32-34%) or in the form of the pure substance (flaked product). According to information from the manufacturer, the resulting formulations as galvanic baths contain 0.3 g/l butynediol, acid pickling solutions 1-5 g/l, paint removers 2-10%, acidic cleaning solutions and acidic derusters ≥ approximately 0.3%. Dependent on the acid concentration, cleaning solutions contain butynediol in concentrations of 0.1-0.3% (20% acid), 0.07-0.2% (10% acid) and 0.03-0.1% (5% acid).

For the production processes different levels of protection may be realised: manual or automated charging, closed and open systems and/or different ventilation systems. In addition, the general use of PPE (here: suitable gloves and eye protection) cannot be presupposed for this branch of industry at all, despite the fact that there are single companies with a reasonable high level of protection. One exception has to be taken into account when corrosive substances are handled. The effect of corrosivity is presupposed to be immediately perceptible over the whole concentration range, so the workers protect themselves with appropriate means. Dermal exposure is assumed to be avoided by using personal protective equipment (gloves and eye protection). On the basis of legal classification and labelling pure butynediol and its concentrated solutions (≥ 50%) are judged as corrosive. It is assumed that the produced formulations as acid pickling and acidic cleaning solutions (acid content of about 15%) and organic paint removers also have to be labelled because of the corrosive effect of other substances in the solutions.

Dermal exposure to non-corrosive solutions containing butynediol must be taken into account, for example in case of production of galvanic baths, acid pickles and weakly acidic cleaning solutions.

Exposure relevant activities are filling, charging, drumming, cleaning, sampling, repair, maintenance activities as well as possibly mixing.

Information on processing and use has been provided by the federal monitoring authorities of Germany. From information supplied with regard to the manufacture of a cleaning product it is clear that only a few cleaning products contain butynediol. The activities of relevance to exposure, mixing and filling, are performed e.g. 2x/month for a period of 10 minutes. Taking account of this information it is assumed that in case of formulations production is

discontinuous and batchwise in general. The duration and frequency of the activities of relevance to exposure are assumed to be 60 minutes/day for 30 days/year.

Based on the above given description, the exposure assessment for the preparation of formulations containing butynediol is subdivided into two scenarios: Scenario 3 is related to the use of the flakes and Scenario 4 is related to the use of the diluted solution (34%).

Inhalative exposure

Workplace measurements

Because of the different levels of protection, exposure scenarios with LEV (3a) and without LEV (3b) are considered. With LEV is assumed to correspond to the chemical large-scale industry. Taking into account the shortened exposure period of one hour, the resultant 8-hour time-weighted average amounts to 0.14 mg/m^3,based on the available measurement results of 1.1 mg/m^3. This estimate is regarded to represent a reasonable worst-case situation for all activities during production and further processing in the chemical industry.

For the exposure scenario without LEV are no measurement data available.

EASE estimation (EASE for Windows 2.0, Aug. 1997)

Exposure by inhalation to dust during the preparation of formulations (e.g. brightening agent, pickling degreaser, acidic cleaning solutions, deruster) with local exhaust ventilation

- Input parameters: T = 20°C, closed system, significant breaching, low dust techniques (flakes), LEV present
- Exposure level: 0 - 1 mg/m^3

Exposure by inhalation to dust during the preparation of formulations (e.g. brightening agent, pickling degreaser, acidic cleaning solutions, deruster) without local exhaust ventilation

- Input parameters: T = 20°C, closed system, significant breaching, low dust techniques (flakes), LEV absent
- Exposure level: 0 - 5 mg/m^3

Representative information on the duration and frequency of exposure is not available. Following the information provided by the Federal Authorities in Germany (e.g. 2x/month, 10 minutes) the duration and frequency of the activities of relevance to exposure are assumed to be 60 minutes/day for 30 days/year. There is an 8-hour TWA (not daily) of 0-0.14 mg/m^3 for workplaces with LEV and 0-0.6 mg/m^3 for workplaces without LEV, considering duration of 1 hour.

Conclusions

The preparation of formulations, e.g. brightening agent, pickling degreaser, acidic cleaning solutions and deruster are clustered because of the similarity of the exposure scenarios.

A comparison of measurement results and EASE estimates reveals that both are in the same order of magnitude for workplaces with LEV.

For the assessment of health risks from inhalative exposure to dust and vapour during the preparation of formulations an 8-hour time weighed average concentration (8-hour TWA) for

Scenario 3a/b (to dust resulting from handling butynediol flakes) of 0.14 mg/m^3 with LEV and 0.6 mg/m^3 without LEV should be taken. For Scenario 4 (to vapour resulting from handling butynediol containing solutions and formulations) the qualitative exposure assessment "very low" (0.01 ppm, 0.038 mg/m³) should be taken because of the physico-chemical properties of the substance (solid, vapour pressure of 0.17 Pa at 20°C, extrapolated).

The duration and frequency of the activities of relevance to exposure are assumed to be 60 minutes/day for 30 days/year.

These levels should be taken as an 8-hour time weighed averages representing the reasonable worst-case situations.

Dermal exposure

For the field of preparation of formulations, e.g. brightening agents, pickling degreasers, acidic cleaning solutions and derusters, it is to be assumed, that PPE (here gloves and eye protection) is not regularly worn with the exception of the handling of corrosive substances. The effect of corrosivity is immediately perceptible, so the workers protect themselves with appropriate means. Repeated dermal exposure is assumed to be avoided by using personal protective equipment (gloves and eye protection). On the basis of legal classification and labelling pure butynediol and its concentrated solutions (≥ 50%) are judged as corrosive. It is assumed that the produced formulations as acid pickling solutions, acidic cleaning solutions and acid pickles (with an acid content of about 15%) and organic paint removers also have to be classified as corrosive because of the corrosive effect of other substances in the solutions. During activities like drumming, cleaning and maintenance potential exposure is assumed only by single contacts e.g. by the unintended contamination during the handling of used gloves.

Since no measurement results are available, an attempt is made to quantify dermal exposure for the above mentioned situations in application of the EASE model, keeping in mind that the model does not provide an appropriate scenario for this situation. Taking into account that dermal contact may occur only by single contacts, however, this situation could be described by the scenario:

- Input parameters: Non dispersive use, direct handling, incidental
- Level of exposure: 0-0.1 mg/cm²/day (pure butynediol, dust)
  0-0.01 mg/cm²/day (org. paint remover, 10% butynediol)
  0-0.0005 mg/cm²/day (acid pickles, 0.5% butynediol)
  0-0.0002 mg/cm²/day (cleaning solution 0.2% butynediol)

For dermal exposure to non corrosive solutions as the diluted butynediol solution (34% butynediol) or the non corrosive formulations like the galvanic bath (0.03% butynediol), weakly acid pickles (0.5% butynediol) and cleaning solutions (0.2% butynediol) it is to be assumed, that PPE (here gloves and eye protection) are not regularly worn. The corresponding dermal exposure is assessed for the unprotected worker in application of the EASE model.

- Input parameters: Non dispersive use, direct handling, intermittent
- Level of exposure: 0.1-1 mg/cm^2/day
  0.03-0.34 mg/cm²/day (solution, 34% butynediol)
  0.0005-0.005 mg/cm²/day (weakly acid pickles, 0.5% butynediol)
  0.0003-0.003 mg/cm²/day (galvanic bath, 0.3% butynediol)

0.0002-0.002 mg/cm²/day (cleaning solution 0.2% butynediol)

Considering an exposed area of 420 cm^2 (area corresponds to the surface area of the palms of two hands), the dermal exposure amounts to 0-42 mg/person/day (pure substance), respectively 0-4.2 (org. paint remover, 10% butynediol), respectively 0-0.21 (acid pickles, 0.5% butynediol) and up to 0.084 (cleaning solution 0.2% butynediol) for dermal exposure during handling (e.g. filling) of the pure substance and formulations which are classified and labelled as corrosive. If the non corrosive solution or formulations are used the dermal exposure amounts to 14.3-143 mg/person/day (solution, 34% butynediol), respectively 0.2-2.1 mg/person/day (weakly acid pickles, 0.5% butynediol), 0.1-1.3 mg/person/day (galvanic bath, 0.3% butynediol) and 0.08-0.84 mg/person/day (cleaning sol. 0.2% butynediol) should be taken.

Conclusions

For assessing the health risks of dermal exposure in the area of production of formulations (Scenario 3), an exposure level of 0-42 mg/person/day should be taken. Exposure to the eyes is largely avoided by using eye protection. This exposure assessment is based on the assumption that suitable gloves are worn, because of the corrosivity effect of the substance determined by classification and labelling.

For assessing the health risks during activities in connection with non-corrosive substances (Scenario 4) an exposure level of 14.3-143 mg/person/day (diluted solution) should be taken. It cannot be presupposed that eye protection is regularly used.

Dermal exposure has to be assessed for the manufacturing of formulations in the large-scale chemical industry on the one hand and in the industrial area on the other hand. Exposure levels for other exposure scenarios with lower concentrations of butynediol are assumed to be in the same order of magnitude or below the assessed level.

Since the exposure does not continue throughout the day in the case of filling either, the actual exposure is estimated to be lower, but it is not known to what extent, because cleaning of the hands could be done only before breaks. So the exposure could last for a maximum duration of 4 hours and a lower amount will be kept because washing may not be 100% effective. In addition, it is assumed that the production of flakes is batchwise. A frequency of 30 days/year is assumed.

4.1.1.2.3 Use of acid pickling and Ni-plating baths in the electroplating industry (Scenario 5-8)

In the electroplating industry butynediol is used as a corrosion inhibitor in acid pickling baths (1-5 g/l butynediol, 20% acid) for the surface pre-treatment of metals and as a brightening agent, particularly in the case of nickel deposition (butynediol content 0.3 g/l). Due to the formation of hydrogen in pickling baths and oxygen in nickel baths, aerosols containing butynediol are released. According to information provided by one producer, butynediol is used in the case of nickel deposition particularly for electrochemical nickel deposition (with a content of butynediol of 0.3 g/l and nickel between 30 and 330 g/l).

Exposure to emitted aerosols as a result of gas release is to be expected during activities which are regularly performed at electroplating plants (manual dipping and removing of

plating-racks, operating semiautomatic machines, check patrols). Exposure to vapour is assumed to be of relevance if cleaning and maintenance activities are performed.

For the production processes different levels of protection may be realised: manual or automated charging, closed and open systems and/or different ventilation systems. In addition, the general use of PPE (here: suitable gloves and eye protection) cannot be presupposed for this branch of industry at all, despite the fact that there are single companies with a reasonable high level of protection. One exception has to be taken into account when corrosive substances are handled. It is assumed that acid pickling solutions (with acid content ≥ 15%) for electroplating processes have to be classified as corrosive because of the corrosive effect of other substances in the solutions. In such cases, repeated immediate skin contact is avoided by using personal protective equipment (gloves and eye protection). During activities as manual dipping and removing of plating-racks, cleaning and maintenance potential exposure is assumed only by single contacts. The corresponding exposure level is assessed by the EASE-model.

Exposure by dermal contact must also be assumed during activities in connection with galvanic baths for nickel plating (approximately 0.03% butynediol) if no personal protective equipment (gloves) is used.

The duration and frequency of the exposure is often depending on the order situation of the single enterprises. As a reasonable worst case pickling and nickel plating is assumed to be carried out at regular intervals distributed over the entire shift. Whereas operations as cleaning and maintenance are performed at wider time intervals assuming e.g. 1 day/month at a short duration of approximately 60 minutes/day.

The inhalative exposure as a result of aerosol emission is estimated by means of comparison by analogy. Based on the available information and possible forms of exposure, the exposure assessment is subdivided into 4 scenarios:

- Scenario 5 is related to exposure to aerosols during acid pickling,
- Scenario 6 is related to exposure to vapour during acid pickling,
- Scenario 7 is related to aerosol during Ni-plating and
- Scenario 8 is related to vapour emission during Ni-plating.

Inhalative exposure

EASE estimation

The EASE model is not appropriate to estimate exposure to aerosol particles.

Comparison by analogy-Scenario 5 (exposure to aerosols during acid pickling)

For the purpose of estimating the inhalative exposure to butynediol containing aerosols during pickling processes (Scenario 5) particularly as a pre-treatment operation before electroplating, occupational exposure to sulfuric acid mists during these processes is considered as an analogous scenario. Sulfuric acid is chosen because it appears also as particle in the atmosphere. An overview of 10 publications (USA) of exposure data of sulfuric acid mists measured between 1975-1986 is shown in the IARC Monographs (IARC, 1992). Measurements before 1975 are not taken into consideration. The concentration of the sulfuric acid in the pickling baths in general is 20% (approximately 230 g/l). 8-hour TWA's of personal (n = 81) and area sampling (n = 56) are in the range of < 0.01-2.94 mg/m^3 and

0.01-5.66 mg/m^3 H_2SO_4; the corresponding arithmetic means are between 0.03-2.97 mg/m^3. Short term values (1981, n = 6, personal sampling) are in the range of 0.67-0.97 mg/m^3. It could not be extracted from the data, whether exposure reduction measures like surface active agents are used. Additional measurements were made in the electroplating industry of Germany in 1997. The measurements relate to exposure to chrome (VI)-compounds, nickel and acid mists in form of aerosols during electrolytic processes. The exposure levels of sulfuric acid mist are in the range of < 0.007-0.058 mg/m^3 (n = 85) corresponding to those measured in the USA (see above, Macho, 2000).

Assuming that the highest level of 5.66 mg/m^3 corresponds to a sulfuric acid content of approximately 230 g/l, the exposure to butynediol (content of 1-5 g/l) is calculated as a worst case to be 0.02 - 0.12 mg/m^3 (8-hour TWA).

Comparison by analogy-Scenario 7 (exposure to aerosols during Ni – plating)

For the purpose of estimating the inhalative exposure to butynediol containing aerosols during Ni-electroplating processes (Scenario 7), exposure to nickel aerosols during these processes is considered as an analogous scenario. The inhalative exposure to butynediol containing aerosols during Ni-plating is estimated by data taken from exposure measurements for nickel aerosols under worst-case conditions (without LEV) during nickel deposition (nickel content 30-300 g/l) using soluble and insoluble electrodes (IARC, 1990; Groß, 1987). Only a low level of gas is formed by use of soluble electrodes whereas insoluble electrodes produce a 10 times higher emission because of the higher formation of oxygen. The latter is seldom used only for complicate work pieces (Groß, 1987). Exposure data for nickel were detected in USA, Finland and Germany in the range of < 0.0002-0.17 mg/m^3 (unknown number of measurements; IARC, 1990). Additional measurements were made in the electroplating industry of Germany in 1997. The measurements relate to exposure to chrome (VI) -compounds, nickel and acid mists in form of aerosols during electrolytic processes. The exposure levels of nickel-aerosols are in the range of < 0.002-0.008 mg/m^3 (n = 43) corresponding to those measured in the USA (see above, Macho, 2000).

Assuming that the highest level of 0.17 mg/m^3 corresponds to a nickel content of 30 g/l, the exposure to butynediol (content of 0.3 g/l) as a worst case is calculated to be 0.002 mg/m^3 during electrolytic nickel deposition.

Gmehling-Weidlich-Scenario 6 and 8 (exposure to vapour during acid pickling and Ni-plating)

Exposure to vapour released of formulations during e.g. cleaning and maintenance is estimated to be very low due to the low vapour pressure of the substance (0.17 Pa). For the purpose of assessing the risks a more quantitative estimation of the exposure to vapour is done for solutions containing 30-34% butynediol resulting in an exposure level of 0.01 ppm (0.038 mg/m³). Because of the smaller concentration of 0.5% butynediol (Scenario 6) and of 0.03 % butynediol (Scenario 8) exposure is expected to be even lower.

Conclusion

For the assessment of health risks for Scenario 5 due to inhalative exposure to aerosols during acid pickling processes an 8-hour time weighed average concentration (8-hour TWA) (aerosol emission) of 0.12 mg/m^3 should be used and for Scenario 7 relating to inhalative exposure to aerosols during nickel plating 0.002 mg/m^3 should be taken.

These levels should be taken as an 8-hour time weighed average representing the reasonable worst-case situation of exposure to aerosol emission. For other exposure scenarios the exposure levels are assumed to be in the same order of magnitude or below the assessed level. E.g. exposure to vapour (Scenario 8) is assessed to be very low inter alia because of the small concentrations of butynediol in the baths.

Pickling and plating processes in electroplating enterprises are carried out at regular intervals over the entire day. Whether these processes are done daily often depend on the order situation. As a reasonable worst-case scenario the duration and frequency of exposure are assumed to be daily and for the entire length of shift.

Dermal exposure

It is assumed that, because of the corrosive effects of other substances in the solutions, acid pickling solutions (butynediol approximately 0.5%), for electroplating processes (Scenario 5 and 6) also have to be classified as corrosive. For such cases, the estimation of a potential exposure to corrosive solutions is discussed above. According to the EASE-model the situation could be described by the scenario:

- Input parameters: Non dispersive use, direct handling, incidental
- Level of exposure: 0-0.1 mg/cm²/day
  0-0.0005 mg/cm²/day (acid pickles, butynediol 0.5%)

Exposure by dermal contact must also be assumed during tasks in connection with galvanic baths for nickel deposition (approximately 0.03% butynediol) if no personal protective equipment (gloves) is used (Scenario 7 and 8). The situation could be described by the following EASE scenario:

- Input parameters: Non dispersive use, direct handling, intermittent
- Level of exposure: 0.1-1 mg/cm²/day
  0.00003-0.0003 mg/cm²/day (Ni-plating, butynediol 0.03%)

Considering an exposed area of 420 cm^2 (area corresponds to the surface area of the palms of two hands), the dermal exposure amounts to 0-0.21 mg/person/day (acid pickles, 0.5% butynediol) for Scenario 5 and 6 and 0.01-0.13 mg/person/day (Ni-plating bath, 0.03% butynediol) for Scenario 7.

In the case of cleaning as well as maintenance and servicing work relating to nickel plating (butynediol content approximately 0.03%) workers may come into direct contact with the substance if no personal protective equipment is used (Scenario 8). Considering an exposed skin area of 840 cm^2 (area corresponds to the surface area of both hands), the dermal exposure amounts to 0.025-0.25 mg/person/day. However, such work is not carried out frequently but, instead, at regular intervals perhaps about 1 x per month for approximately one hour.

In view of the air concentrations, the dermal exposure as a result of aerosols is estimated to be very low.

Conclusion

For assessing the health risks of dermal exposure in the area of the electroplating industry during activities like manual dipping and removing of plating-racks, operating semiautomatic machines, check patrols, cleaning and maintenance we have to distinguish between these scenarios.

For Scenario 5 and 6 acid pickling (butynediol approximately 0.5%), for electroplating processes an exposure level of 0.21 mg/person/day should be taken independent of the tasks. Exposure to the eyes is largely avoided by using eye protection. This exposure assessment is based on the assumption that suitable gloves are worn, because of the corrosivity effect of other substances in the solutions, which is discussed above in more detail.

For assessing the health risks during activities in connection with non-corrosive plating bath during Ni-plating an exposure level of 0.13 mg/person/day (Ni-plating bath, 0.03% butynediol) for Scenario 7 and 0.25 mg/person/day should be taken for Scenario 8. It cannot be presupposed that skin and eye protection is regularly used.

In view of the air concentrations, the dermal exposure as a result of direct aerosol contamination is estimated to be very low (Scenario 5 and 7).

The duration and frequency of the exposure is often depending on the order situation of the single enterprise. As a reasonable worst case pickling and nickel plating is assumed to be carried out at regular intervals distributed over the entire shift. Whereas operations as cleaning and maintenance are performed at wider time intervals assuming e.g. 1 day/month at a short duration of approximately 60 minutes/day.

4.1.1.2.4 Use in organic paint removers (Scenario 9)

Organic paint removers are assumed to be applied comparably to lacquers and paints by brushing, rolling or dipping in different industrial sectors (metal, wood, mechanical engineering, electronic industry, vehicle production), e.g. when products have to be repaired because of substandard processing.

According to the available information, butynediol is used in a percentage of 2-10%.

It is assumed that, because of the corrosive effect of other substances in the formulation paint removers in general also have a corrosive effect.

There is no information to describe the exposure scenario with regard to the duration and frequency of use of the paint remover. As a reasonable worst-case scenario the duration and frequency of exposure are assumed to be daily but shorter than length of shift.

Inhalative exposure

Gmehling-Weidlich

Exposure to vapour for the handling of the formulation is estimated to be very low due to the low vapour pressure of the substance (see **Table 4.1**). For the purpose of assessing the risks a more quantitative estimation of the exposure to vapour is done for solutions containing 30-34% butynediol (see Section 4.1.1.2.1.) resulting in an exposure level of 0.01 ppm (0.038 mg/m³) results. Because of the smaller concentration of 10 % butynediol exposure is expected to be in the same order of magnitude or even lower.

Conclusion

For the assessment of health risks for Scenario 9 from inhalative exposure to vapour during use of organic paint removers very low as a result of the low vapour pressure of butynediol should be used.

These levels represent the reasonable worst-case situation of exposure to vapour. For other exposure scenarios the exposure levels are assumed to be in the same order of magnitude or below the assessed level.

The duration and frequency of exposure are assumed to be daily but shorter than the entire length of shift.

Dermal exposure

It is assumed that, because of the corrosive effects of other substances in the solutions, organic paint removers (10% butynediol) also have to be labelled as corrosive. For such cases, the estimation of a potential exposure to corrosive solutions is discussed above. According to the EASE-model the situation could be described by the scenario:

- Input parameters: Non dispersive use, direct handling, incidental
- Level of exposure: 0 - 0.1 mg/cm²/day
  0 - 0.01 mg/cm²/day (organic paint remover, butynediol 10%)

Considering an exposed area of 420 cm^2 (area corresponds to the surface area of the palms of two hands), the dermal exposure amounts to 0-4.2 mg/person/day (organic paint remover, butynediol 10%).

Conclusion

For assessing the health risks of dermal exposure during application of organic paint removers (butynediol, 10%) by brushing, rolling or dipping in different industrial sectors, e.g. when products has to be repaired because of substandard processing (Scenario 9) 0-4.2 mg/person/day should be taken. Exposure to the eyes is largely avoided by using eye protection. This exposure assessment is based on the assumption that suitable gloves are worn, because of the corrosivity effect of other substances in the solutions, which is discussed above in more detail.

The duration and frequency of exposure are assumed to be daily but shorter than length of shift.

4.1.1.2.5 Use in acidic solutions for the removal of scale (Scenario 10 and 12)

Butynediol is used in non-corrosive acidic cleaning solutions for the removal of scale (boiler scale, milk scale, fruit scale, beer scale) from containments. They are applied in different industrial (Scenario 10) and skilled trade (Scenario 12) sectors. For the removal of scale mainly the solution is filled in the containment, and after a certain time of reaction drained off again.

They are applied in different industrial (Scenario 10) and skilled trade (Scenario 12) sectors.

Exposure relevant activities are filling, time of reaction and draining off.

There is no information to describe the exposure scenario with regard to the duration and frequency of use of the solutions. The frequency of exposure could be occasionally. Duration of inhalative exposure may last the entire length of the shift whereas the duration of dermal exposure may last shorter than shift length (approximately 1 hour).

The use of PPE (here respiratory protection, gloves and eye protection) is not regarded to be a general measure to reduce exposure.

The exposure assessment is subdivided into

- Scenario 10 related to industrial applications and
- Scenario 12 related to skilled trade applications.

Inhalative exposure

Gmehling-Weidlich

Exposure to vapour for the handling of the formulation is estimated to be very low due to the low vapour pressure of the substance. For the purpose of assessing the risks a more quantitative estimation of the exposure to vapour is done for solutions containing 30-34% butynediol (see Section 4.1.1.2.1.) resulting in an exposure level of 0.01 ppm (0.038 mg/m³) results. Because of the smaller concentration of 0.2% butynediol exposure is expected to be even lower.

Conclusion

For the assessment of health risks for Scenario 10 and 12 from inhalative exposure to vapour during use of acidic cleaning solutions for the removal of scale (filling, time of reaction and draining off) "very low exposure" as a result of the low vapour pressure of butynediol should be used as the reasonable worst-case estimate.

The duration and frequency of exposure are assumed to be occasionally and over the entire length of shift.

Dermal exposure

Exposure by dermal contact must be assumed during tasks as filling and draining off if no personal protective equipment (gloves and eye protection) is used. The situation could be described by the following EASE scenarios.

Use in the industrial sector, Scenario 10:
- Input parameters: Non dispersive use, direct handling, intermittent
- Level of exposure: 0.1-1 mg/cm²/day
  0.0002-0.002 mg/cm²/day (descaling solution, butynediol 0.2%)

Use in the skilled trade sector, Scenario 12:
- Input parameters: Non dispersive use, direct handling, extensive
- Level of exposure: 1-5 mg/cm²/day
  0.002-0.01 mg/cm²/day (descaling solution, butynediol 0.2%)

Considering an exposed area of 420 cm^2 (area corresponds to the surface area of the palms of two hands), the dermal exposure amounts to 0.08-0.84 mg/person/day (descaling solution, butynediol 0.2%) for Scenario 10 and 0.84-4.2 for Scenario 12. There is no information to describe the exposure scenario with regard to the duration and frequency of use of the solutions. In the case of cleaning solutions for the removal of scale it is assumed that the frequency of use is relatively low (e.g. 1 day/month) and that the duration of dermal contact is short (e.g. 60 minutes/day). Since the exposure does not continue throughout the day, the actual exposure is estimated to be lower, but, as discussed above, it is not known to what

extent, because cleaning of the hands could be done only before breaks. So the exposure could last for a maximum duration of 4 hours and a lower amount will be kept because washing is not 100% effective.

Conclusion

For assessing the health risks during activities in connection with non-corrosive solutions for the removal of scale (filling, draining off) an exposure level of 0.08-0.84 mg/person/day (descaling solution, butynediol 0.2%) for Scenario 10 and 0.84-4.2 mg/person/day for Scenario 12 should be taken. It cannot be presupposed that PPE (here gloves and eye protection) is regularly used.

The duration and frequency of exposure are assumed to be occasionally and shorter than length of shift (approximately 1 hour).

4.1.1.2.6 Use in acidic solutions for the removal of rust (Scenario 11 and 13)

Butynediol is used in non-corrosive acidic cleaning solutions for the removal of rust from metal objects by means of acids. They are applied in different industrial (Scenario 11) and skilled trade (Scenario 13) sectors. Metal objects like screw connections normally are cleaned by diving in a deruster bath for a certain time of reaction (up to one week could be possible).

Exposure relevant activities are filling, dipping, time of reaction and draining off.

There is no information to describe the exposure scenario with regard to the duration and frequency of use of the acidic solutions. The frequency of exposure could be frequently or always. Duration of inhalative exposure may last the entire length of the shift whereas the duration of dermal exposure may last shorter than shift length (approximately 1 hour).

The use of PPE (here respiratory protection, gloves and eye protection) is not regarded to be a general measure to reduce exposure.

The exposure assessment is subdivided into

- Scenario 11 related to industrial applications and
- Scenario 13 related to skilled trade applications.

Inhalative exposure

Gmehling-Weidlich

Exposure to vapour for the handling of the formulation is estimated to be very low due to the low vapour pressure of the substance. For the purpose of assessing the risks a more quantitative estimation of the exposure to vapour is done for solutions containing 30-34% butynediol (see Section 4.1.1.2.1.) resulting in an exposure level of 0.01 ppm (0.038 mg/m³) results. Because of the smaller concentration of 0.2% butynediol exposure is expected to be even lower.

Conclusion

For the assessment of health risks for Scenario 11 and 13 from inhalative exposure to vapour during use of acidic cleaning solutions for the removal of rust (filling, dipping and draining

off) very low as a result of the low vapour pressure of butynediol should be used as a reasonable worst-case estimate.

The duration and frequency of exposure are assumed to be daily and over the entire length of shift.

Dermal exposure

Exposure by dermal contact must also be assumed during tasks as filling, dipping and draining off if no personal protective equipment (gloves and eye protection) is used. The situation could be described by the following EASE scenarios.

Use in the industrial sector, Scenario 11:

- Input parameters: Non dispersive use, direct handling, intermittent
- Level of exposure: 0.1-1 mg/cm²/day
  0.0002-0.002 mg/cm²/day (deruster solution, butynediol 0.2%)

Use in the skilled trade sector, Scenario 13:

- Input parameters: Non dispersive use, direct handling, extensive
- Level of exposure: 1-5 mg/cm²/day
  0.002-0.01 mg/cm²/day (deruster solution, butynediol 0.2%)

Considering an exposed area of 420 cm^2 (area corresponds to the surface area of the palms of two hands), the dermal exposure amounts to 0.08-0.84 mg/person/day (descaling solution, butynediol 0.2%) for Scenario 11 and 0.84-4.2 for Scenario 13. There is no information to describe the exposure scenario with regard to the duration and frequency of use of the solutions. In the case of cleaning solutions for the removal of rust it is assumed that the frequency of use is relatively often (frequently or always) but that the duration of dermal contact is short (e.g. 60 minutes/day). Since the exposure does not continue throughout the day, the actual exposure is estimated to be lower, but, as discussed above, it is not known to what extent, because cleaning of the hands could be done only before breaks. So the exposure could last for a maximum duration of 4 hours and a lower amount will be kept because washing is not 100% effective.

Conclusion

For assessing the health risks during activities in connection with non-corrosive solutions for the removal of rust (filling, dipping, draining off) an exposure level of 0.84 mg/person/day (descaling solution, butynediol 0.2%) for Scenario 11 and 4.2 mg/person/day for Scenario 13 should be taken. It cannot be presupposed that PPE (here gloves and eye protection) is regularly used.

The duration and frequency of exposure are assumed to be daily but shorter than length of shift (approximately 1 hour).

4.1.1.2.7 Summary

98% of butynediol are applied as an internal intermediate to produce butanediol and butenediol.

The remainder (approximately 2%) is used as flakes and aqueous solution (32-34%) in further processing to polyols, auxiliaries for the paint industry and flameproofing agents as well as in the production of formulations. The most frequent product types are metal surface treatment and acidic cleaning solutions in which butynediol is used as an additive.

For occupational exposure there are 13 scenarios:

- Scenario 1, 2: Production of butynediol and further processing as an intermediate (4.1.1.2.1)
- Scenario 3, 4: Preparation of formulations, e.g. pickling, cleaning solutions (4.1.1.2.2)
- Scenario 5-8: Use of acid pickling and Ni-plating baths in the electroplating industry (4.1.1.2.3)
- Scenario 9: Use in organic paint removers (4.1.1.2.4)
- Scenario 10, 12: Use in acidic solutions for the removal of scale (4.1.1.2.5)
- Scenario 11, 13: Use in acidic solutions for the removal of rust (4.1.1.2.6)

Inhalative and dermal exposure levels are given in **Table 4.1** and **4.2**, respectively. The main sources of inhalative exposure are drumming (Scenario 2) and of dermal exposure filling works (Scenario 4).

Additional there is incomplete information on other uses of the substance, e.g. as a car cleaning agent. Since these use patterns are probably very seldom, the corresponding exposure situations are judged to be of minor relevance for butynediol.

For the large-scale chemical industry, it is assumed that the production and further processing of butynediol is mainly performed in closed systems. Exposure occurs if the systems are breached for certain activities, e.g. drumming (Scenario 1, 2, **Table 4.1**).

For inhalative exposure at the workplace dust must be taken into consideration during the handling of the flakes. In contrast inhalative exposure to vapour of the butynediol solutions and formulations is assessed to be very low on account of the physico-chemical properties of the substance (solid, vapour pressure of approximately 0.2 Pa at 20°C, extrapolated).

Based on legal classification and labelling pure butynediol and its concentrated solutions (≥ 50%) are judged as corrosive. Besides of that formulations like e.g. acidic cleaning solutions are also assumed to act as corrosive because of corrosive properties of other ingredients. Presupposed that this effect is perceptible over the whole concentration range, in these cases suitable gloves and eye protection are used regularly. As concerning dermal exposure to the non-corrosive solution one producer provided information that suitable gloves (tested according to EN 374) are used regularly. This is considered in assessing dermal exposure using the EASE model assuming that single dermal contacts can occur although suitable gloves are used (Scenario 1, 2, 3, 5, 6, 8, **Table 4.2**). For all other scenarios (4, 7, 8, 10, 11, 12, 13), dermal exposure is assessed for the unprotected worker.

Table 4.1 Summary of inhalative exposure data of butynediol which are relevant for occupational risk assessment

Inhalative exposure								
Scenario number, Area of production and use	Form of exposure	Activity	Duration [hours/day]	Frequency [days/year]	Shift average concentration [mg/m³]	Method	Short-term concentration [mg/m³]	Method
Production and further processing								
1) large-scale chemical industry (solution, 34% butynediol)	vapour	drumming, repair, sampling, cleaning, maintenance	shift length	daily	very low [1)]	EASE	-	-
2) large-scale chemical industry (e.g. flakes)	dust	drumming, repair, sampling, cleaning, maintenance	shift length (expert judgment)	daily	1	exp. judg.	-	-
Further processing to formulations								
3) preparation of formulations (e.g. flakes)	dust	filling, charging, drumming, cleaning, maintenance	1	30	a) 0.14(with LEV) b) 0.6(without LEV)	exp. judg. EASE	-	-
4) preparation of formulations (solution, 34% butynediol)	vapour	filling, charging, drumming, cleaning, maintenance	1	30	very low [1)]	exp. judg.	-	-
Use of formulations								
5) acid pickling processes (0.5% butynediol)	aerosol	manual dipping, operating semiauto. machines	shift length (assumed)	daily	0.12	exp. judg.	-	-
6) acid pickling processes (0.5% butynediol)	vapour	manual dipping, operating semiauto. machines	shift length (assumed)	daily	very low [1)]	exp. judg.	-	-
7) nickel plating (0.03% butynediol)	aerosol	manual dipping, operating semiauto. machines	shift length (assumed)	daily	0.002	exp. judg.	-	-

Table 4.1 continued overleaf

Table 4.1 continued Summary of inhalative exposure data of butynediol which are relevant for occupational risk assessment

Inhalative exposure								
Scenario number, Area of production and use	Form of exposure	Activity	Duration [hours/day]	Frequency [days/year]	Shift average concentration [mg/m³]	Method	Short-term concentration [mg/m³]	Method
8) nickel plating (0.03% butynediol)	vapour	manual dipping, operating semiauto. machines, cleaning, maintenance	shift length (assumed)	daily	very low 1)	exp. judg.	-	-
9) organic paint removers (10% butynediol)	vapour	brushing, rolling, dipping	shorter than shift length (assumed)	daily	very low 1)	exp. judg.	-	-
10) acidic solutions for the removal scale (0.2% butynediol; industrial sector)	vapour	filling, time of reaction, draining off	shift length (assumed)	occasionally	very low 1)	exp. judg.	-	-
11) acidic solutions for the removal of rust (0.2% butynediol; industrial sector)	vapour	filling, dipping, time of reaction, draining off	shift length (assumed)	daily	very low 1)	exp. judg.	-	-
12) acidic solutions for the removal scale (0.2% butynediol; skilled trade sector)	vapour	filling, time of reaction, draining off	shift length (assumed)	occasionally	very low 1)	exp. judg.	-	-
13) acidic solutions for the removal of rust (0.2% butynediol; skilled trade sector)	vapour	filling, dipping, time of reaction, draining off	shift length (assumed)	daily	very low 1)	exp. judg.	-	-

1) Expert judgment (low vapour pressure of the pure substance of 0.17 Pa), rough estimation: < 0.04 mg/m³

Table 4.2 Summary of dermal exposure data of butynediol which are relevant for occupational risk assessment

Dermal exposure								
Scenario number, Area of production and use	Form of exposure	Activity	Frequency [days/year]	Contact level [1)]	Level of exposure [mg/cm²/day]	Exposed area [cm²]	Shift average [mg/p/day]	Method (use of gloves)
Production and further processing								
1)large-scale chemical industry (solution, 34% butynediol)	liquid	drumming, repair, sampling, cleaning, maintenance	Daily	incidental	0 – 0.03	420	0 – 13	EASE (regular use (proper - non-proper use)
2) large-scale chemical industry (e.g. flakes)	solid	drumming, repair, sampling, cleaning, maintenance	Occasionally	incidental	0 – 0.1	420	0 – 42	EASE[2)]
Further processing to formulations								
3) preparation of formulations (e.g. flakes)	solid	filling, charging, drumming, cleaning, maintenance	30	incidental	0 – 0.1	420	0 – 42	EASE[2)]
4) preparation of formulations (solution, 34% butynediol)	liquid	filling, charging, drumming, cleaning, maintenance	30	intermittent	0.03 – 0.34	420	14.3 - 143	EASE (irregular use)
Use of formulations								
5) acid pickling processes (0.5% butynediol)	liquid	manual dipping, operating semiauto. Machines	Occasionally	incidental	0 – 0.0005	420	0 – 0.21	EASE [3)]
6) acid pickling processes (0.5% butynediol)	liquid	cleaning, maintenance, servicing work	Occasionally	incidental	0 – 0.0005	420	0 – 0.21	EASE [3)]

Table 4.2 continued overleaf

Table 4.2 continued Summary of dermal exposure data of butynediol which are relevant for occupational risk assessment

Use of formulations								
7) nickel plating (0.03% butynediol)	liquid	manual dipping, operating semiauto. machines	Daily	intermittent	0.00003 – 0.0003	420	0.1 – 0.13	EASE (irregular use)
Dermal exposure								
Scenario number, Area of production and use	Form of exposure	Activity	Frequency [days/year]	Contact level [1)]	Level of exposure [mg/cm^2/day]	Exposed area [cm^2]	Shift average [mg/p/day]	Method (use of gloves)
8) nickel plating (0.03% butynediol)	liquid	cleaning, maintenance, servicing work	12	intermittent	0.00003 – 0.0003	840	0.025 – 0.25	EASE (irregular use)
9) organic paint removers (10% butynediol)	liquid	brushing, rolling, dipping	occasionally	incidental	0 – 0.01	420	0 – 4.2	EASE [3)]
10) acidic solutions for the removal scale (0.2% butynediol; industrial sector)	liquid	filling, time of reaction, draining off	occasionally	intermittent	0.0002 – 0.002	420	0.08 – 0.84	EASE (irregular use)
11) acidic solutions for the removal of rust (0.2% butynediol; industrial sector)	liquid	filling, dipping, time of reaction, draining off	daily	intermittent	0.0002 – 0.002	420	0.08 – 0.84	EASE (irregular use)
12) acidic solutions for the removal scale (0.2% butynediol; skilled trade sector)	liquid	filling, time of reaction, draining off	occasionally	extensive	0.002 – 0.01	420	0.84 – 4.2	EASE (irregular use)
13) acidic solutions for the removal of rust (0.2% butynediol; skilled trade sector)	liquid	filling, dipping, time of reaction, draining off	daily	extensive	0.002 – 0.01	420	0.84 – 4.2	EASE (irregular use)

1) Contact level according to the EASE model
2) dermal exposure for incidental contacts with corrosive substance / formulations
3) expert judgement (with respect to the corrosive properties of other substances in the solution)

4.1.1.3 Consumer exposure

4.1.1.3.1 Inhalation exposure

The Consexpo computer program version 3.0 is used to estimate inhalation exposure of consumers to butynediol (Appendix A).

All exposures are referred to female adults having a body weight of 60 kg and an inhalation rate of 24,100 cm³/minute (CONSEXPO default) and an absorbed fraction of 100% (default).

Cleansing agents and disinfectants for sanitary installations

Cleansing products will be applied using wiping cloth, which is put by hand into a bucket containing the diluted product, which is then wiped onto a surface. Thus, for estimation of inhalation exposure to butynediol from this use category the Consexpo scenario "House keeping, cleaning indoors" and "Evaporation from Mixture" were used. The cleaning liquid (content of 2% butynediol) is diluted 1/100 to a final concentration of 0.02% butynediol (= 0.02 g) which is put onto an area of 2 m². A daily use with a duration time of 10 minutes and a contact time of 2 hours were assumed. From this scenario, the mean event concentration will account for 0.00014 mg/m³, a cumulative (worst case) dose of 0.007 µg/kg bw/day can be calculated as exposure by inhalation. Room volume in this scenario is 20 m³, the personal volume (user) is 5 m³ and the ventilation rate is 4 m³ per hour.

Car cleansing products

For estimation of inhalation exposure to butynediol from this use category the Consexpo scenarios "Cleaning car/motor bike" and "Evaporation from a Mixture" were used. A liquid cleaning solution containing 1% of butynediol (= 1 g, undiluted) is put onto an area of 0.5 m² inside a car. A weekly use with a duration time of 10 minutes and the duration of contact of 30 minutes were assumed for this scenario. Room volume in this scenario is 5 m³ (approximate car internal volume) and the ventilation rate is 1 m³ per hour. From this scenario, a mean event concentration of 0.0026 mg/m³ was estimated; for inhalation exposure a cumulative worst-case estimate of 0.004 µg/kg bw/day can be calculated as exposure by inhalation.

Descaling agents

For estimation of inhalation exposure to butynediol from this use category the Consexpo contact scenario "House keeping, cleaning indoors" in connection with the exposure scenario "Evaporation from mixture" was used. A liquid solution containing 1% of butynediol (=1 g, undiluted) is put onto an area of 2 m² (e.g. tiles in a bathroom). The duration of use is 10 minutes, the contact time is 2 hours and the frequency of use is twice a month. From this scenario, a mean event concentration of 0.007 mg/m³ can be estimated. For inhalation exposure a cumulative worst-case estimate of ~ 0.02 µg/kg bw/day can be calculated. Room volume in this scenario is 20 m³ and the ventilation rate is 4 m³ per hour.

<u>Total inhalation exposure of the consumer</u>

The cumulative inhalation exposure of the consumer to butynediol calculated for all kinds of use would be in range of about 0.03 µg/kg bw/day (yearly average). For risk assessment

purposes the inhalation exposure by use of descalers is carried forward (mean concentration 0.007 mg/m³), whereas the other exposures will be neglected because of considerably lower butynediol concentrations.

4.1.1.3.2 Dermal exposure

Cleansing agent and disinfectants for sanitary installations

The use of the Consexpo program reveals a cumulative worst case dermal exposure of 0.0003 mg/kg bw/day. This calculation is based on the use of the Consexpo "Fixed product volume scenario" (TGD Chapter 2, Appendix IV, eq. 3; EC, 1994) and contact scenario "House keeping, cleaning indoors" as described above. The mean event concentration on skin is 0.0002 mg/cm³. The volume contacting the skin is 8.4 ml (840 cm² (= surface hands) · 0.01 cm (= thickness of layer). The dilution factor is 100. The absorption fraction is approximately 1%. (It is assumed that within 24 hours 100% of the substance is absorbed via the skin. Relating this amount to a contact time of 10 minutes, an amount of approximately 1% will be absorbed (This assumption is only applicable if after 10 minutes hands are washed).

This calculation is based on the assumption that no protective clothing e.g. gloves are used. It can be assumed that the exposure may be much lower if protecting cloth is worn.

Car cleansing products

The use of the Consexpo program reveals a cumulative worst case dermal exposure of 0.00024 mg/kg bw/day. This calculation is based on the use of the Consexpo "Fixed product volume scenario" (TGD Chapter 2, Appendix IV, eq. 3; EC, 1994) and the defaults for the Consexpo contact scenario "Repairing car motor bike" as described above. The volume contacting the skin (applied volume) is 1 ml (= splashes), and a mean average butynediol concentration on skin of 0.01 mg/cm³ was estimated. The dilution factor is 1. The absorption fraction is approximately 1%. (It is assumed that within 24 hours 100% of the substance is absorbed via the skin. Relating this amount to a contact time of 10 minutes, an amount of approximately 1% will be absorbed. This assumption is only applicable if after 10 minutes hands are washed).

This calculation is based on the assumption that no protective clothing e.g. gloves are used. It can be assumed that the exposure may be much lower if protecting cloth is worn.

Descaling agents

The use of the Consexpo program reveals a cumulative worst case dermal exposure of 0.0001 mg/kg bw/day. This calculation is based on the use of the Consexpo "Fixed product volume scenario" (TGD Chapter 2, Appendix IV, eq. 3; EC, 1994) and the defaults for the Consexpo contact scenario "Evaporation from mixture" as described above. The volume contacting the skin (applied volume) is 1 ml (= splashes). A concentration of butynediol on skin of 0.01 mg/cm³ was estimated. The absorption rate has been estimated to ~ 1%. (It is assumed that within 24 hours 100% of the substance is absorbed via the skin. Relating this amount to a contact time of 10 minutes, an amount of approximately 1% will be absorbed. This assumption is only applicable if after 10 minutes hands are washed). There is no dilution.

This calculation is based on the assumption that no protective clothing e.g. gloves are used. It can be assumed that the exposure may be much lower if protecting cloth is worn.

Dermal exposure via the air can be neglected due to the low vapour pressure of butynediol.

Total dermal exposure of the consumer

The resulting total dermal exposure of the consumer to butynediol will be in a range of about 0.0006 mg/kg bw/day which is primarily represented by exposure to the substance in cleansing agents.

4.1.1.3.3 Total exposure of the consumer

For risk characterisation related to chronic exposure, a value of ~ 0.67 µg/kg bw/day is carried forward which is calculated as a daily dose from inhalation and dermal exposure. There is no information on uses through spray products available.

4.1.1.4 Humans exposed via the environment

According to Appendix VII of Chapter 2 of the TGD (EC, 1994), the indirect exposure to humans via the environment, i.e. through food, drinking water and air is estimated.

As a worst-case scenario, the maximum intake due to exposure in the vicinity of a point source is calculated. The local concentrations are taken from the scenarios for metal surface treatment and external processing of the substance (see Section 3.1.2.4, 3.1.3 and 3.1.4). This is compared to an average intake due to exposure via the regional background concentration (see Section 3.1.6).

The following input parameters were used for the calculations:

Table 4.3 Input parameter for the calculation of the exposure via the environment

	local scenario	regional scenario
annual averaged concentration in surface water*	5 µg/l**	0.3 µg/l
annual averaged concentration in the atmosphere*	$2.8 \cdot 10^{-5}$ mg/m^3	$2.6 \cdot 10^{-12}$ mg/m^3
concentration in porewater of agricultural soil	$1 \cdot 10^{-4}$ mg/l	$1 \cdot 10^{-6}$ mg/l
concentration in agricultural soil	-	$1.8 \cdot 10^{-7}$ mg/kg $_{ww}$
concentration in grassland soil	$1.7 \cdot 10^{-5}$ mg/kg $_{ww}$	-
concentration in groundwater	$1 \cdot 10^{-4}$ mg/l	$1 \cdot 10^{-6}$ mg/l

* For the estimation of indirect exposure via the environment the local concentrations calculated for the emission episodes are averaged over the whole year.

** The local aquatic concentration of 6.3 µg/l calculated for the use of the substance in metal surface treatment was averaged over the year. The higher results from the generic release scenarios for production and processing were not used, because the effluent measurements indicate, that with regard to the whole year this would clearly overestimate the indirect exposure.

The resulting total daily dose is: $DOSE_{tot} = 0.004$ mg·kg $_{bw}^{-1}$·d^{-1} (local scenario)

$OSE_{tot} = 0.008$ µg·kg $_{bw}^{-1}$·d^{-1} (regional scenario)

The calculated total doses comprise the following routes:

Table 4.4 Routes of intake

intake route	% of total dose	
	local	regional
drinking water	3.7	95
air	0.1	< 0.01
stem	96	4
root	0.01	0.1
meat	< 0.01	< 0.01
milk	0.02	0.01
fish	0.01	0.3

The main route of indirect exposure is the intake via stem for the local scenario. The regional background concentration leads to a predominant intake via drinking water.

4.1.1.5 Combined exposure

It is possible for an individual to be exposed to butynediol at work, from consumer products and indirectly via the environment. However, the exposure levels resulting from butynediol containing consumer products (about 0.03 µg/kg bw/day) and the levels that would be received indirectly from environmental sources (0.004 mg/kg bw/day for the local scenario (via stem) and 0.008 µg/kg bw/day via drinking water) are lower as compared to different occupational exposure scenarios (see **Table 4.8**). Thus, they will not significantly contribute to the daily body burden received at work.

4.1.2 Effects assessment: Hazard identification and Dose (concentration) - response (effect) assessment

4.1.2.1 Toxico-kinetics, metabolism and distribution

Electrophilic reactions of butynediol are favoured due to the high electron-density of the triple bond. Relatively low pH 4 in an aqueous solution (20 g/l) indicates acidic character of the hydrogen atom in the hydroxy group.

The physico-chemical data (vapour pressure of approximately 0.17 Pa at 20°C, water solubility of about 750 g/l, partition coefficient (log Pow) of -0.73 and molecular weight of 86 g/mol) indicate that butynediol can be absorbed via the oral, dermal and respiratory routes, but there is no quantitative data on the extent of absorption available.

Specific investigations about toxicokinetic behaviour and metabolism are not available. It can be anticipated that in a first metabolic step butynediol is enzymatically activated to the corresponding reactive aldehyde capable of reacting with biologically relevant nucleophiles. Using purified horse liver and rainbow trout hepatic cytosol alcohol dehydrogenase (ADH) preparations, the propensity of butynediol to inhibit enzyme activity, in both the presence and the absence of reduced glutathione, was ascertained (Bradbury and Christensen, 1991). The involvement of ADH in the metabolic activation was additionally shown by inhibition experiments with rat liver extracts. Pyrazole, an inhibitor of ADH, competitively inhibited the oxidation of butynediol (Taberner and Pearce, 1974). Cytochrome P450-dependent metabolism can not be excluded, because a low increase of aminopyrine demethylase activity was detected (Komsta et al., 1989).

4.1.2.2 Acute toxicity

4.1.2.2.1 Studies in animals

Oral

Based on the available studies, butynediol is to be considered as acute toxic by oral administration: Oral LD50 values of 132 mg/kg body weight for male and of 176 mg/kg for female rats are documented (Jedrychowski et al., 1992a). Two cats died after oral administration of 50 mg/kg body weight and rabbits dosed with 100 mg/kg died within 24 hours (BASF, 1959). Aqueous solutions of the pure substance showed similar effects (Jedrychowski et al., 1992a); the technical grade solutions containing hexamethylenetetramine and form-aldehyde are more toxic than solutions of pure butynediol (BASF, 1959).

The main clinical signs of butynediol toxicity are apathy, disturbances of balance, convulsions, tremors and diarrhoea, the predominant effects at necropsy being congestion of the internal organs, pulmonary oedema and haemorrhages, and fatty infiltration of the liver.

Inhalation

Acute toxicity after a single 4-hour inhalative exposure (head-nose inhalation system) to butynediol (liquid aerosol of aqueous solutions, MMAD 0.5-1.0 µm) has been tested recently in an acute inhalation toxicity study with rats: No male but 4/5 female rats died after exposure to 0.69 mg/l, all animals died at 1.03 mg/l. The LC50 for male and female rats was estimated to be approximately 0.69 mg/l. The predominant effects at necropsy were red discoloration in lungs and light brown discoloration in livers, erosion/ulceration of glandular stomach or general congestion. Irregular and accelerated respiration was observed in all groups up to one day after exposure (BASF 1996a).

In a "time-saturation test" butynediol was heated (70°C) to build up an aerosol with 200 l air/hour. The results of exposure in the inhalation hazard test are dependent on the temperature at which the atmosphere is produced and the duration of exposure: Thus, all 12 rats exposed to an atmosphere enriched or saturated with butynediol at 20°C for 8 hours survived, while exposure to an atmosphere produced at 70°C was tolerated for 2 hours but was fatal to all 6 rats after exposure for 8 hours, mortalities occurring 4.5-24 hours after exposure. No data on the concentration tested were reported. Clinical signs: Increased breathing after 35 minutes, apathy after 3 hours. At necropsy no macroscopically visible changes were observed (BASF, 1959).

Dermal

In acute dermal toxicity studies butynediol was applied either as a solid (using 11 rats) or as a 40% aqueous solution (using 16 rats) at a dose of 5,000 mg/kg bw for 24 hours. The solid substance did not cause any mortality when applied dermally, but the same dose applied as 40% aqueous solution killed 8/16 rats within 48 hours. At necropsy, changes in livers and kidneys demonstrated severe hyperaemia and different stages of degeneration, including necrosis (Jedrychowski et al., 1992a).

Dermally applied in rats, butynediol has proven to be harmful, showing dermal LD50 values in the range of 659 mg/kg up to 1,240 mg/kg bw within two studies performed according to current EU guidelines: In a dermal study with female rats doses of 1,250, 1,600 and 2,000 mg/kg were applied to groups of 5 female rats each (24 hours occlusion, physiological saline as vehicle). Doses of 1,250 and 1,600 mg/kg caused deaths of 3/5 female rats each, resulting in a dermal LD50 of 1,240 mg/kg. Impaired breathing, impaired mobility, ptosis, and blood crusted snout and eye lids were observed. At necropsy, in victims blood in intestines and discolouration of liver and spleen were detected, while surviving animals did not show macroscopically visible changes (Hoechst AG, 1988). In a second study, doses of 50, 100 and 2,000 mg/kg were applied dermally to groups of 5 male rats, doses of 1,250 and 1,600 mg/kg to groups of 5 female rats and doses of 400 and 2,000 mg/kg to groups of 5 male and 5 female rats each (24 hours occlusion, physiological saline as vehicle). No deaths were observed after application of 50 mg/kg, 1/5 males died at 100 mg/kg, 2/5 males died at 200 mg/kg, 2/5 males and 0/5 females at 400 mg/kg, 3/5 females at 1,250 mg/kg and at 1,600 mg/kg, 4/5 males and 5/5 females died after application of 200 mg/kg. Impaired breathing, impaired mobility, hunched posture, ptosis, blood crusted snout, and eye lids were observed. At necropsy, in victims blood in stomach and intestines and discolouration of lung, liver and spleen were detected, while surviving animals did not show microscopically visible changes. This study resulted in a dermal LD50 of 424 mg/kg bw for male and a dermal LD50 of 983 mg/kg bw for female rats (Hoechst AG, 1990).

4.1.2.2.2 Studies in humans

No data available

4.1.2.2.3 Conclusion

Butynediol is toxic after oral administration (oral LD_{50}, rat: 132 to 176 mg/kg body weight) and by inhalation (LC50, rat: 0.69 mg/l/4hour), and harmful following dermal absorption of aqueous solutions (dermal LD50, rat: 659 to 1,240 mg/kg body weight). Liver and kidneys were the primary targets and different stages of degeneration, including necrosis, were observed. Based on the acute toxicity data for inhalation and oral administration, classification as toxic and labelling with R 23/25 (toxic by inhalation and if swallowed) is warranted. According to the data for dermal exposure butynediol is labelled with R 21 (harmful in contact with skin).

4.1.2.3 Irritation/Corrosivity

4.1.2.3.1 Studies in animals

Numerous skin and eye irritation studies have been carried out in rabbits, with butynediol in various preparations and at various dilutions, giving differing results. This is due to the fact, that normally not the pure substance or aqueous solutions thereof are tested but mixtures containing amines or formaldehyde.

Skin irritation/corrosivity of pure butynediol has been examined in two well documented studies using solid butynediol with a purity of > 99% or the solid moistened with water: In a test according to OECD guideline 404, 6 rabbits were tested with 0.5 g of the pure solid substance. After an exposure time of 4 hours all rabbits showed severe erythema and oedema within 24 hours and exhibited necrosis within 6 days. An exposure time of 3 minutes did not cause necrosis (Hüls AG 1985a). No dermal irritation in rabbits with intact skin, slight reddening after application to abraded skin were found after application of 0.3 g of the solid moistened with water and also tested with aqueous solutions containing either 40% or 20% of the substance occlusively applied for 24 hours exposure periods (Jedrychowski et al., 1992a).

Eye irritation was investigated in three valid studies: In the first study according to OECD - Guideline 405, a dose of 100 mg of butynediol caused in all rabbits moderate irritation of iris, cornea and conjunctivae, but 1/6 rabbits exhibited irreversible corneal opacity (Hüls AG 1985b). Minimal conjunctival erythema but marked lacrimation was observed in a Draize test performed with 4 rabbits and 100 mg of the substance (Jedrychowski et al., 1992a). Similar effects (corneal opacity grade 1 in 1/3 rabbits reversing within 3 days, moderate conjunctival irritation reversing within 2 days) demonstrated a third test (OECD Guideline 405) using 3 rabbits and 0.1 ml bulk volume (47 mg) of commercial grade butynediol (BASF AG, 1986).

4.1.2.3.2 Studies in humans

No data available

4.1.2.3.3 Conclusion

Pure undiluted butynediol has proven to cause corrosion by contact with skin. No irritant effects on rabbit skin were observed with 20% and 40% butynediol solutions. In contact with eyes the substance can cause irreversible corneal opacity. According to EU guidelines butynediol is classified as corrosive (C) and causes burns (R 34).

4.1.2.4 Sensitisation

4.1.2.4.1 Studies in animals

Skin sensitising effects of butynediol were studied in three studies in guinea pigs.

In a Magnusson Kligman test (OECD Guideline 406), using an intradermal induction dose of 5% in physiological saline, topical induction with 25% (pre-treated with 10% sodium lauryl sulfate) and challenge with 25% butynediol in physiological saline, 1/18 treated animals revealed a positive response after 24 hours. No skin reactions were observed in control animals (RCC, 1990).

A sensitisation rate of 25% was reported in a second study (Magnusson Kligman test). Animals received dermal challenge concentration of 25% aqueous butynediol following induction of the test animals with 0.5% in paraffin oil intradermally and 25% topical. 5/20 treated animals revealed a positive response after 24 and 48 hours. No skin reactions were observed in control animals (Hüls AG, 1985c).

The substance has not shown any skin sensitising effects in a third Magnusson Kligman test with 22 animals in the test group and 8 animals in control group, using an intradermal induction of 2%, topical induction with 20% and challenge with 5% and 20% butynediol (Jedrychowski et al., 1992a).

There is no information available on the potential of butynediol to produce respiratory sensitisation in animals.

4.1.2.4.2 Studies in humans

In man, two cases of contact allergy caused by butynediol have been described: A 41-year-old female cleaner developed dermatitis on the face, hands and forearms after having used a new cleaning agent for a few months. The dermatitis appeared about 12 hours after contact with the agent and settled when she was not using it. Patch testing with the components of the cleaning agent produced a strong reaction to butynediol. The compound was present in the cleaning agent at low concentration (0.7%) as corrosion inhibitor. Patch testing of 55 control persons with 1% butynediol in water was negative (Baadsgaard and Jorgensen, 1985).

A 54-year-old male worker had worked for years in the storeroom of a galvanic department. He came into contact with a considerable number of materials such as simple solvents, surfactants, paints and synthetic resins. He also handled diamino-diphenylsulfone and butynediol additives to be used in nickel baths. He developed an itchy dermatitis on his hand and lower arms, which continued although he wore rubber gloves. He was patch tested with

various substances and other chemicals. The only substance to give a two plus positive reaction at 48 hour was a 2% butynediol solution in water (Malten, 1980).

Ten workers with suspicion of allergic contact eczema who were probably accidentally exposed to butynediol were asked for voluntary patch testing for possible sensitisation; 6 of these 10 workers were willing to undergo the test. Pure butynediol and technical grade butynediol were applied as a 0.5% aqueous solution. Furthermore, formaldehyde which is a precursor for synthesis and an impurity in technical grade butynediol was also tested. Whereas formaldehyde did not show a positive reaction in these individuals, 4/4 tested in 2001 showed clear evidence of sensitisation. Two other workers tested in 1990 and 1994 had positive patch test reactions (BASF AG, 2001).

A 20-year old patient whose occupation involved nickel-plating developed itchy dermatitis on the dorsum of his left hand, extending to the upper arm. By patch testing butynediol (1% in water) was identified as the causative agent. Since the substance is not routinely patch tested it is unclear how often it is overlooked as the causative allergen in occupational contact dermatitis. The authors recommend the inclusion of butynediol in patch testing of exposed workers (Blaschke et al., 2001).

There is no information available on respiratory sensitisation.

4.1.2.4.3 Conclusion

With three Magnusson Kligman tests reaction rates of 0%, 5% or 25% were observed. Only one of the studies, where a reaction rate of 5% (1/18 animals) was noted, was conducted in compliance with the OECD Test Guideline 406. The two other tests (reaction rates 0% or 25%) did not meet the criteria for testing according to the OECD Test Guideline 406 with respect to test concentration and pre-treatment with sodium laurylsulfate. In summary, it can be concluded from these animal studies that butynediol possesses a weak sensitisation potential.

Based on the human experience showing the occurrence of contact allergy at the workplace the substance has been classified as “sensitising” and labelled with R 43 - May cause sensitisation by skin contact.

4.1.2.5 Repeated dose toxicity

4.1.2.5.1 Oral exposure

The repeated dose toxicity study of Jedrychowski et al. (1992b) was assessed as a valid study. In this oral 28-day study eight male and female Wistar Imp:DAK rats were administered by gavage with doses of 1, 10 and 50 mg/kg bw/day from a test substance containing approximately 99% butynediol. Test parameters were clinical signs, hematology, clinical chemistry (without serum bilirubin), and body weights, organ weights (adrenals, kidneys, liver, spleen and testes. Histopathologic examination was limited to adrenals, heart, small and large intestine, kidneys, liver, lungs, ovaries, pancreas, spleen, stomach, testes.

Three males and three females of the high dose group died during the testing period. Deaths occurred in males on days 26, 27, 28, and in females on days 7, 7 and 26. Body weight gain for males in the high dose group was significantly lower and food consumption was slightly lower than in the control group.

Haematological examination yielded significantly decreased erythrocyte count (-21%), hematocrit value (-11%) and haemoglobin concentration (-11%) in female rats given the high dose. The erythrocyte count was also significantly diminished in mid dose females (-11%). The number of reticulocytes (males: +148%, females: +100%) and leukocytes (males: +50%, females: +72%) were significantly increased in both sexes of the high dose level. A higher leukocyte count was caused by a significant increase of neutrophils (males: +68%, females: -55%) and lymphocytes (males: +37%, females: +53%).

In high dose groups significant differences of parameters of serum chemistry were reported as follows: in both sexes an increase in sorbitol dehydrogenase activity, in females an increase of total protein concentration and in males an increase of glucose level.

The absolute and relative liver weights and the relative kidney weights of both sexes in the high dose group were significantly increased. In addition, the relative liver weights of mid dose females and the absolute kidney weights of high dose females were significantly elevated.

Histopathology in animals that died showed congested internal organs, pulmonary oedema and severe changes in liver and kidneys, which included diffuse hepatic parenchymal necrosis, accompanied by reactive mononuclear cells and granulocytes, fatty changes, as well as renal tubular degeneration and interstitial mononuclear cell infiltration in the kidney.

Microscopic examination of animals killed terminally revealed liver lesions of mid and high dose groups. These were reported as ‘swelling of parenchymal cells, increased polymorphism of the hepatocyte nuclei, some parenchymal cells with large nuclei and chromatin margination, and numerous binuclear cells’. The authors interpreted such lesions as hepatocyte hyperplasia. While all animals in the high dose groups had these changes, only two males and three females in mid dose groups were affected. The intensity of other changes (increased nuclear differentiation, the number of binuclear cells and intraparenchymal infiltration) was comparable in mid and high dose groups. No hepatic changes were observed in low dose groups. Mononuclear cell infiltration and numerous megakaryocytes in the red pulp of the spleen were observed in 2/8 males and 1/8 females of mid dose groups, and in 2/5

males and 3/5 females of the high dose groups. No adverse effect was seen in animals which received 1 mg/kg bw/day; this dose was considered to be the NOAEL.

Toxic effects have also been reported in studies of limited reliability:

- In a range-finding study in rats without histopathologic examination no indication on neurotoxicity from grip strength and hot plate tests or other relevant toxic effect was observed after oral application of 5, 10, and 20 mg/kg bw/day butynediol (purity 98.8%) on 5 days (BASF 1992). The analytical concentration was 80% (low dose) 87% (mid dose) and 98.5% (high dose) of the target concentration. The only treatment-related effect was a significant increase of cholesterol values in high dose males.
- In a shortly summarised report (Komsta et al., 1989) on an oral 14-day study on rats (10 animals/sex/group) treated with gavage administration of 0 (water), 1, 10 or 100 mg/kg bw/day butynediol. All animals were examined for clinical signs, body weight, hematology and clinical chemistry parameters, organ weights of five organs, gross changes at necropsy and histopathology on 30 organs/tissues (except nasal cavities). One male of the high dose groups and one female of the low dose group died after eight doses, but their deaths were reported to be unrelated to treatment. Animals administered to 100 mg/kg showed blood-tinged nasal discharges, piloerection and diarrhea, lower body weight gain (males), increased relative liver weight (males and females), increased cholesterol levels (males and females), increased serum calcium and decreased glucose levels (females). A slight induction of mixed function oxidase activity (microsomal aminopyrine demethylase activity) was found in fresh liver samples of females. Hematological examinations revealed a decrease of red cell counts, hemoglobin content and hematocrit in females only. There were no significant treatment-related histological changes observed in organs investigated (brain included) of either males or females.

In a single study (Knyshova, 1968), of which original data are not available, it is reported that butynediol has adverse effects on the nervous system. Oral administration of butynediol to male rats (6 rats/group) at doses of 0, 0.04, 0.2 and 2 mg/kg bow/day for 6 months did not alter general behaviour, body weight or blood values (haemoglobin content, numbers of erythrocytes, leukocytes, and thrombocytes, and coagulation time). Animals of the high-dose group showed delayed conditioned reflexes with a 40% increase in the latency period. In addition, reduced cholinesterase**,** decreased content of sulfhydryl groups (SH groups), and increased transaminase activities were seen, as well as an alteration in the serum protein profile. In the brain, the number of Nissl bodies were reduced and the neuroglia content was increased, as well as the content of SH groups was reduced. In the liver, there was fatty degeneration, sclerotic zones and reduced glycogen values, while in other organs localised hyperaemia occurred. No information available on the purity, analytical concentration, stability of test substance or central nervous localisations examined.

4.1.2.5.2 Inhalation exposure

Sixteen male and female Wistar rats per test group were head-nose exposed to liquid aerosol of an aqueous solution of butynediol (99.5%) for 6 hours per day, 5 days per week (BASF, 1998). The target concentrations of treatment groups were 0.5, 5 and 25 mg/m³, which were comparable to the analytical concentrations (max. ± 4%). A concurrent control group was exposed to clean air. Half of the animals (satellite groups) were examined after 10 exposures (15 study days); the other half (main groups) were examined after 20 exposures (30 study days). Identical examination were performed before, during and after exposure containing

clinical examination (twice daily/at least once daily), body weight (once weekly), ophthalmoscopy (prior to and at the end of exposure), functional observational batteries and motor activity measurements (on 5 animals/sex of all groups prior to and after 8 exposures, and after 18 exposures in main groups only), hematology and clinical chemistry (on 5 animals/sex/group at the end of exposure), necropsy, weighing of selected organs, gross pathology evaluation and histopathology of several organs/tissue as required by OECD 412. In addition, neuropathology examinations were performed on three animals per sex and group sacrificed and preserved by perfusion fixation.

No treatment-related deaths or neurofunctional abnormalities were observed. In the 25 mg/m³ groups, semiquantitative evaluation of urine test strips revealed higher incidence of increased levels of urobilinogen in two males and females each after day 30 of the study and one female after 15 days of study. No other treatment-related findings in other organs were observed in histopathology and neuropathology examinations.

10 and 20 exposures to butynediol aerosols at concentrations of 5 and 25 mg/m³ resulted in focal squamous metaplasia and inflammation in the most rostral part of the larynx. Focal inflammation at the tracheal bifurcation was observed in the 25 mg/m³ test groups only after 20 exposures. All changes were graded minimal to slight (see **Table 4.5**).

Butynediol inhalation did not induce systemic toxic effects at the concentrations tested. Other lesions or dysfunction did not accompany the increase of urobilinogen. Therefore the NOAEC for systemic toxicity was 25 mg/m³. Due to laryngeal metaplasia and inflammation at concentrations of 5 mg/m³ and above, the NOAEC for local effects on the respiratory tract was 0.5 mg/m³.

Table 4.5 Treatment-related effects of butynediol exposure on the respiratory tract after 10 exposures satellite groups) and after 20 exposures (main groups)

	Males				Females			
mg/m³*	0	0.5	5	25	0	0.5	5	25
Main groups	5	5	5	5	5	5	5	5
Larynx								
Metaplasia squamous			2	4			5	5
Inflammation focal			1	2			1	2
Trachea								
Inflammation focal				2				2
Satellite groups	5	5	5	5	5	5	5	5
Larynx								
Metaplasia squamous			4	4			5	5
Inflammation focal				4				4
Trachea								
Inflammation focal					1			

* Concentration of butynediol
** Number of animals examined

In a dose-finding study (BASF, 1997), butynediol aerosol at concentrations of 0, 25, 100 and 300 mg/m³ was head-nose exposed on 5 days (6 hours/day) to five Wistar rats of each sex per

group. The study design and test parameters were comparable to the above mentioned 30-day study except that no specific examinations on neurofunction were performed and histopathology was performed on selected organs including four levels of the nose, three levels of the larynx, the trachea, lungs, mediastinal lymph nodes, liver, kidneys, spleen and thymus. The 300 mg/m³ concentration was lethal for one animal of each sex during the exposure period (on study day 2 and 3). Clinical findings were confined to this concentration. They consisted in signs of upper respiratory tract irritation (bloody nasal crusts, accelerated respiration) and reduction of general health (piloerection, tremor, squatting posture). Urine samples of males and females exposed to 300 mg/m³ were discoloured from dark yellow to light orange. Body weight development was slightly retarded in the male and female animals. The body weight gain in these animals was significantly reduced compared to the control animals.

Clinical pathology showed increased gamma-GT activities, bilirubin and cholesterol levels and decreased urea levels in the serum of both sexes. Increased levels of urobilinogen were detected in the urine of male and female animals. The two animals that died prematurely showed mucosal erosions/ulcers in the glandular stomach (male and female), erosions/ulcers of the forestomach and prominent acinar pattern in the liver, black red discoloration of the jejunal content, and few red brown foci in the adrenal cortex (female). No abnormal gross findings were observed in the remainder animals of the 300 mg/m³ groups. Histopathology of the liver revealed slight to moderate single cell necrosis (four females), liver cell dystrophy (two males and one female) and increased mitotic figures (one female). Inflammation and/or epithelial changes in nasal cavity and/or larynx were present in all animals of the high dose groups. They consisted of hyperaemia, increased/bloody mucus deposition, purulent rhinitis, focal unilateral or bilateral disarrangement of the olfactory epithelium (at levels III and IV of the nasal cavity), or atrophy of olfactory epithelium in the nasal cavity (one male only). Mixed cellular inflammation, hyperplasia and focal/diffuse metaplasia of the transitional epithelium of the larynx. Focal disarrangement of the olfactory epithelium occurred at levels III and IV of the nasal cavity; they were characterised by the loss of polar arrangement of the nuclei and by reduced/missing cytoplasma at the apical cell rim. Microscopic findings in the premature died animals were: congestion of liver, nasal cavity, lungs, kidneys, mediastinal lymph nodes, severe liver dystrophy, vacuolar degeneration and dystrophic calcification of the cortico-medullary area in the kidneys, severe lymphocytic necrosis in the thymus, severe lymphocytic depletion in the spleen, erosions/ulceration in the glandular stomach and/or forestomach, increased mucus in the nasal cavity, disarrangement of the olfactory epithelium, inflammation in the epiglottis (larynx level I), and blood resorption in the mediastinal lymph nodes.

At 100 mg/m³ butynediol increased urobilinogen levels in urine, inflammation, increased/bloody mucus, focal disarrangement of olfactory epithelium in the nasal cavity, and inflammation, hyperplasia and focal/diffuse metaplasia of the laryngeal mucosa were observed.

The 25 mg/m³ butynediol concentration caused a higher incidence of increased urobilinogen levels in urine incidence as well as increased/bloody mucus in the nasal cavity, inflammation and metaplasia of the laryngeal mucosa.

4.1.2.5.3 Other application routes

There were no data on repeated dose toxicity with the dermal route of exposure.

Table 4.6 Summary of butynediol-related effects in rats after repeated exposure by oral or inhalation route

	Oral studies			Inhalation studies	
	BASF 1992	Komsta 1989	Jedrychoski et al.1992b	BASF 1997	BASF 1998
Study design	0,5,10,20 mg/kg bw/day 5 days	0,1,10,100 mg/kg bw/day 14 days	0,1,10,50 mg/kg bw/day 28 days	0,25,100, 300 mg/m³ 5 days	0,0.5,5,25 mg/m³ 30 days
Critical dose for classification Xn			150 mg/kg bw/day		750 mg/m³
Effect:					
Mortality			*50 mg/kg	300 mg/m³	
Bad general health status		100 mg/kg		300 mg/m³	
Body weight gain↓		100 mg/kg	50 mg/kg	300 mg/m³	
Hematology					
Anemia		100 mg/kg	50 mg/kg		
Leukocytosis			50 mg/kg		
Clinical chemistry					
Gamma-GT↑				300 mg/m³	
Bilirubin↑				300 mg/m³	
Cholesterol↑	20 mg/kg	100 mg/kg			
Urinalysis					
Urine discoloration				300 mg/m³	
Urobilinogen↑				≥25 mg/m³	25 mg/m³
Liver					
Weight↑		100 mg/kg	≥ 10 mg/kg		
Degeneration/necrosis/ dystrophy			≥ 10 mg/kg	300 mg/m³	
Kidneys					
Weight↑			50 mg/kg		
Tubular/vacuolar degeneration			50 mg/kg	300 mg/m³§	
Cortico-med. calcification				300 mg/m³§	
Spleen					
Lymphocytic depletion				300 mg/m³§	
Extramed.haematopoiesis			≥ 10 mg/kg		
Thymus					
Lymphocytolysis				300 mg/m³§	

Table 4.6 continued overleaf

Table 4.6 continued Summary of butynediol-related effects in rats after repeated exposure by oral or inhalation route

	Oral studies			Inhalation studies	
	BASF 1992	Komsta 1989	Jedrychoski et al.1992b	BASF 1997	BASF 1998
Stomach/Forestomach					
Mucosa erosion/ulceration				300 mg/m³§	
Nasal cavity					
Bloody discharge/mucus		100 mg/kg		≥ 100 mg/m³	
Increased mucus				≥ 100 mg/m³	
Inflammation				≥ 100 mg/m³	
Disarrangement/atrophy olfactory epithelium				≥ 100 mg/m³	
Larynx					
Inflammation				≥ 25 mg/m³	≥ 5 mg/m³
Metaplasia				≥ 25 mg/m³	≥ 5 mg/m³
Hyperplasia				≥ 100 mg/m³	
Trachea					
Inflammation					25 mg/m³
N(L)OAEL(C)	NOAEL 10 mg/kg bw/day	NOAEL 10 mg/kg bw/day	NOAEL 1 mg/kg bw/day	LOAEC 25 mg/m³	$NOAEC_{loc}$ 0.5 mg/m³ $NOAEC_{sys}$ 25 mg/m³

* Dose/concentration at which the effect was observed
§ Restricted to the unscheduled deaths

4.1.2.5.4 Discussion on toxic effects of butynediol

Morbidity occurred after butynediol exposure on day 28 at a dose of 50 mg/kg bw/day and after inhalation of butynediol concentration of 300 mg/m³ on 5 consecutive days. The deaths on day 7 until day 28 in the oral study and after exposure period on day 2 and 3 in the inhalation study were not related to acute toxic effects.

Signs of non-specific toxicity due to repeated butynediol exposure were depressed general health status and growth in rats exposed to 100 mg/kg bw/day on 14 days, to 50 mg/kg bw/day after 28 days of treatment or to 300 mg/m³ during a 30-day treatment period.

Target organs showing butynediol-related lesions were the liver (oral and inhalation route), the kidney (oral and inhalation route), the haematopoietic system (oral route) and the respiratory tract (inhalation route) (see **Table 4.6**).

Severe liver lesions were reported in animals that died unintentional and were considered as a possible cause of deaths at 50 mg/kg bw/day butynediol in the oral 28-day study (Jedrychoswki et al., 1992b) and at 300 mg/m³ in the 5-day inhalation study (BASF, 1997).

In the study of Jedrychowski and co-workers (1992b), oral doses of 10 mg/kg bw/day and 50 mg/kg bw/day of butynediol caused cell degeneration/necrosis in hepatocytes. Whereas cell death of hepatocytes was observed in premature deaths, the authors considered altered

hepatocytes in the surviving animals to represent hyperplasia. The rapporteur does not support this interpretation. Swelling of liver cells, chromatin margination and large nuclei are also known characteristics of cell degeneration preceding cell death. In response of this, the number of binucleated hepatocytes was increased. The increased activity of sorbitol dehydrogenase, a cytosol enzyme highly specific for liver parenchyma in rats which is released following early changes in membrane permeability may be interpreted to support the supposed degenerative lesions. In addition, no consistent finding supporting the interpretation as adaptive hyperplasia of liver cells were described in other studies.

Degenerative and sclerotic liver lesions were also reported in male rats at dose of 2 mg/kg bw/day of butynediol for 6 months (Kynshova, 1968). Changes of the serum protein may be related to the liver effects. Coincidental findings of liver effects were reported in a 5-day inhalation study for dose finding in rats. At the concentration of 300 mg/m³ butynediol changes like increased gamma-GT activities, single cell necrosis and dystrophy gave evidence for liver cell toxicity.

Anemia was observed at 50 mg/kg bw/day butynediol in female rats treated orally on 28 days. Although the red cell parameters were not changed in other test groups, the increased occurrence of spleen megakaryocytes in each sex of the mid and high doses as well as increased reticulocyte counts in males and females of the high dose group were indicative for compensatory elevated (extramedullary) haematopoietic activity. Haematoxic effects of butynediol were confirmed by the findings of Komsta et al. (1989). Anemia was evident in females at 100 mg/kg bw/day, whereas males had no change in red blood cells suggesting a reduced sensitivity to this specific effect.

The type of anemia can not clearly be identified. There are some indications that the anemia was caused by haemolysis. Higher bilirubin levels were found in the 5-day inhalation study that can possibly be related to increased destruction of hemoglobin. At 300 mg/m³ increased serum concentrations of bilirubin were observed, at concentrations of 25 mg/m³ and above urobilinogen was increased in the urine. Urinalysis with a standard stick method showed that urobilinogen was consistently elevated in the urine of some animals at 25 mg/m³ of the 15-day/30-day inhalation study. In healthy animals, bilirubin is excreted through the bile into the gastrointestinal tract, where it is converted to urobilinogens by bacterial reduction. Normally, a small fraction of urobilinogens is reabsorbed and excreted into the urine. Elevated urine levels of urobilinogen can be used as an indicator of an increased rate of haemolysis. However, the causal relationship is considered equivocal because no significant change of red cell parameter was reported in the inhalation studies. On these parameters no information is available from oral studies.

The mucosa lesions in the stomach and/or forestomach were only seen in animals that died at inhalation exposure to 300 mg/m³. Suppressive effects on lymphoid compartments of the spleen and thymus were also restricted to these animals. As no other consistent findings was reported in other studies, these findings were considered to be more likely non-specific effects resulting from the agonal stress situation rather than a specific immunosuppressive effect.

In the kidneys, there were tubular lesions reported as (vacuolar) degeneration and dystrophic calcification of the cortico-medullary area in animals treated orally at 50 mg/kg bw/day and in animals exposed to aerosol concentration of 300 mg/m³. As the kidneys were affected in animals that died spontaneously, these lesions are considered as related to the death.

Adverse effects on the mucosa of the respiratory tract were seen after repeated inhalation of concentrations of 5 mg/m³ and above. With increase of the butynediol concentrations the number of localisations affected increased.

The most sensitive site that showed squamous metaplasia and inflammation at butynediol concentration of 5 mg/m³ and above after a 30-day study period was the larynx. Similar lesions were reported in the 5-day study at 25 mg/m³ butynediol and at higher concentrations. After a 30-day treatment to 25 mg/m³ butynediol inflammatory cell infiltration was seen in the trachea. Only at 100 mg/m³ and above laryngeal hyperplasia and inflammation and degenerative lesions of the nasal cavity mucosa were observed.

In general, main toxic effects of orally administered butynediol on liver, kidney and red blood cells are considered to be of relevance for human health because none of them represents a rat specific phenomenon and no other reason for restraining interspecies extrapolation is known. On the basis of the effects described following oral administration of the substance, butynediol is classified as harmful: danger of serious damage to health by prolonged exposure if swallowed (R-phrase R48/22).

With respect to the inhalation exposure, butynediol induced local toxic effects on the respiratory tract consisting of metaplasia and inflammation in the larynx (at ≥ 5 mg/m³), trachea (at ≥ 25 mg/m³), nasal cavity (at ≥ 100 mg/m³), and toxic effects in the liver, kidneys, thymus, spleen, stomach and forestomach indicating systemic toxic effects as well as mortality and growth retardation after repeated inhalation to butynediol concentrations of 300 mg/m³. Toxic effects of butynediol after repeated inhalation may be discussed as borderline for the extension of R48 towards the inhalation route regarding the following pros and cons:

- Repeated/prolonged exposure to butynediol at concentrations up to 25 mg/m³ induced several effects on the respiratory tract, which are described as minimal to slight. With regard on the severity grades of lesions, a classification does not seem to be needed.
- However, laryngeal metaplastic and inflammatory changes started at a very low concentration (at 5 mg/m³ and above, after 28-day inhalation) that was 150 fold below the critical concentration for classification (750 mg/m³).
- The occurrence of metaplasia means that the mucosa was replaced by another epithelium. The most common metaplasia at the larynx, the squamous metaplasia, was observed. Metaplastic changes of the respiratory epithelium are considered to be a regenerative adaptive response to substances or the effects of chronic inflammation. In contrast to liver cells where adaptation includes increased metabolic activity as an adaptation to enhance cellular functions, the regenerative adaptation in the respiratory tract by metaplasia results in an epithelium with reduced susceptibility to or with improved protection from toxicants. It can be reversible, but with increasing severity or extension it may interfere with normal respiratory clearance and defence function. Then, metaplasia of the larynx can be considered to be an adverse effect.
- The highest concentration (25 mg/m³) tested in the 30-day study was 30 fold below the critical dose for classification (750 mg/m³). The severity grades of laryngeal effects were minimal to slight at concentrations up to 25 mg/m³. Prolongation of exposure was shown to decrease the minimal effective concentration that induced inflammation and metaplasia at the larynx (from 25 mg/m³ after 5-day exposure to 5 mg/m³ after 30-day period). An increase in severity/extension of lesions is expected if higher test doses would have been tested.

- Prolongation of the inhalation period to butynediol increases the number of target sites. After exposure on 28 days, the trachea showing inflammatory changes was also a target site at 25 mg/m³. There is indication from the dose-range study that additional target sites at the respiratory tract are hit if the higher concentration would have been tested in the 28-day study. After exposure on 5 days to 100 mg/m³ and above inflammation, increased mucus production, and epithelial lesions of the olfactory epithelium of the nasal cavity were identified.
- It has to be expected that relevant systemic toxic effects occur at concentrations above 25 mg/m³. 300 mg/m³ butynediol exposed during a period of only 5 days caused some preliminary deaths and severe toxic effects in the liver, kidney, spleen, thymus, and gastrointestinal tract. As mortality occurred on day 2 and 3 of this study, deaths were considered to be related to acute toxicity. No data are available on systemic toxic effects at concentrations higher than 25 mg/m³ and below 300 mg/m³.
- The study report arguments that because of the expected local and systemic toxicity no higher concentration than 25 mg/m³ was chosen for the 30-day inhalation study. The expected maximum tolerated dose for repeated dose studies was considerably lower than the LC50 value of 690 mg/m³ from acute inhalation toxicity tests.
- Comparing the target organs of the oral and inhalation route identical target organs were identified to be the liver (in descendants and survivors) and the kidney (in descendants).
- The adverse effects after oral and inhalation exposures are not specific for animals; this sufficiently indicates a potential to induce similar effects in humans.
- The effects at low concentrations (except early deaths on day 2 and 3 after exposure to 300 mg/m³) are not covered by other toxic endpoints.

Conclusively, there is concern that butynediol induces significant health damage after prolonged inhalation exposure. However, the actual database does not warrant labelling with R48/20.

Concern on neurotoxicity

There was some concern on possible neurotoxicity of butynediol by the study of Knyshova (1968). Other studies administering higher doses did not reveal consistent findings or did not contain specific tests or histopathologic examination to give relief from this concern.

Microscopic examinations of the central and peripheral nervous system and tests on neurofunctional disorders were not included in the study of Jedrychowski and co-workers (1992b). Negative neurofunctional tests in the short term study (BASF, 1992) were not suitable to clarify the concern from the study of Knyshova (1968), because of its short treatment period (5 days), dose regimen (high dose of 20 mg/kg bw/day) and the absence of microscopic examinations. Komsta and co-workers (1989) reported no histomorphologic lesion of the brain, the number of sections or details on the brain localisations were not known, and additional localisations of the nervous system were not examined. However, a recent study clearly demonstrated that the concern was not supported by the findings of a 15-day/30-day inhalation study on rats (BASF, 1998). A battery of tests on neurofunction and motor activity and histopathologic examinations of several localisations of nervous tissue obtained by standard fixation and perfusion fixation did not give any indication on neurofunctional or neurotoxicologic effects. Based on all data available, there is at present no valid concern that butynediol can affect the nervous system.

NOAEL/NOAEC

Oral route

The study by Jedrychowski et al. (1992b) was accepted as valid study and is therefore appropriate to derive a NOAEL for quantitative risk assessment procedures on the oral route. A NOAEL of 1 mg/kg bw/day of butynediol results from this oral 28-day study. The 6-month study on butynediol (Knyshova, 1968) is not considered for the derivation of a NOAEL because of limited reliability.

Inhalation exposure

No systemic toxic effects were seen in a 30-day inhalation study on rats (BASF, 1998), therefore $NOAEC_{sys}$ was 25 mg/m³.

The most sensitive effect of butynediol was metaplasia and inflammation of the larynx at concentrations of 5 mg/m³ and above. The NOAEC for local effects on the respiratory tract was 0.5 mg/m³.

4.1.2.6 Mutagenicity

4.1.2.6.1 *In vitro* studies

Bacterial systems

A well conducted bacterial mutation test with Salmonella typhimurium strains TA 1,535, TA 1537, TA 1,538, TA 98 and TA 100 was negative in concentrations up to 5,000 µg/plate with and without S-9 mix (BASF, 1981).

In vitro systems with mammalian cells

A chromosomal aberration assay with V79 cells (CCR, 1989; 1991) was negative without S-9 mix in doses up to 860 µg/ml in two independent experiments; the mitotic index was not drastically decreased by any of the used concentrations.

With S-9 mix, an equivocal result was obtained which gave neither a clear evidence for mutagenicity nor a clear-cut negative result: Three independent experiments were run with sampling times of 18 hours and 28 hours. In one experiment increased aberration frequencies were induced by doses of 100 and 300 µg/ml with 18 hours sampling (8.5% each, negative control 3.0%). In a second experiment again 8.5% aberrant cells were found for 300 µg/ml with 28 hours sampling (negative control, 2.0%) A third experiment was negative (no details available). Although the mitotic index was decreased at the highest dose, there was no drastic inhibition of mitotic activity. Experiments 1 and 2 with S-9 mix were re-analysed for sampling time 18 hours, and again in experiment 1 increased aberration frequencies were found at 100 and 300 µg/ml. A re-analysis of the second experiment for sampling time 28 hours and of the third experiment was not conducted.

4.1.2.6.2 *In vivo* studies

An *in vivo* bone marrow micronucleus test with NMRI mice was negative after single intraperitoneal administration of 17.5, 35 or 70 mg/kg (RCC-CCR, 1998). The investigation was well-designed and in line with the current guideline OECD 475/EU B11 and GLP. Micronucleus frequencies in polychromatic erythrocytes were recorded 24 and 48 hours after treatments; 5 male and 5 female mice were used per dose. Toxic reactions were expressed at 70 mg/kg; in pre-experiments severe toxicity was observed at higher doses.

4.1.2.6.3 Conclusion

In vitro, butynediol showed no genotoxic potential in a bacterial gene mutation test. An equivocal finding, neither positive nor negative, was obtained with regard to induction of chromosomal aberrations. *In vivo*, a bone marrow micronucleus test was negative for doses up to the toxic range. Altogether, there is no relevant concern with respect to germ cell mutagenicity of butynediol.

4.1.2.7 Carcinogenicity

There are no data on carcinogenic properties of butynediol revealed from experimental animal studies.

4.1.2.8 Toxicity for reproduction

4.1.2.8.1 Studies in animals

Fertility impairment

Butynediol was investigated for impairment of reproductive performance and fertility in a study according to OECD Guideline for Testing of Chemicals No. 415 which was supplemented by additional examinations, i.e. of estrous cycle, sperm parameters and of parameters of sexual maturation in selected reared offspring (BASF-Report, Project-No 76R0226795119, 1999).

Butynediol (purity: 99.5%) was administered continuously via drinking water at concentrations of 0, 10, 80 and 500 ppm (calculated to a mean uptake of approximately 1, 7.6 and 40 mg/kg bw/day) to groups of 25 male and female Wistar rats [Chbb:THOM] (F0 parental generation) during the period of premating (at least 76 days), mating, gestation and lactation up to day 21 post partum, to which F1 pups were raised. Thereafter, F1 weanlings with the exception of 1 male and 1 female pup/litter and all F0 adult animals were sacrificed. From the selected F1 weanlings groups of 25 males and 25 females per test group were taken and continued on butynediol drinking water at the same dose level as their parents and reared until sexual maturation occurred and were killed thereafter. Based on their water intake the mean substance uptake for reared F1 weanlings was calculated to about 1.8, 13.7 and 76.9 mg /kg bw/day according to the drinking water concentrations of 10, 80 and 500 ppm.

Parental animals (F0) were examined for their mating and reproductive performances. The state of health of F0 and F1 animals was checked daily. Food and water consumption of the

F0 animals was determined regularly during premating, gestation and lactation and for the selected F1 animals once weekly. Body weights of F0 animals and of selected F1 animals were determined once weekly, and of F0 females during gestation (on days 0, 7, 14, 20) and lactation (on days 1, 4, 7, 14, 21). Furthermore, the body weights of the selected F1 animals were additionally determined on the day of preputial separation/vaginal opening.

All F0 animals were assessed by gross pathology (including weight determination of several organs) and subjected to extensive histopathological examination with special attention on organs of the reproductive system.

Sperm head counts and sperm morphology were assessed in F0 males of the control and high dose group at scheduled sacrifice, while sperm motility was examined in all F0 males.

Estrous cycle data were evaluated for all F0 females over a three week period prior to mating and throughout the following mating period (up to 14 days) until evidence of mating occurred. In addition, the estrous stage of each female was determined on the day of scheduled sacrifice.

F1 pups were sexed, and weighed on the day after birth and on days 4, 7, 14 and 21 and their viability recorded. At sacrifice on day 21 all pups were examined macroscopically at necropsy (including weight determination of brain, spleen and thymus in one pup/sex/litter). The selected F1 weanlings were reared and sexual maturation (day of preputial separation/vaginal opening) was determined. Thereafter, these animals were killed and examined macroscopically.

There were no substance related mortalities or clinical signs or signs of disturbance of behaviour in any of the male and female F0 animals in any of the dose groups. Also, no particular clinical findings were reported for F0 dams during the period of gestation and of lactation. Whereas F0 males did not show any substance-related effects on food intake statistically significant reduction in food consumption was noted for F0 females during all periods of administration for the high dose (500 ppm) group. Statistically significant reductions in drinking water consumption were observed for the high (500 ppm) and mid (80 ppm) dose groups and were most pronounced in F0 females at 500 ppm during the period of gestation (up to 37% less than controls) and of lactation (up to 24% than controls). Whereas F0 males did not show any substance related effects on mean body weight /body weight gains the F0 females of the high (500 ppm) dose group revealed lower body weights/ body weight gain during all periods of administration most pronounced during the period of lactation (body weight gain about 64% lower than controls). Organ pathology revealed substance related statistically significantly increased absolute/relative kidney weights (both F0 sexes) and absolute/relative liver weights (F0 females) as well as statistically significantly decreased absolute/relative weights of the adrenal glands and of thymus (F0 females) at the 500 ppm dose level and statistically significantly increased absolute/relative kidney weights (both F0 sexes) and absolute/relative liver weights (F0 females) at the 80 ppm dose level. No substance related specific impairment of the reproductive organs in any of the dose groups had been observed.

The numbers of homogenisation resistant testicular spermatids or caudal sperm and the percentages of abnormal and normal sperm were similar between the examined high dose group and the concurrent control group. There was a slight but statistically significant reduction in mean sperm motility (80%) in the high dose F0 males in comparison to the concurrent control (89%). However, since laboratory historical control data from a total of 16 one- and two-generation studies revealed a range of mean sperm motility values of 79%

(minimum) and 93% (maximum), this finding in the high dose F0 males is not considered a substance-related effect.

Evaluation of the estrous cycle data over the three weeks estrous determination period prior to mating revealed no substance-related effect in all test groups.

Male mating index and fertility index varied between 96 to 100% without showing any relation to dosing. Also, the female mating index and fertility index varied between 96 to 100% without showing any relation to dosing. The mean duration of gestation was very similar in all groups and the variation (between 21.8 and 21.9 days) was negligible. The gestation index was 100% for all groups, indicating that all pregnant females delivered live F1 pups. There was no substance-related effect in the mean number of implantation sites; post implantation loss (in %) and the mean number of delivered pups per dam. The live birth index, which varied between 98% and 99%, did not show any dose-related differences between the groups.

The evaluation of the offspring revealed that there were no substance-related differences between the control and the 10, 80 and 500 ppm F1 pups concerning peri/postnatal mortality and viability. Also F1 pups did not show any clinical signs up to weaning which could be attributed to the treatment. The sex distribution and sex ratios of live F1 pups on the day of birth and on day 21 p.p. did not show any substantial differences. Mean body weights and body weight gain were statistically significantly reduced in the 500 ppm group from day 7, respectively, day 14 p.p. onwards. Corresponding to the significant decrease in mean pup body weights at 500 ppm also statistically significantly impaired absolute and relative organ weights were determined for brain and thymus. Macroscopic examination of the offspring did not reveal any differences between the test groups neither in the type nor the number of pup necropsy observations.

Reared offspring that had been continued for determination of sexual maturation (up to a period of three to four weeks after weaning) did not show any mortality or clinical signs or signs of disturbance of general behaviour in any of the groups during the treatment period. Drinking water consumption was statistically significantly reduced (22% less than control) only in the 500 ppm group. Food intake was statistically significantly reduced in the high dose group males during the entire treatment period and in females only during week 0-1. Also, at 500 ppm body weights /body weight gains were statistically significantly reduced in males (9% lower than controls) for the entire period and in females (11% lower than controls) during week 0-1. Sexual maturation data revealed that the mean age for vaginal opening was slightly but statistically significantly delayed in the high dose group (33.6 days in contrast to 31.1, 31.5 and 30.8 for the 0, 10 and 80 ppm groups, respectively) and that the mean age for preputial separation was slightly but statistically significantly delayed in the high dose group (46.2 days in contrast to 44.6 7 44.9 and 45.6 for the 0, 10 and 80 ppm groups, respectively). However, these observations were not assessed as a direct substance specific delay of sexual maturation since the body weight /body weight gains in the phase until weaning were affected and moreover, the body weights were statistically significantly reduced in the observation period after weaning. Therefore, these recognised effects were considered to be a result of a general retardation of development.

In conclusion for butynediol no adverse effects on reproductive capacity and capability were revealed from a study in rats according to OECD-Guideline 415. There was neither indication for adverse impairment of male reproductive organs and of spermatology nor of female reproductive organs and of female estrous cycle. From this study a NOAEL/fertility of

500 ppm according to a mean uptake of 40 mg/kg body weight per day can be derived. Signs of developmental retardation (impaired postnatal weight gain associated with a delay in sexual maturation) were observed in the F1 progeny, however at a dose level that clearly indicated systemic toxicity in the parental animals and in their dams. Based on the findings of reduced water intake and organ weight impairment in the parental F0 animals at 80 ppm a NOAEL for general, systemic toxicity of 10 ppm according to a mean uptake of 1 mg/kg body weight per day can be derived, which is in good accordance with the NOAEL derived from the evaluation of other studies with repeated administration of butynediol (see Section 4.1.2.5).

Developmental toxicity

Butynediol was evaluated for maternal and developmental toxicity in a teratology study according to the OECD Guideline for Testing of Chemicals No. 414 in pregnant Wistar rats (BASF AG, 1995, Hellwig et al., 1997). The data from a preceding preliminary study (BASF AG 1992) were considered additionally.

Butynediol was administered (aqueous solution in doubly distilled water) at doses of 0, 10, 40, and 80 mg/kg body weight by gavage in a volume of 10 ml/kg body weight during the period of major organogenesis (gestational days 6 - 15). From the results of a preceding preliminary toxicity study on pregnant females the 80 mg/kg body weight dose level was included since it was expected to produce some overt signs of maternal toxicity.

18-22 pregnancies had been confirmed per group and the dams were monitored for food consumption, weight gain and clinical signs of toxicity during the investigation. At sacrifice on gestational day 20 gravid uterine weights, as well as number of corpora lutea, implantation sites, resorptions, fetal deaths and live fetuses were recorded for each dam. Live fetuses (222-330 per group) were examined for weight, sex, and gross morphological abnormalities. Visceral and skeletal examinations were also performed.

With the experimental conditions of this study signs of maternal toxicity were observed at the high dose level (80 mg/kg body weight) substantiated by reduced food intake (about 21% less than the controls), statistically significant loss of body weight, the intercurrent death of one dam and some clinical signs (piloerection) in another dam. All these findings were confined only to the beginning of the treatment period (gestational days 6-8). In this dose group visceral and skeletal examinations revealed no malformations. Any effects reported from this dose group were restricted to a statistically significant increase of the ratio of affected fetuses/litter with accessory 14th rib (3.9) and of the ratio of affected fetuses/litter with dilated renal pelvis and/or hydroureter (20.9) in comparison to the respective ratios of affected fetuses/litter in the concurrent controls. No such changes, however, were revealed for the occurrence of these two variations when evaluated in terms of either fetal incidence or of litter incidence. The finding of an increased ratio of affected fetuses/litter is due to uncommonly low occurrence of these variations in the concurrent controls. Incidences for accessory 14^{th} rib and for dilated renal pelvis and/or hydroureter from this study also fit to the data obtained from laboratory historical controls (see **Table 4.7**). Thus, the finding on increased ratios of affected fetuses/litter in the dose group of 80 mg/kg body weight is not considered a substance-related specific effect.

Table 4.7 Incidences of accessory 14th rib and of dilated renal pelvis and/or hydroureter in the teratology study on rats (OECD Guideline 414)

	Laboratory historical control	Test group concurrent control	Test group 80 mg/kg/day
14th rib			
Litter incidence	mean: 6.8% range: 0%-16%	0.0%	14%
Dilated renal pelvis and/or hydroureter			
Litter incidence	mean: 58.7% range: 0%-100%	9.3%	20%

At sacrifice the pregnancy rates were 100% and no substance-related impairment of gestational parameters were observed. Fetal viability was 100% and there was no impairment of fetal body weight or gross morphological appearance.

A specific embryotoxic, fetotoxic or teratogenic potential was not identified with doses up to 80 mg/kg body weight.

In the preceding preliminary study (20, 40 and 60 mg/kg bw, 5 pregnant females/group) the evaluation of the fetuses was very limited due to prior sacrifice of the dams. However, clear indications of maternal toxicity were revealed for the high dose at sacrifice on gestational day 16, while marginal indications of maternal toxicity were observed at the intermediate and low dose level.

In conclusion for butynediol no adverse effects on prenatal development were revealed from a study in rats according to OECD-Guideline 414. From this study a NOAEL/developmentaltoxicity of 80 mg/kg body weight/day can be derived. The NOAEL/maternal toxicity was 40 mg/kg body weight/day and the LOAEL/maternal toxicity was 80 mg/kg body weight/day (mortality, body weight loss, clinical signs).

4.1.2.8.2 Studies in humans

No data available

4.1.2.8.3 Conclusion

There are no human data available on toxicity for reproduction. Assessment of the available animal data from studies with rats does not indicate a specific toxic potential of butynediol adverse to reproduction and/or development including any teratogenic effects by the oral route of administration. Moreover, there are no indications for substance-related interference with spermatology and/or estrous cyclicity. Other routes of application have not been investigated. An oral NOAEL/fertility of 40 mg/kg bw/day was derived from a guideline according 1-generation study and an oral NOAEL/developmental toxicity of 80 mg/kg bw/day was derived from a study according to OECD Guideline 414.

4.1.3 Risk characterisation

4.1.3.1 General aspects

In animals butynediol is absorbed via the oral and dermal routes of exposure; absorption via the lungs is demonstrated recently in an acute inhalation toxicity study.

Specific investigations about toxicokinetic behaviour and metabolism are not available. It may be anticipated, however, that in a first mebabolic step butynediol is enzymatically activated to the corresponding aldehyde by liver alcoholdehydrogenase. Cytochrome P450-dependent metabolism can not be excluded, because a low increase of aminopyrine demethylase activity was detected.

Assessment of the available data on acute toxic effects indicate that in the rat butynediol is toxic by inhalation (LC50 of 0.69 mg/l/4 hours) and by oral ingestion and harmful following dermal absorption (LD50 values oral: 132-176 mg/kg bw, and dermal: 659-1,240 mg/kg bw). Human data on acute toxicity are not available. Butynediol has demonstrated corrosivity to skin and eyes of rabbits. Human data on local irritancy/corrosivity are not available. In man, two cases of contact allergy caused by butynediol have been described. Animal data on three Magnusson Kligman tests demonstrate that the substance shows a weak sensitisation potential. Butynediol has been classified as sensitising. There is no information available on respiratory sensitisation.

An oral 28-day study on rats revealed toxic effects on liver, kidney and hematopoietic system at doses from 10 mg butynediol/kg bw/day. The dose of 50 mg/kg bw/day caused mortality in males and females. Histopathology showed congested internal organs, pulmonary oedema and severe changes in liver and kidneys, which included diffuse hepatic parenchymal necrosis, accompanied by reactive mononuclear cells and granulocytes, fatty changes, as well as renal tubular degeneration and interstitial mononuclear cell infiltration in the kidney. An oral NOAEL of 1 mg/kg bw/day was derived from the oral 28-day study. A preliminary concern on neurotoxicity from an oral 6-month study with reduced reliability was not confirmed by the results from a 30-day inhalation study on rats that included a battery of examinations on the neurofunction and motor activity and histopathology of the nervous system.

Indications of local toxic effects on the respiratory tract were observed on 30-day liquid aerosol exposure to rats: Epithelial changes of the nasal cavity at 100 mg/m³ and above, tracheal inflammation at 25 mg/m³, and metaplasia and inflammation of the larynx at 5 mg/m³ and above. The NOAEC for systemic toxicity was 25 mg/m³; the NOAEC for local effects on the respiratory tract was 0.5 mg/m³. Inhalation exposure on 5 days to butynediol aerosol resulted also in inflammation and metaplasia of the laryngeal mucosa at concentrations of 25 mg/m³ and above. The liver and kidney were also affected by repeated inhalation exposure on 5 days at a concentration of 300 mg/m³. Additionally this concentration caused some treatment-related deaths, growth retardation and, in unscheduled deaths only, toxic effects on the spleen, thymus and gastrointestinal tract.

There is no information on the health effects in humans of repeated exposure to butynediol.

The bacterial mutation assays did not reveal a genotoxic potential. An *in vitro* chromosomal aberration assay gave an equivocal result. *In vivo*, a bone marrow micronucleus test was negative up to toxic doses. Altogether, there is no relevant concern with respect to germ cell

mutagenicity of butynediol. There are no experimental data on carcinogenicity available. Based on results of mutagenicity testing butynediol is not anticipated to be a genotoxic carcinogen.

There are no human data available on toxicity for reproduction. Assessment of the available animal data from studies with rats does not indicate a specific toxic potential of butynediol adverse to reproduction and/or development including any teratogenic effects by the oral route of administration. Moreover, there are no indications for substance-related interference with spermatology and/or estrous cyclicity. An oral NOAEL/fertility of 40 mg/kg bw/day was derived from a one-generation study according OECD Guideline 415 and an oral NOAEL/developmental toxicity of 80 mg/kg bw/day was derived from a study according to OECD Guideline 414.

4.1.3.2 Workers

4.1.3.2.1 Introduction to occupational risk assessment

Butynediol is a solid substance with a vapour pressure of < 1 Pa at 20°C. Approximately 98% of butynediol is used as a chemical intermediate in manufacturing companies. About 2% of butynediol are sold in the form of flakes and as an aqueous solution for the production of further chemicals. The occupational exposure scenarios have been described and discussed in Section 4.1.1.3. Exposure routes to be considered at the workplace are inhalation (dust, aerosols and vapour) and skin contact to the solid substance (flakes) and to butynediol solutions. In case of ranges of shift average exposure levels (see **Table 4.2**), the upper boundary of the given exposure range is taken forward to risk characterisation.

The toxicological data on butynediol are described and discussed in Section 4.1.2. Quantitative human toxicity data is not available, thus risk estimations are based on animal data. The experimental threshold levels identified in the hazard assessment part of the report are taken forward to occupational risk assessment. The toxicological profile of butynediol is essentially determined by its local toxicity (skin sensitisation, respiratory tract irritation, skin and eye irritation/corrosivity).

Considerations on oral, inhalative and dermal absorption

In order to calculate internal body burdens and internal NAELs, the percentage of absorption via different routes of exposure has to be established.

Toxicokinetic data for the assessment of oral, dermal and inhalative absorption of butynediol are not available. Butynediol was tested orally and by inhalation; dermal toxicity studies with repeated exposure were not performed.

Dermal LD50 values are about 5 times higher than the oral LD50 values. The partition coefficient (log Pow) of butynediol is approximately –1. These data seem to indicate a dermal absorption of butynediol lower than oral absorption. However, because there are various limitations in using LD50 values for the assessment of relative oral and dermal absorption percentages, these data will not be used quantitatively for butynediol risk assessment.

Preliminary assessment of oral versus inhalative absorption percentages might be based upon relative toxic potency in oral and inhalation studies. Subacute inhalation testing of butynediol

resulted in a systemic NOAEC of 25 mg/m³ (higher doses not tested). It has to be expected that relevant systemic toxicity occurs at concentrations above 25 mg/m³, because rat exposure to 300 mg/m³ for 5 days caused lethality and severe toxic effects in different organs/tissues. 25 mg/m³ corresponds to an intake by inhalation of 7.2 mg/kg/day (rat respiratory rate of 0.8 l/min/kg, 6 hours/day). The oral rat LOAEL (subacute toxicity study) to be compared with is 10 mg/kg/day. Based on this comparison of oral and inhalation intake in mg/kg/day the oral route of exposure seems to be a little more potent than the inhalation route. With the assumption that inhalation toxicity starts immediately beyond the NOAEC of 25 mg/m³, a clear difference in relative potency cannot be deduced.

Against the background of these toxicity data, it is proposed to base butynediol risk assessment on the assumption of similar absorption percentages for all three routes of application (oral, inhalation, dermal). For corresponding calculations of internal doses, for all routes of exposure 100% absorption is assumed.

Regarding repeated dose toxicity, it is proposed to base dermal risk assessment on the inhalation data rather than on the oral data. As outlined above, a clear difference in relative potency (comparison of subacute oral and inhalation adverse effect levels) cannot be deduced. In the subacute oral rat study a dose ten times lower than the LOAEL was tested. Thus the oral NOAEL of 1 mg/kg/day might be relatively low because of the dose scaling used. In addition, the kinetics of absorption and bioavailability, by theoretical reasons, is assumed to be more similar for the inhalation and dermal route than for the inhalation and oral (by gavage) route.

Occupational exposure levels and internal body burden

In **Table 4.8** the route-specific external exposure data are summarised. For both routes of exposure, the frequency of exposure is explicitly indicated. For those scenarios with long-term exposure via both routes of exposure the internal body burden (assuming 100% absorption for all routes of exposure) is calculated.

The highest exposure level with daily frequency of exposure by inhalation is reported to be 1 mg/m³ for Scenario 2. For dermal exposure, the highest exposure level with daily frequency is calculated to be 13 mg/person/day for Scenario 1. For Scenario 4 much higher dermal exposure levels are calculated (143 mg/p/day); for this scenario however, 30 isolated days of exposure per year are assumed which is considered to be some sort of ‘repeated acute exposure’.

Table 4.8 Occupational exposure levels and internal body burden

Area of production and use			Inhalation		Dermal		Internal body burden [1] forrepeated exposure in mg/p/day		
			Shift average in mg/m³	Frequency of exposure	Shift average in mg/p/d	Frequency of exposure	Inhalation	Dermal	Combined
Production and further processing									
1	Large-scale chemical industry (vapour/ 34% solution)		0.04	daily	13	daily	0.4	13	13.4
2	Large-scale chemical industry, flakes, with LEV		1	daily	42	occasional	-	-	-
Further processing to formulations									
3 a/b	Preparation of formulations (dust)	a) + LEV	0.14	30 days/year	42	occasional	-	-	-
		b) - LEV	0.6	30 days/year			-	-	-
4	Preparation of formulations (vapour / 34% solution)		0.04	30 days/year	143	30 days/year	-	-	-
Use of formulations									
5	Acid pickling processes (content: 0.5%, corrosive because other ingredients) (aerosol)		0.12	daily	0.21	occasional	-	-	-
6	Acid pickling processes (vapour/ 0.5% solution, corrosive because other ingredients)		0.04	daily	0.21	occasional	-	-	-
7	Ni-plating (content: 0.03%) (aerosol)		0.002	daily	0.13	daily	0.02	0.13	0.15
8	Ni-plating (vapour/ 0.03% solution)		0.04	daily	0.25	12d/y	-	-	-
9	Organic paint removers (vapour/ 10% solution) corrosive because other ingredients		0.04	daily	4.2	occasional	-	-	-
10	Acidic solutions for the removal of scale (industrial area) (vapour/ 0.2% solution)		0.04	occasional	0.84	occasional	-	-	-
11	Acidic solutions for the removal of rust (industrial area) (vapour/ 0.2% solution)		0.04	daily	0.84	daily	0.4	0.84	1.24
12	Acidic solutions for the removal of scale (skilled trade) (vapour/ 0.2% solution)		0.04	occasional	4.2	occasional	-	-	-
13	Acidic solutions for the removal of rust (skilled trade) (vapour/ 0.2% solution)		0.04	daily	4.2	daily	0.4	4.2	4.6

1) Based on the assumption of 100% inhalative and dermal absorption; breathing volume of 10 m3 per shift

Physiological default values

- Body weight, rat 250 g
- Body weight, worker 70 kg
- Respiratory rate, rat at rest 0.8 l/min/kg
- Respiratory rate, worker at rest 0.2 l/min/kg
- Respiratory volume of worker during 8 hours at rest 6.7 m³
- Respiratory volume of worker during 8 hours of light activity 10 m³

Calculation of MOS values

MOS values are calculated as quotient of experimental NOAEL (or LOAEL) from animal or human studies and workplace exposure levels. If the route of application in animal or human studies is different from the actual occupational exposure the dose units of the experimental and exposure data have to be adapted previously to the MOS calculation. As result of this adaptation a "starting point" for the MOS calculation is identified.

The exposure routes considered in occupational risk assessment are inhalation and dermal contact. The MOS values for exposure by each route are considered separately.

The combined MOS-value is calculated as quotient of the internal NAEL (i.e. the external NOAEL multiplied with the percentage of absorption) and total internal body burden.

For scenarios with **conclusion (ii)** for both of the relevant exposure routes, the significance of the MOS for combined exposure is considered. Combined MOS values are not routinely calculated for scenarios where **conclusion (iii)** has been drawn for either or both of the exposure routes separately, as the possible concerns are already identified for the specific route of exposure.

Evaluation of MOS values

For various toxicological endpoints risk evaluation is mainly based on MOS values. In order to get consistent conclusions for different chemicals substance-specific adjustment factors are taken into account. Firstly scientifically based adjustment factors are used for the extrapolation of animal data to the worker population. Secondly, the uncertainties in the specific calculations are weighed by expert judgement and expressed as an additional "uncertainty factor".

Risk assessment based on MOS values implies the identification of a minimal MOS as decision mark between **conclusion (ii)** and **(iii)**. The value of the minimal MOS results from the multiplicative combination of different adjustment factors and the uncertainty factor. These factors may be different for each toxicological endpoint. If the MOS value for a certain exposure scenario is below the minimal MOS, the corresponding risk situation is considered to be of concern. A MOS value higher than the minimal MOS indicates no concern.

This decision making process is identical to the following consideration: Division of the starting point for the MOS calculation by the minimal MOS results in a dose level which by direct comparison with the occupational exposure levels may serve as trigger for decisions. Concern has to be reached for scenarios above that trigger value which, in the context of the risk assessment report, may be called 'critical exposure level'.

Interspecies extrapolation

Experimental and human butynediol data allowing for the assessment of interspecies differences are not available. As default method, interspecies extrapolation for butynediol relies upon the concept of metabolic rate scaling. For inhalation exposure, this principle implies that a specific inhalation exposure level (in mg/m³) is toxicologically equivalent in rats and humans (if the duration of exposure and the status of physiological activity is identical). For interspecies extrapolation of oral or dermal data metabolic rate scaling results in 4-times lower effective dose levels in humans (in mg/kg/day) compared to rats.

Adjustment for breathing volumes

When using an experimental NOAEC in mg/m³ the following consideration is essential for worker risk assessment: In subacute/subchronic inhalation studies rats are routinely exposed for 6 hours per day; the respiratory minute volume for the rat is assumed to be 0.8 l/min/kg. Metabolic rate scaling implies that the human NAEL (in mg/p/day) is calculated based on a daily exposure of 6 hours, a human respiratory rate of 0.2 l/min/kg (which is determined by the scaling model) and the experimental NOAEC in mg/m³. Thus, the metabolic rate scaling model determines the human NAEL (in mg/p/day). A breathing rate of 0.2 l/min/kg for 6 hours is identical to a breathing volume of 5 m³ for a person of 70 kg. That implies a human NAEL (in mg/p/day) that results from the NOAEC in mg/m³ multiplied with 5 m³.

For risk characterisation purposes however, a daily breathing volume of 10 m³ is assumed for workers (8 hour exposure and light activity). According to Haber's law the toxicological consequence of breathing 10 m³ is different from breathing 5 m³ of the same contaminated air. Thus, for evaluation of MOS values, based on the experimental NOAEC (rat, 6 hours per day) and assuming a human breathing volume of 10 m³, a factor of 2 is used for adjustment for breathing volumes.

Duration adjustment

From substance-specific data for various chemicals it is known, that the duration of a toxicology study may significantly influence the NOAEL. Longer study duration frequently implies a lower NOAEL. Based on average values, duration adjustment for systemic effects for subacute to chronic exposures uses the default factor of 6; duration adjustment for subchronic to chronic exposure is accounted for with a factor of 2 (Kalberlah and Schneider, 1998).

For substances causing respiratory tract effects by inhalation a separate evaluation of duration dependency of threshold levels was performed. Duration adjustment factors identified for these local effects are comparable to those for systemic effects (Kalberlah et al., 1999).

For butynediol, experimental data do allow for a substance-specific discussion of duration adjustment. Thus, for butynediol, the default factors for local and systemic effects are modified (see next Sections).

Duration adjustment for systemic effects

There are two toxicity studies with oral application, which may be compared in order to get information on a decrease of the systemic threshold level with longer duration of exposure. In the subacute oral toxicity study (Wistar rat, by gavage) a NOAEL of 1 mg/kg/day and a LOAEL of 10 mg/kg/day (liver, spleen) is reported. In the one-generation fertility study

(Wistar rat, drinking water) exposure of parental animals include a premating period of at least 76 days and a mating period of up to 14 days. The NOAEL for parental animals in that study with subchronic exposure conditions is 1 mg/kg/day, the LOAEL is 7.6 mg/kg/day (liver, kidney). Comparison of the dose-response relationship of both studies does not indicate a substantial change of the subacute and subchronic threshold level.

Butynediol toxicity was investigated by inhalation in three studies with exposure durations of 1, 2 and 4 weeks. The dose levels of butynediol tested were not set in a way to derive clear threshold levels. Thus these inhalation studies are not as suitable for giving information on duration dependency of systemic toxicity as the oral studies.

For systemic effects, similar threshold levels for subacute and subchronic exposure are assumed. The default duration factor for subchronic versus chronic exposure is 2. Because there are differences of the experimental design of the subacute and the one-generation study leaving some uncertainties in the evaluation of duration dependency, it is proposed at least to use the subchronic/chronic duration factor of 2 for the assessment of chronic exposure scenarios.

Duration adjustment for local effects by inhalation

Butynediol data on portal-of-entry effects in the respiratory tract do indicate that the default duration adjustment factor of 6 should not be used. The critical adverse effect near the threshold levels of the 1, 2 und 4 week inhalation studies is larynx inflammation and metaplasia. Comparing the toxic effects to the larynx for the 1, 2 and 4 week study for the relatively high dose level of 25 mg/m³, there is a clear indication, at least for that period of exposure duration, that the degree of severity does not increase with longer duration of exposure. In the one-week study, changes were graded slight to moderate, in the two- and four-week study the corresponding changes were graded minimal to slight. The LOAEC of 5 mg/m³ (larynx) and the NOAEC of 0.5 mg/m³ are identical for the two-week and the four-week study. Because the changes in the larynx were graded minimal to slight at the LOAEC of 5 mg/m³ and progression of the severity of effects to the larynx does not seem to occur at 25 mg/m³, and because the NOAEC experimentally tested is one order of magnitude lower than the LOAEC, it is proposed to use the experimental NOAEC of 0.5 mg/m³ from the subacute rat inhalation study for chronic exposure situations as well. Based on these considerations the duration adjustment factor for local effects by inhalation is proposed to be 1.

Intraspecies extrapolation

There are no substance-specific data which allow quantifying possible sensitivity differences within workers. For evaluation of MOS values, a specific intraspecies extrapolation factor is not used. To a certain extent the aspect of human variability might be covered by the uncertainty considerations introduced into the risk evaluation.

Uncertainty considerations

The adjustment factors outlined (route-to-route extrapolation, species extrapolation including adjustment for breathing rates, duration adjustment) either rely upon general knowledge in the toxicology of chemicals or on substance-specific data. They are intended to be ‘central tendency’ point estimates. The multiplicative combination of these factors is supposed to result in an overall ‘central tendency’ point estimate as well.

Actual risks may be less or more pronounced than estimated. Because of the limited degree of confidence in many experimental data a further numerical adjustment factor is deemed necessary to account for the degree of scientific uncertainty. This degree of scientific uncertainty may vary from chemical to chemical. This uncertainty factor may be different for each toxicological endpoint and may account for several aspects, which by their nature are not easy to quantify (e.g. the reliability of the data base, the biological relevance of the observed effects, the slope of the dose response curve or the variability of the human population). To give some orientation, it is proposed to use an uncertainty factor of about 5 when starting risk assessment based on toxicity data from a subacute oral study. The uncertainty factor may be lower in case of additional relevant data (human data available, route-to-route extrapolation not necessary) or in case of adverse effects that are not considered severe. The uncertainty factor usually is higher than 5 in case of specific reprotoxicity. By experience, uncertainty factors between 1 and 10 have been chosen for different risk situations.

4.1.3.2.2 Acute toxicity

Acute inhalation toxicity

Acute inhalation toxicity of butynediol was tested for the liquid aerosol of an aqueous solution. The LC50 (4 hours) for male and female rats was estimated to be 690 mg/m³. At 260 and 320 mg/m³ (lowest concentrations tested) clinical examination revealed some signs of respiratory tract irritation and of general toxicity. No mortality occurred at these concentrations.

To be more confident about the evaluation of acute systemic risks by inhalation, cross-checking of acute toxicity data against repeated dose toxicity data might be helpful. In the 5-day dose finding inhalation study (BASF 1997) the NOAEC for systemic effects is reported to be 100 mg/m³. In the subacute inhalation study (BASF 1998) no systemic toxic effects were seen at 25 mg/m³.

Acute systemic effects were not detected at the experimental exposure level of 100 mg/m³. For Scenario 2, the workplace scenario with the highest exposure level by inhalation (1 mg/m³) the MOS value of 100 is calculated. Based on the magnitude of this lowest MOS of 100 for the various exposure scenarios, additionally taking into account the conclusions for repeated dose toxicity (systemic effects) **conclusion (ii)** is reached without further discussion of possible adjustment factors. **Conclusion (ii)**.

Acute dermal toxicity

The dermal LD50 value for rats was estimated to be ≥ 659 mg/kg. Liquid preparations, but not the solid substance caused mortality when applied dermally. For calculation of direct MOS values, the dermal LD50 of 659 mg/kg is multiplicated with a human body weight of 70 kg (46,130 mg/person).

Based on the dermal LD50 as starting point of risk assessment, a minimal MOS of about 100 might be appropriate (factor 4 for metabolic rate scaling, factor 5 for the extrapolation of the LD50 to an anticipated dose without lethality, an additional uncertainty factor of 5).

The highest dermal exposure level of 14.3-143 mg/person/day is calculated for the preparation of formulations (34% solution, Scenario 4). This dermal exposure is assessed for

the unprotected worker in application of the EASE model. The lowest MOS, based on the upper range of the EASE estimate, calculates to 323. Based on the proposal of a minimal MOS of 100 and taking into account that the upper range of the EASE estimate is used for the calculation of MOS and that dermal absorption at high dose levels might be lower than assumed, there seems to be no concern for acute dermal toxicity for all exposure scenarios. **Conclusion (ii)**.

Acute risks by combined exposure

Scenario 4 is the exposure scenario with the highest dermal exposure level (see Section before). This scenario which describes the preparation of a 34% solution of butynediol is the scenario with the highest internal body burden as well. However, it has to be recognised that the contribution of inhalation exposure to the internal body burden is minimal (0.4 mg/p/day by inhalation compared to 143 mg/p/day by dermal contact). Therefore, no additional concern for combined exposure is indicated. **Conclusion (ii)**.

4.1.3.2.3 Irritation/Corrosivity

Acute Respiratory Tract Irritation

In an acute inhalation toxicity test signs of respiratory tract irritation were detected at 260 mg/m³ (lowest concentration tested). In a 5-day dose-finding study (BASF 1997) 25 mg/m³ (lowest concentration tested) caused local respiratory effects (larynx inflammation and metaplasia). The subacute NOAEC for local effects in the respiratory tract is 0.5 mg/m³, the corresponding LOAEL with marginal to slight effects is 5 mg/m³. For acute inhalation, this level of 5 mg/m³ might be very near to the NAEC for local effects; this value is taken forward to risk assessment.

For the evaluation of MOS values for acute respiratory tract irritation (see **Table 4.9**) two adjustment factors are used. A factor of 2 is proposed to reflect 8-hour exposure and light activity of workers compared to the conditions of the experimental rat study. Because the no effect level for acute respiratory tract irritation is not experimentally verified, and thus there is some remaining uncertainty that the starting point of 5 mg/m³ is a clear NAEC, an additional uncertainty factor of 2 seems adequate. Based on these considerations a minimal acceptable MOS of 4 is proposed for acute irritation by inhalation. The corresponding critical exposure level is about 1 mg/m³.

The highest exposure level of 1 mg/m³ (Scenario 2) results in the lowest MOS of 5; for this borderline situation concern is indicated. For the remaining scenarios no concern is derived. **Conclusion (iii)** for Scenario 2.

Dermal and Eye Irritation/Corrosivity

Butynediol itself is a corrosive substance. Based on interpretation of available data, the EU classification and labelling working group agreed on specific concentration limits for butynediol: Concentrations of greater than 50% are considered to be corrosive, concentrations between 25% and 50% are assumed to be irritant to skin and eye.

In some areas of production and use (Scenarios 2, 3, 5, 6, and 9) handling of corrosive material is assumed; either because of butynediol in its undiluted form or because of other

corrosive ingredients. It is practical experience that exposure to corrosive materials is avoided to a large extent. Potential exposure to corrosive substances is anticipated to occur only occasionally. Daily repeated skin contact to corrosive preparations will be avoided by various control measures including personal protective equipment (gloves, eye protection). If the required protection (based on current R34 classification) is strictly adhered to, **conclusion (ii)** for corrosivity is justifiable.

A solution with 34% of butynediol is considered to be irritating to skin and eyes. It cannot be excluded that there is repeated non-proper handling of this solution (Scenario 1 and 4) resulting in skin and eye exposure. Therefore, it is concluded that handling of these solutions is of concern for workers with regard to eye and skin irritation. However, if the required protection (based on current R36/38 classification) is strictly adhered to, **conclusion (ii)** for skin and eye irritation is justifiable.

4.1.3.2.4 Sensitisation

Skin Sensitisation

It can be concluded from results of three Magnusson Kligman tests that butynediol possesses a weak skin sensitisation potential. Based on the human experience showing some cases of contact allergy at the workplace butynediol has been classified and labelled as a skin sensitiser; the general concentration limit of 1% for skin sensitisation was considered adequate for butynediol. Against that background of information concern is derived for all dermal exposure scenarios with a butynediol concentration greater than 1%. **Conclusion (iii)** for Scenarios 1, 2, 3, 4 and 9.

Respiratory Sensitisation

There are no animal data available on respiratory sensitisation. For preliminary risk assessment butynediol is not suspected to be a respiratory sensitiser, thus corresponding risk due to inhalation exposure is not considered to be of concern. **Conclusion (ii)**.

4.1.3.2.5 Repeated dose toxicity

Wistar rats were exposed (head-nose) to liquid aerosol of an aqueous solution of butynediol (99.5%) for 6 hours per day, 5 days per week (BASF 1997 and 1998). There was a dose-finding study with exposure for 5 days. In the main study half of the animals was examined after 10 exposures (15-day study), the other half was examined after 20 exposures (30-day study). In addition to the standard investigations, neuropathology examinations were performed. The target concentrations were 0.5, 5 and 25 mg/m³. Butynediol inhalation did not induce systemic effects at the concentrations tested. Thus the NOAEC for systemic toxicity is 25 mg/m³. Due to minimal to slight laryngeal metaplasia and inflammation at concentrations of 5 mg/m³ and above, the NOAEC for local effects on the respiratory tract is 0.5 mg/m³.

Local effects by repeated inhalation

The NOAEC for local effects on the respiratory tract taken forward to risk assessment is 0.5 mg/m³ (subacute rat inhalation study).

Factors to be taken into account during MOS evaluation are (for explanation see introductory Sections): A factor of 2 is used for adjustment for breathing volumes. A factor of 1 is chosen for duration adjustment. There is a dose difference of one order of magnitude between the NOAEC and LOAEC; furthermore, there are only minimal to slight local effects at the LOAEC of 5 mg/m³ and at 25 mg/m³. Thus the actual NAEC might be higher than the experimental NOAEC. This aspect is taken into account with an adjustment factor of ½. Additionally there is an overall uncertainty factor of 3, which is lower than 5 beyond the background that route-to-route extrapolation is not necessary.

Thus, the minimal MOS calculates to 3 (2 · ½ · 3). Based on the starting point of 0.5 mg/m³ as NOAEC used for the calculation of MOS values, the corresponding 'critical exposure level' at the workplace is about 0.2 mg/m³.

Table 4.9, which is designed for risk assessment for both acute and repeated exposure, contains all exposure levels, irrespective of frequency of exposure. MOS values calculated for local effects by repeated inhalation range from 0.5 up to 250. Based on the proposed minimal acceptable MOS of 3 the exposure Scenarios 2 and 3b are considered to be of concern. In both scenarios, the exposure level of butynediol dust leads to concern. **Conclusion (iii)** for Scenarios 2 and 3b.

Table 4.9 Local effects by inhalation

			Acute exposure			Repeated exposure	
Starting point for MOS calculation			5 mg/m³			0.5 mg/m³	
Minimal MOS			4			3	
Critical exposure level			1 mg/m³			0.2 mg/m³	
			EXPOSURE (mg/m³)	MOS	CONCLUSION	MOS	CONCLUSION
Production and further processing							
1	Large-scale chemical industry (vapour/ 34% solution)		0.04	125		12.5	
2	Large-scale chemical industry, flakes, with LEV		1	5	iii	0.5	iii
Further processing to formulations							
3a/b	Preparation of formulations (dust)	a) + LEV	0.14	36		3.6	
		b) - LEV	0.6	8.3		0.8	iii
4	Preparation of formulations (vapour / 34% solution)		0.04	125		12.5	
Use of formulations							
5	Acid pickling processes (content: 0.5%, corrosive because other ingredients) (aerosol)		0.12	42	ii for all other scenarios	4.2	ii for all other scenarios
6	Acid pickling processes (vapour/ 0.5% solution, corrosive because other ingredients)		0.04	125		12.5	
7	Ni-plating (content: 0.03%) (aerosol)		0.002	2500		250	
8	Ni-plating (vapour/ 0.03% solution)		0.04	125		12.5	
9	Organic paint removers (vapour/ 10% solution) corrosive because other ingredients		0.04	125		12.5	
10	Acidic solutions for the removal of scale (industrial area) (vapour/ 0.2% solution)		0.04	125		12.5	
11	Acidic solutions for the removal of rust (industrial area) (vapour/ 0.2% solution)		0.04	125		12.5	
12	Acidic solutions for the removal of scale (skilled trade) (vapour/ 0.2% solution)		0.04	125		12.5	
13	Acidic solutions for the removal of rust (skilled trade) (vapour/ 0.2% solution)		0.04	125		12.5	

Systemic effects by repeated inhalation exposure

Based on the subacute inhalation study in rats the NOAEC of 25 mg/m³ is used for calculation of MOS values for systemic effects. It has to be expected that relevant systemic toxicity occurs at concentrations above 25 mg/m³, because rat exposure to 300 mg/m³ for 5 days caused lethality and severe toxic effects in different organs/tissues.

For evaluation of MOS values adjustment factors may be taken into account (for explanation see introductory Sections): A factor of 2 accounts for adjustment of breathing volumes. The factor for duration adjustment is proposed to be 2. It is proposed to use an overall uncertainty factor of 3, which is lower than 5 because there is no need for route-to-route extrapolation.

Multiplication of these factors results in an overall factor of 12, which is identical to the minimal MOS. The 'critical exposure level' that triggers concern is about 2 mg/m³. This 'critical exposure level' is one order of magnitude higher than the corresponding level for local effects by repeated inhalation.

Table 4.10 only contains the exposure levels for those areas of production and use, for which a long-term (daily) exposure is assumed (for details of frequency of exposure see **Table 4.8**). It may be helpful to recognise, that exposure levels for occasional or intermittent exposure are lower than the highest exposure level for daily frequency of exposure. Based on the minimal acceptable MOS of 12 there is no exposure scenario that leads to concern. The highest inhalation exposure level is 1 mg/m³ (Scenario 2), resulting in the lowest MOS of 25 for systemic effects by repeated inhalation. **Conclusion: (ii)**.

Systemic effects by repeated dermal contact

Experimental studies with repeated dermal exposure to butynediol are not available. Dermal risk assessment is based upon the subacute inhalation data (see Section 'considerations on oral, inhalative and dermal absorption'). Thus, the starting point for calculation of MOS values is based upon the subacute NOAEC of 25 mg/m³ (6 hours/day).

25 mg/m³ corresponds to an intake by inhalation of 7.2 mg/kg/day (respiratory rate of 0.8 l/minutes/kg for the rat, 6 hours/day). Assuming a human body weight of 70 kg, a NAEL of 504 mg/p/day is calculated as starting point for dermal risk assessment.

For the evaluation of MOS values, the following factors are proposed: A factor of 4 is used for metabolic rate scaling. For duration adjustment a factor of 2 is taken. The default uncertainty factor is 5. An overall assessment factor of 40, which is identical to the minimal MOS, is calculated.

Table 4.10 only contains the dermal exposure levels for those areas of production and use, for which a long-term (daily) exposure is assumed (for details of frequency of exposure see **Table 4.8**). The most critical dermal exposure scenario with a daily frequency of exposure of 13 mg/person/day is Scenario 1 (production of the 34% solution of butynediol in the large-scale chemical industry; regular, but non-proper use of suitable gloves, upper value of EASE estimate). This exposure level is considered to be a borderline situation. Because there is some evidence that bioavailability following dermal contact might be somewhat lower than by inhalative or oral exposure, it is proposed not to derive concern for this and all other dermal exposure scenarios with daily frequency of exposure. Higher levels of exposure (42 mg/p/day and 143 mg/p/day) are reported for Scenarios 2, 3 und 4. Because of a low frequency of exposure (see **Table 4.8**) for these exposure scenarios repeated dose toxicity is not anticipated to occur. **Conclusion (ii)**.

Local effects by repeated dermal contact

For butynediol specific experimental data on local effects by repeated dermal contact are not available. It is not known, whether and to what extent prolonged exposure to butynediol preparations changes the degree and incidence of skin and eye irritancy. If the required protection (based on current R36/38 classification) is strictly adhered to, **conclusion (ii)** for skin and eye irritation by repeated dermal contact seems to be justifiable.

Repeated dose toxicity (Combined exposure)

For the toxicological evaluation of the total internal body burden (which is caused by inhalation and dermal contact) it is proposed to rely upon the inhalation toxicity data as well (see Section 'considerations on oral, inhalative and dermal absorption'). The relevant NOAEC from the subacute rat inhalation study is 25 mg/m³.

The inhaled amount of the substance, using the rat respiratory minute volume of 0.8 l/minutes/kg and the exposure duration of 360 minutes/day calculates to 7.2 mg/kg/day. Multiplication of this rat NOAEL with a human body weight of 70 kg results in a NAEL of 504 mg/p/day. Because of the assumption of 100% absorption by all routes of exposure, this external NAEL is used as internal NAEL as well. The internal NAEL of 504 mg/p/day is taken forward to the calculation of combined MOS values.

Combined MOS values (see **Table 4.10**) were calculated by dividing the internal NAEL of 504 mg/p/day by the internal body burden for the exposure Scenarios 1, 7, 11 and 13; the same decision criteria as for repeated dermal exposure are used. Again, Scenario 1 is a borderline situation. However, because there is no substantial contribution of inhalation exposure to internal body burden (0.4 mg/p/day versus 13 mg/p/day for dermal contact) no specific concern is derived for this and the other scenarios for combined exposure. **Conclusion (ii)** for all scenarios.

Table 4.10 Repeated dose toxicity, systemic effects

			Inhalation			Dermal			Combined		
Starting point for MOS calculation			25 mg/m³			504 mg/p/day			504 mg/p/day		
Minimal acceptable MOS			12			40			40		
Critical exposure level			2 mg/m³			12.6 mg/p/day			12.6 mg/p/day		
			Exposure (mg/m³)	MOS	Conclusion	Exposure (mg/p/day)	MOS	Conclusion	Exposure (mg/p/day)	MOS	Conclusion
Production and further processing											
1	Large-scale chemical industry (vapour/ 34% solution)		0.04	625		13	39		13.4	38	
2	Large-scale chemical industry, flakes, with LEV		1	25							
Further processing to formulations											
3 a/b	Preparation of formulations (dust)	a) + LEV									
		b) - LEV									
4	Preparation of formulations (vapour / 34% solution)										
Use of formulations											
5	Acid pickling processes (content: 0.5%, corrosive because other ingredients) (aerosol)		0.12	208	ii for all scenarios			ii for all scenarios			ii for all scenarios
6	Acid pickling processes (vapour/ 0.5% solution, corrosive because other ingredients)		0.04	625							
7	Ni-plating (content: 0.03%) (aerosol)		0.002	12,500		0.13	3,880		0.15	3,360	
8	Ni-plating (vapour/ 0.03% solution)		0.04	625							
9	Organic paint removers (vapour/ 10% solution) corrosive because other ingredients		0.04	625							
10	Acidic solutions for the removal of scale (industrial area) (vapour/ 0.2% solution)										
11	Acidic solutions for the removal of rust (industrial area) (vapour/ 0.2% solution)		0.04	625		0.84	600		1.24	406	
12	Acidic solutions for the removal of scale (skilled trade) (vapour/ 0.2% solution)										
13	Acidic solutions for the removal of rust (skilled trade) (vapour/ 0.2% solution)		0.04	625		4.2	120		4.6	110	

4.1.3.2.6 Mutagenicity

In vitro, butynediol showed no genotoxic potential in a bacterial gene mutation test; an equivocal finding, neither positive nor negative was obtained with regard to induction of chromosomal aberrations. *In vivo*, a bone marrow micronucleus test was negative for doses up to the toxic range. There is no relevant concern with respect to germ cell mutagenicity. Corresponding risks at the workplace are not anticipated to occur. **Conclusion (ii)**.

4.1.3.2.7 Carcinogenicity

There are no carcinogenicity data available. Based on results of mutagenicity testing butynediol is not anticipated to be a genotoxic carcinogen. No concern is derived. **Conclusion (ii)**.

4.1.3.2.8 Toxicity for reproduction

Fertility Impairment and Developmental toxicity

Butynediol does not cause fertility impairment in a one-generation study in rats (drinking water). There were neither indications for adverse effects to male reproductive organs and spermatology nor to female reproductive organs and female estrous cycle. From this study a NOAEL for fertility impairment of 40 mg/kg/day (dose levels tested: 1, 7.6 and 40 mg/kg/day) can be derived. This NOAEL for fertility impairment is clearly higher than the corresponding NOAEL for general systemic toxicity of 1 mg/kg/day which itself is in good accordance with the NOAEL derived from the evaluation of other studies with repeated administration of butynediol.

For butynediol no adverse effects on embryonic or fetal development were revealed in a prenatal toxicity study in rats. From this study a NOAEL for developmental toxicity of 80 mg/kg/day (highest dose tested) can be derived. The NOAEL for maternal toxicity was 40 mg/kg/day. There was mortality, body weight loss and clinical signs at the higher dose of 80 mg/kg/day.

Thus, a NOAEL of 40 mg/kg/day for fertility impairment and a NOAEL of 80 mg/kg/day for developmental toxicity is taken forward to risk assessment. Both NOAELs for reprotoxicity are clearly higher than the NOAEL of 7.2 mg/kg/day, which was taken as basis for the calculation of MOS values for repeated dose toxicity. Focusing on risk assessment it has to be stressed that a specific reprotoxic potential of butynediol has not been identified.

MOS values are based on that NOAELs multiplicated with a human body weight of 70 kg. Thus the starting point for MOS calculation (concerning fertility impairment) is 2,800 mg/p/day. With the assumption of 100% absorption via different routes of exposure, the latter value is identical to the internal NAEL for fertility impairment. Evaluation of MOS values is based on an overall assessment factor of 20 (factor 4 for metabolic rate scaling, factor 5 as uncertainty factor).

To get an overview on the overall risk situation, the internal NAEL for fertility impairment of 2,800 mg/p/day is compared with the highest internal body burden for butynediol. With reference to **Table 4.8** exposure Scenario 4 with an internal body burden of 143 mg/p/day is the most critical scenario. This internal body burden is exclusively caused by dermal contact.

The combined MOS value for this scenario is about 20 (2,800/143) and thus is identical to the minimal MOS. It should be recognised, that this high exposure level is the upper range of the EASE estimate and that exposure frequency is some sort of repeated acute exposure (30 days/year).

Based on available data, that do not indicate a specific reprotoxic potential of butynediol, supplemented by limited quantitative considerations, **conclusion (ii)** is reached for all exposure scenarios (route-specific and combined) for both types of reprotoxicity.

4.1.3.2.9 Summary on occupational risk assessment

For butynediol an overall **conclusion (ii)** is reached for all toxicological endpoints except for a) local effects in the respiratory tract by acute and repeated inhalation exposure and b) skin sensitisation.

Butynediol is a corrosive material; butynediol is considered to be irritating to the eye and skin in a concentration range of 25% to 50%. It is assumed that control measures exist which, if implemented and complied with, reduce the risk of skin and eye irritation/corrosivity.

Table 4.11 Endpoint-specific overall conclusions

Toxicological endpoints	Overall conclusion (ii)	Conclusion (iii) for at least one scenario
Acute inhalation toxicity	ii	
Acute dermal toxicity	ii	
Acute risks by combined exposure	ii	
Acute respiratory tract irritation		iii
Dermal and Eye irritation/ corrosivity	ii	
Skin sensitisation		iii
Respiratory sensitisation	ii	
Local effects by repeated inhalation exposure		iii
Local effects by repeated dermal contact	ii	
Systemic effects by repeated inhalation exposure	ii	
Systemic effects by repeated dermal contact	ii	
Systemic effects by combined exposure	ii	
Mutagenicity	ii	
Carcinogenicity	ii	
Reproductive toxicity: Fertility impairment and developmental toxicity	ii	

Regarding respiratory tract irritation, risk reduction measures are considered to be necessary for those exposure scenarios in which butynediol is handled as a solid substance (Scenario 2: production and further processing; Scenario 3b: further processing to formulations). Concern is expressed for repeated inhalation exposure (both scenarios) and for acute inhalation exposure (only Scenario 2). The other exposure scenarios with handling of liquid butyndiol preparations are not judged to be of concern. Based on available toxicity data, local effects in the respiratory tract are considered to be more critical than the corresponding systemic

effects. This difference in potency is visualised by the critical exposure levels of 0.2 mg/m³ for local effects by repeated exposure and of 2 mg/m³ for systemic effects.

In addition to its substantial irritation potential (skin, eye, respiratory tract) butynediol has been proved to be a weak skin sensitiser. Concern has been derived for the exposure scenarios with butynediol itself and preparations with a butynediol concentration of greater than 1%.

For the purpose of increasing the transparency and consistency of decision making **Table 4.12** ("Most critical toxicological endpoints and exposure scenarios") is introduced in the risk assessment report.

Conclusions for all occupational exposure scenarios (in the original order) are listed in **Table 4.13**.

For butynediol, occupational exposure limits are not reported. Within the context of Council Regulation 793/93 toxicological data have been generated that do allow the establishment of a health-based occupational exposure level.

Table 4.12 Most critical toxicological endpoints and exposure scenarios

			Toxicological endpoints listed in order of increasing critical exposure level		
Exposure scenarios listed in order of decreasing exposure levels		Exposure level in mg/m³	Local effects by repeated inhalation	Acute respiratory tract irritation	Systemic effects by repeated inhalation
			0.2 mg/m³	1 mg/m³	2 mg/m³
2	Production and further processing, large –scale chemical industry, flakes, with LEV	1	iii	iii	
3b	Further processing to formulations, preparation of formulations (dust) without LEV	0.6	iii		
3a	Further processing to formulations, preparation of formulations (dust) with LEV	0.14			
5	Use of formulations, acid pickling processes (content: 0.5%, corrosive because other ingredients) aerosol	0.12			
Other scenarios		< 0.05			

Table 4.13 Conclusions for all occupational exposure scenarios

Exposure Scenarios			Local effects by acute inhalation	Local effects by repeated inhalation	Sensiti-sation	Other toxico-logical endpoints
Production and further processing						
1	Large-scale chemical industry (vapour/ 34% solution)				iii	
2	Large-scale chemical industry, flakes, with LEV		iii	iii	iii	
Further processing to formulations						
3 a/b	Preparation of formulations (dust)	a) + LEV			iii	
		b) - LEV		iii		
4	Preparation of formulations (vapour / 34% solution)				iii	
Use of formulation						
5	Acid pickling processes (content: 0.5%, corrosive because other ingredients) (aerosol)		conclusion (ii) for all other scenarios	conclusion (ii) for all other scenarios		conclusion (ii) for all other scenarios
6	Acid pickling processes (vapour/ 0.5% solution, corrosive because other ingredients)					
7	Ni-plating (content: 0.03%) (aerosol)					
8	Ni-plating (vapour/ 0.03%solution)					
9	Organic paint removers (vapour/ 10% solution) corrosive because other ingredients				iii	
10	Acidic solutions for the removal of scale (industrial area) (vapour/ 0.2% solution)				conclusion (ii) for all other scenarios	
11	Acidic solutions for the removal of rust (industrial area) (vapour/ 0.2% solution)					
12	Acidic solutions for the removal of scale (skilled trade) (vapour/ 0.2% solution)					
13	Acidic solutions for the removal of rust (skilled trade) (vapour/ 0.2% solution)					

4.1.3.3 Consumers

4.1.3.3.1 Acute toxicity

Following the exposure assessment, consumers are not expected to be exposed to butynediol in the range of hazardous doses which can be derived from acute oral or dermal toxicity figures based on animal LD50 values (oral:132-176 mg/kg bw, dermal: 659-1,240 mg/kg bw). Therefore, the substance is of no concern for the consumer in relation to acute oral or dermal toxicity.

However, the inhalative route of exposure may be of concern, because in rats butynediol has demonstrated an inhalative LC50 of 0.69 mg/l/4 hours. The LC0 was 0.32 mg/l/4 hours. The margin of safety between the LC0 of 320 mg/m³ and the estimated mean event concentration for consumers using sanitary disinfectants (0.014 mg/m³) is considered to be sufficient.

Conclusion (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

4.1.3.3.2 Irritation/Corrosivity

Human data on the local irritation potential of butynediol are not available.

In animals, irritation and corrosivity have shown to be the main effects at the site of contact (skin, eyes). Skin and eyes can be severely affected on contact with the substance due to the corrosive properties. Based on the reported data, butynediol is classified as “C, corrosive” and labelled “R 34, causes burns”.

Following the exposure assessment, consumers are expected to be exposed to butynediol. Given the levels of the substance contained in consumer products it can be assumed that irritant concentrations of butynediol will not occur, especially in the diluted cleansing solutions used by consumers.

Conclusion (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

4.1.3.3.3 Sensitisation

In man, few cases of contact allergy caused by butynediol have been described. Based on the reported data, butynediol has been classified as “sensitising” and labelled with R 43 - May cause sensitisation by skin contact. The result of three Magnusson Kligman tests in animals revealed a weak sensitisation potential.

Given the low concentrations of butynediol in the diluted cleansing solutions which are below the general concentration limit of 1% for skin sensitisation it can be assumed that sensitising concentrations of the substance will not occur.

Conclusion (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

4.1.3.3.4 Repeated dose toxicity

On 30-day-inhalation exposure of rats, butynediol induced local toxic effects on the respiratory tract consisting of metaplasia and inflammation in the larynx (at ≥ 5 mg/m³), trachea (at ≥ 25 mg/m³), nasal cavity (at ≥ 100 mg/m³), and toxic effects in the liver, kidneys, thymus, spleen, stomach and forestomach indicating systemic toxic effects as well as mortality and growth retardation after repeated inhalation of concentrations of 300 mg/m³. The NOAEC for local effects on the respiratory tract was 0.5 mg/m^3, whereas a NOAEC for systemic effects of 25 mg/m³ was derived.

An oral 28-day study on rats revealed toxic effects on liver, kidney and hematopoietic system at doses from 10 mg butynediol/kg bw/day. The dose of 50 mg/kg bw/day caused mortality in males and females. A NOAEL of 1 mg/kg bw/day results from this oral 28-day study.

There was some concern on possible neurotoxicity of butynediol. However, a recent study clearly demonstrated that the concern was not supported by the findings of a 15-day/30-day inhalation study on rats.

For the decision on the appropriateness of MOS, the following aspects have been considered and taken into account:

Overall confidence in the database

The data taken into account for performing the risk characterisation have been evaluated with regard to their reliability, relevance and completeness according to Section 3.2 of the TGD (EC, 1994). The data were published in peer reviewed journals or submitted to the Competent Authority in private reports being adequately detailed and in accordance with internationally recognised guidelines and to GLP.

The findings of all studies are not contradictory so that the judgement can be based on the database.

There are no reasons to assume limited confidence.

Uncertainty arising from the variability in the experimental data

From the studies cited above only one study allows deriving a NOAEL for oral application (Jedrychowski et al., (1992b). The study was well performed and the results reported were in conformity with the findings of the other studies. Microscopic examinations of the central and peripheral nervous system, however and tests on neurofunctional disorders were not included in the study of Jedrychowski and co-workers (1992b).

From a 30-day inhalation study according OECD-Guideline 412 NOAECs for local as well as systemic effects were derived. Repeated inhalation exposure of rats on 5 days to butynediol aerosol at a concentration of 300 mg/m³ affects the liver and kidney. Additionally this concentration caused some treatment-related deaths, growth retardation and, in unscheduled deaths only, toxic effects on the spleen, thymus and gastrointestinal tract. Thus, there is conformity between the results of studies with different administration routes.

One study in rats (Knyshova, 1968) reports neurotoxic effects, however this study was judged to be of limited reliability (lack of original data). However, based on a recent study data there is at present no valid concern that butynediol can affect the nervous system.

There are no reasons to assume a special extent of uncertainty which have to be taken into account.

Intra- and interspecies variation

Specific investigations about toxicokinetic behaviour and metabolism are not available.

Therefore there is concern, which has to be expressed in the magnitude of the MOS.

The nature and severity of the effect

The effect described are effects on the respiratory tract and on liver, kidney and hematopoietic system. These effects are considered as serious health effects. Exposure related deaths occurred at 300 mg/m³ (inhalation) and at 50 mg/kg bw/day (oral route).

There are no reasons to assume that the effects shown in the animal experiments are limited to the species tested, thus being not of relevance for humans. Therefore there is concern, which has to be expressed in the magnitude of the MOS.

Dose response relationship

The LOAEC for systemic effects was 100 mg/m³. The dose of 300 mg/m³ caused mortality (hint to a steep dose-response relationship).

There is concern, which has to be expressed in the magnitude of the MOS.

Differences in exposure (route, duration, frequency and pattern)

The estimated total chronic body burden with an assumed absorption of 100% is compared with a NOAEC of 30 days duration.

There are no reasons to assume that special concern can be derived from this procedure.

The human population to which the quantitative and/or qualitative information on exposure applies

Following the exposure scenario there is no reason to assume a special risk for elderly, children or other people suffering from special diseases like obesity or persons with high bronchial reactivity. However as toxicokinetics are not known it cannot be excluded that persons suffering from liver or kidney diseases are at risk due to higher internal exposure.

Other factors

There are no other factors known which have to be considered in the interpretation of the margin of safety.

<u>MOS for inhalation exposure scenario-local respiratory effects</u>

During application of descaling agents the consumer may be exposed to a concentration of 0.007 mg/m^3 butynediol (for 10 minutes).

The margin of safety for local effects between the calculated exposure level of 0.007 mg/m³and the NOAEC for local effects of 0.5 mg/m³ is judged to be sufficient taking

into account all assumptions being applied in the exposure estimation scenario, because a worst-case calculation was performed (application of 100 g of product with a maximum content of 2% butynediol, daily frequency and short application time of 10 minutes). Moreover, the adverse effects in the larynx were graded minimal to slight at the LOAEC of a 5 mg/m³ (10-fold higher concentration as compared to the NOAEC, i.e. no steep dose response-relationship).

Conclusion (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

MOS for total exposure (dermal and inhalation) of the consumer:

Proper use of the cleansing agents/disinfectants products, car cleansing products, and descaling agents will result in a cumulative butynediol exposure (worst case) in the range of about 0.67 µg/kg bw/day.

In repeated dose toxicity studies on rats (30-day inhalation) the NOAEC for systemic effects was 25 mg/m³. The derived concentration in air is converted as follows to the inhaled amount of the substance using the respiratory minute volume 0.8 l/minute/kg and exposure duration of 360 minutes/day:

0.025 mg/l · 0.8 l/min/kg · 360 minutes/day = 7.2 mg/kg bw/day.

The margin of safety between the exposure estimate 0.00067 mg/kg bw/day and the NOAEL 7.2 mg/kg bw/day is judged to be sufficient taking in account all assumptions being applied in the exposure estimation.

Conclusion (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

4.1.3.3.5 Mutagenicity

In vitro, butynediol showed no genotoxic potential in a bacterial gene mutation test and an equivocal finding was obtained in a chromosomal aberration assay. *In vivo*, a bone marrow micronucleus test was negative up to toxic doses. There is no relevant concern with respect to mutagenicity.

Conclusion (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

4.1.3.3.6 Carcinogenicity

There are no data on carcinogenic properties of butynediol from experimental animals. Based on results of mutagenicity testing butynediol is not anticipated to be a genotoxic carcinogen.

Conclusion (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

4.1.3.3.7 Toxicity for reproduction

Following the exposure assessment consumers may be exposed to butynediol via different routes to variable amounts up to 0.00067 mg/kg bw/day.

The available animal data from studies with rats does not indicate a specific toxic potential of butynediol adverse to reproduction and/or development including any teratogenic effects by the oral route of administration. Moreover, there are no indications for substance-related interference with spermatology and/or estrous cyclicity. An oral NOAEL/fertility of 40 mg/kg bw/day was derived from a one-generation drinking water study (OECD Guideline 415) and an oral NOAEL/developmental toxicity of 80 mg/kg bw/day was derived from a study according to OECD Guideline 414. Other routes of application have not been investigated.

For the decision on the appropriateness of MOS, the following aspects regarding the critical effect as well as exposure have been considered and taken into account:

Overall confidence in the database

The data taken into account for performing the risk characterisation have been evaluated with regard to their reliability, relevance and completeness according to Section 3.2 of the TGD (EC, 1994). The data were submitted to the Competent Authority in private reports being adequately detailed and in accordance with internationally recognised guidelines and to GLP.

The findings of all studies are not contradictory so that the judgement can be based on the database (see Section 4.1.2.8).

There are no reasons to assume limited confidence.

Uncertainty arising from the variability in the experimental data

No special concerns have to be raised from this point.

Intra- and interspecies variation

There are no indications to limit the findings to a single species.

The nature and severity of the effect

Marginal effects (an increased incidence of variations) have been observed in the developmental study. However, embryo-/fetotoxicity are only present at maternally toxic doses.

Dose-response-relationship

The mentioned effects were observed at the highest dose, leading to maternal toxicity.

There is no reason to assume concern which has to be expressed in an increased MOS taking into account the exposure level.

Differences in exposure (route, duration, frequency and pattern)

Following the exposure assessment, the consumer may be exposed to butynediol via different routes.

MOS for total exposure (dermal and inhalation) of the consumer:

Reproductive toxicity - fertility

A NOAEL of 40 mg/kg bw/day was derived from a one-generation drinking water study on rats. The margin of safety between the calculated exposure level of 0.00067 mg/kg bw/day and the NOAEL (oral) of 40 mg/kg bw/day is judged to be sufficient.

Conclusion (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

Reproductive toxicity – developmental toxicity

From the gavage study on rats a NOAEL of 80 mg/kg bw/day was derived for embryo-fetotoxic effects. Thus, the margin of safety between the calculated exposure level of 0.00067 mg/kg bw/day and the NOAEL (oral) of 80 mg/kg bw/day is judged to be sufficient.

Conclusion (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

4.1.3.4 Humans exposed indirectly via the environment

Indirect exposure via the environment is calculated using two scenarios (local and regional). Following the local scenario data (at a point source) an intake of a total daily dose of 0.004 mg/kg bw/day is calculated (as a worst case). Following the data for the regional scenario, the respective figure is smaller (0.008 µg/kg bw/day).

Repeated dose toxicity

From the repeated dose toxicity study in rats (28-day oral) a NOAEL of 1 mg/kg bw/day was derived.

Comparison indirect exposure - Local scenario/NOAEL

$$\frac{\text{Indirect exposure}}{\text{NOAEL}} = \frac{0.004\ \text{mg/kg bw/d}}{1\ \text{mg/kg bw/d}}$$

Comparison indirect exposure - Regional scenario/NOAEL

$$\frac{\text{Indirect exposure}}{\text{NOAEL}} = \frac{0.000008\ \text{mg/kg bw/d}}{1\ \text{mg/kg bw/d}}$$

The margin of safety between the calculated exposure for the local as well as regional scenario and the NOAEL is judged to be sufficient. Thus, the substance is of no concern in relation to indirect exposure via the environment.

Conclusion (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

Reproductive toxicity - fertility

A NOAEL of 40 mg/kg bw/day was derived from a one-generation drinking water study on rats.

Local scenario

The margin of safety between the indirect exposure (local) of 0.004 mg/kg bw/day and the NOAEL of 40 mg/kg bw/day is judged to be sufficient.

Regional scenario

The margin of safety between the indirect exposure (regional) of 0.000008 mg/kg bw/day and the NOAEL of 40 mg/kg bw/day is judged to be sufficient.

Conclusion (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

Reproductive toxicity – developmental toxicity

From the gavage study on rats a NOAEL of 80 mg/kg bw/day was derived for embryo-/fetotoxic effects.

Local scenario

The margin of safety between the indirect exposure (local) of 0.004 mg/kg bw/day and the NOAEL of 80 mg/kg bw/day is judged to be sufficient.

Regional scenario

The margin of safety between the indirect exposure (regional) of 0.000008 mg/kg bw/day and the NOAEL of 80 mg/kg bw/day is judged to be sufficient.

Conclusion (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

4.1.3.5 Combined exposure

It is possible for an individual to be exposed to butynediol at work, from consumer products and indirectly via the environment. However, the exposure levels resulting from butynediol containing consumer products (about 0.03 µg/kg bw/day) and the levels that would be received indirectly from environmental sources (0.004 mg/kg bw/day for the local scenario (via stem) and 0.008 µg/kg bw/day via drinking water are lower as compared to different occupational exposure scenarios (see **Table 4.8**). Thus, they will not significantly contribute to the daily body burden received at work.

Therefore the conclusions reached for workers (see **Table 4.11**: Endpoint-specific overall conclusions) apply to combined exposure.

4.2 HUMAN HEALTH (PHYSICO-CHEMICAL PROPERTIES)

With regard to the physico-chemical properties and with regard to the occupational and consumer exposure described in Section 4.1.1.2 and 4.1.1.3 butynediol is not excepted to cause specific concern relevant to human health.

There is no need for further information and/or testing with regard to physico-chemical properties. **Conclusion (ii)**.

5 RESULTS

5.1 ENVIRONMENT

Conclusion (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

5.2 HUMAN HEALTH

5.2.1 Human health (toxicity)

5.2.1.1 Workers

Conclusion (iii) There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account.

Regarding respiratory tract irritation, risk reduction measures are considered to be necessary for those exposure scenarios in which butynediol is handled as a solid substance (Scenario 2: production and further processing; Scenario 3b: preparation of formulations, without LEV). Concern is expressed for repeated inhalation exposure (both scenarios) and for acute inhalation exposure (only Scenario 2).

In addition to its substantial irritation potential (skin, eye, respiratory tract) butynediol has been proved to be a weak skin sensitiser. Concern has been derived for the exposure scenarios with butynediol itself and preparations with a butynediol concentration of greater than 1%.

For butynediol, occupational exposure limits are not reported. Within the context of Council Regulation 793/93 toxicological data have been generated that do allow the establishment of a health-based occupational exposure level.

5.2.1.2 Consumers

Conclusion (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

5.2.1.3 Humans exposed via the environment

Conclusion (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

5.2.2 Human Health (risk from physico-chemical properties)

Conclusion (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

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ABBREVIATIONS

ADI	Acceptable Daily Intake
AF	Assessment Factor
ASTM	American Society for Testing and Materials
ATP	Adaptation to Technical Progress
AUC	Area Under The Curve
B	Bioaccumulation
BBA	Biologische Bundesanstalt für Land- und Forstwirtschaft
BCF	Bioconcentration Factor
BMC	Benchmark Concentration
BMD	Benchmark Dose
BMF	Biomagnification Factor
BOD	Biochemical Oxygen Demand
bw	body weight / *Bw*, *bw*
C	Corrosive (Symbols and indications of danger for dangerous substances and preparations according to Annex II of Directive 67/548/EEC)
CA	Chromosome Aberration
CA	Competent Authority
CAS	Chemical Abstract Services
CEC	Commission of the European Communities
CEN	European Standards Organisation / European Committee for Normalisation
CEPE	European Committee for Paints and Inks
CMR	Carcinogenic, Mutagenic and toxic to Reproduction
CNS	Central Nervous System
COD	Chemical Oxygen Demand
CSTEE	Scientific Committee for Toxicity, Ecotoxicity and the Environment (DG SANCO)
CT_{50}	Clearance Time, elimination or depuration expressed as half-life
d.wt	dry weight / dw
dfi	daily food intake
DG	Directorate General
DIN	Deutsche Industrie Norm (German norm)
DNA	DeoxyriboNucleic Acid
DOC	Dissolved Organic Carbon
DT50	Degradation half-life or period required for 50 percent dissipation / degradation
DT90	Period required for 90 percent dissipation / degradation
E	Explosive (Symbols and indications of danger for dangerous substances and preparations according to Annex II of Directive 67/548/EEC)

EASE	Estimation and Assessment of Substance Exposure Physico-chemical properties [Model]
EbC50	Effect Concentration measured as 50% reduction in biomass growth in algae tests
EC	European Communities
EC10	Effect Concentration measured as 10% effect
EC50	median Effect Concentration
ECB	European Chemicals Bureau
ECETOC	European Centre for Ecotoxicology and Toxicology of Chemicals
ECVAM	European Centre for the Validation of Alternative Methods
EDC	Endocrine Disrupting Chemical
EEC	European Economic Communities
EINECS	European Inventory of Existing Commercial Chemical Substances
ELINCS	European List of New Chemical Substances
EN	European Norm
EPA	Environmental Protection Agency (USA)
ErC50	Effect Concentration measured as 50% reduction in growth rate in algae tests
ESD	Emission Scenario Document
EU	European Union
EUSES	European Union System for the Evaluation of Substances [software tool in support of the Technical Guidance Document on risk assessment]
F(+)	(Highly) flammable (Symbols and indications of danger for dangerous substances and preparations according to Annex II of Directive 67/548/EEC)
FAO	Food and Agriculture Organisation of the United Nations
FELS	Fish Early Life Stage
foc	Organic carbon factor (compartment depending)
GLP	Good Laboratory Practice
HEDSET	EC/OECD Harmonised Electronic Data Set (for data collection of existing substances)
HELCOM	Helsinki Commission -Baltic Marine Environment Protection Commission
HPLC	High Pressure Liquid Chromatography
HPVC	High Production Volume Chemical (> 1000 tonnes/annum)
IARC	International Agency for Research on Cancer
IC	Industrial Category
IC50	median Immobilisation Concentration or median Inhibitory Concentration
ILO	International Labour Organisation
IPCS	International Programme on Chemical Safety
ISO	International Organisation for Standardisation
IUCLID	International Uniform Chemical Information Database (existing substances)
IUPAC	International Union for Pure and Applied Chemistry
JEFCA	Joint FAO/WHO Expert Committee on Food Additives

JMPR	Joint FAO/WHO Meeting on Pesticide Residues
Koc	organic carbon normalised distribution coefficient
Kow	octanol/water partition coefficient
Kp	solids-water partition coefficient
L(E)C50	median Lethal (Effect) Concentration
LAEL	Lowest Adverse Effect Level
LC50	median Lethal Concentration
LD50	median Lethal Dose
LEV	Local Exhaust Ventilation
LLNA	Local Lymph Node Assay
LOAEL	Lowest Observed Adverse Effect Level
LOEC	Lowest Observed Effect Concentration
LOED	Lowest Observed Effect Dose
LOEL	Lowest Observed Effect Level
MAC	Maximum Allowable Concentration
MATC	Maximum Acceptable Toxic Concentration
MC	Main Category
MITI	Ministry of International Trade and Industry, Japan
MOE	Margin of Exposure
MOS	Margin of Safety
MW	Molecular Weight
N	Dangerous for the environment (Symbols and indications of danger for dangerous substances and preparations according to Annex II of Directive 67/548/EEC
NAEL	No Adverse Effect Level
NOAEL	No Observed Adverse Effect Level
NOEL	No Observed Effect Level
NOEC	No Observed Effect Concentration
NTP	National Toxicology Program (USA)
O	Oxidising (Symbols and indications of danger for dangerous substances and preparations according to Annex II of Directive 67/548/EEC)
OC	Organic Carbon content
OECD	Organisation for Economic Cooperation and Development
OEL	Occupational Exposure Limit
OJ	Official Journal
OSPAR	Oslo and Paris Convention for the protection of the marine environment of the Northeast Atlantic
P	Persistent
PBT	Persistent, Bioaccumulative and Toxic

PBPK	Physiologically Based PharmacoKinetic modelling
PBTK	Physiologically Based ToxicoKinetic modelling
PEC	Predicted Environmental Concentration
pH	logarithm (to the base 10) (of the hydrogen ion concentration $\{H^+\}$
pKa	logarithm (to the base 10) of the acid dissociation constant
pKb	logarithm (to the base 10) of the base dissociation constant
PNEC	Predicted No Effect Concentration
POP	Persistent Organic Pollutant
PPE	Personal Protective Equipment
QSAR	(Quantitative) Structure-Activity Relationship
R phrases	Risk phrases according to Annex III of Directive 67/548/EEC
RAR	Risk Assessment Report
RC	Risk Characterisation
RfC	Reference Concentration
RfD	Reference Dose
RNA	RiboNucleic Acid
RPE	Respiratory Protective Equipment
RWC	Reasonable Worst-Case
S phrases	Safety phrases according to Annex IV of Directive 67/548/EEC
SAR	Structure-Activity Relationships
SBR	Standardised birth ratio
SCE	Sister Chromatic Exchange
SCHER	Scientific Committee on Health and Environmental Risks
SDS	Safety Data Sheet
SETAC	Society of Environmental Toxicology And Chemistry
SNIF	Summary Notification Interchange Format (new substances)
SSD	Species Sensitivity Distribution
STP	Sewage Treatment Plant
T(+)	(Very) Toxic (Symbols and indications of danger for dangerous substances and preparations according to Annex II of Directive 67/548/EEC)
TDI	Tolerable Daily Intake
TG	Test Guideline
TGD	Technical Guidance Document
TNsG	Technical Notes for Guidance (for Biocides)
TNO	The Netherlands Organisation for Applied Scientific Research
ThOD	Theoritical Oxygen Demand
UC	Use Category

UDS	Unscheduled DNA Synthesis
UN	United Nations
UNEP	United Nations Environment Programme
US EPA	Environmental Protection Agency, USA
UV	Ultraviolet Region of Spectrum
UVCB	Unknown or Variable composition, Complex reaction products of Biological material
vB	very Bioaccumulative
VOC	Volatile Organic Compound
vP	very Persistent
vPvB	very Persistent and very Bioaccumulative
v/v	volume per volume ratio
w/w	weight per weight ratio
WHO	World Health Organisation
WWTP	Wastewater Treatment Plant
Xn	Harmful (Symbols and indications of danger for dangerous substances and preparations according to Annex II of Directive 67/548/EEC)
Xi	Irritant (Symbols and indications of danger for dangerous substances and preparations according to Annex II of Directive 67/548/EEC)

Appendix A CONSEXPO report

Cleansing and disinfectants

Generated by CONSEXPO 3.0

Compound: But-2-yne-1,4-diol (CAS: 110-65-6)
Subject: person
Weight: 60.000 kg

Contact

Contact scenario:	House keeping, cleaning indoors
Parameter definition of scenario:	
Duration of contact per event:	120.000 min
Duration of actual use per event:	10.000 min
Frequency of contact:	1.000 1/day
Start of contact:	0.00e+00 min

Inhalation

Exposure

Scenario:	evaporation from mixture

Person uses product (room volume, ventilation and release area personal).

Personal volume=	5.000000 m^3.
Mean event concentration (average case):	1.408e-04 mg/m^3
Year average (average case):	1.187e-05 mg/m^3
Mean event concentration (cumulative worst case):	1.408e-04 mg/m^3
Year average (cumulative worst case):	1.187e-05 mg/m^3

Exposure estimates based on the following parameters:

Release area:	2.000 m^2
Temperature:	293.000 Kelvin
Ventilation rate:	4.000 m^3/hr
Room volume:	20.000 m^3
Weight fraction:	2.00e-02%
Molweight solvent:	18.000 g/mol

Uptake

Model:	fraction model
Average case estimate:	1.505e-01 mg/year
	6.868e-06 mg/(kg.day)
Cumulative worst case estimate:	1.505e-01 mg/year
	6.868e-06 mg/(kg.day)

Uptake estimates based on the following parameters:

Absorbed fraction:	100.000%
Inhalation rate:	24100.000 cm^3/min

Respirable fraction: 1.000 fraction

Dermal

Exposure

Scenario: fixed volume of product
Mean event concentration during use (average case): 2.000e-04 mg/cm³
Year average (average case): 1.687e-05 mg/cm³
Mean event concentration during use (cumulative worst case): 2.000e-04 mg/cm³
Year average (cumulative worst case): 1.687e-05 mg/cm³

Exposure estimates based on the following parameters:

Product density: 1.000 g/cm³
Applied product volume: 8.400 cm³
Weight fraction of compound: 2.000%
Dilution before use: 100.000 times

Uptake

Model: fraction model
Average case estimate: 6.209e-00 mg/year
2.833e-04 mg/(kg.day)
Cumulative worst case estimate: 6.209e-00 mg/year
2.833e-04 mg/(kg.day)

Uptake estimates based on the following parameters:

Absorbed fraction: 1.000%

Oral

No exposure

Total dose

Average case

(Semi)chronic dose 2.902e-04 mg/kg bw/day (year averaged)
Acute dose 2.904e-04 mg/kg bw/day of application

Cumulative worst case

(Semi)chronic dose 2.902e-04 mg/kg bw/day (year averaged)
Acute dose 2.904e-04 mg/kg bw/day of application

Car **cleansing products**

Generated by CONSEXPO 3.0

Compound:	But-2-yne-1,4-diol (CAS: 110-65-6)
Subject:	person
Weight:	60.000 kg

Contact

Contact scenario:	Cleaning car/motor bike
Parameter definition of scenario:	
Duration of contact per event:	30.000 min
Duration of actual use per event:	10.000 min
Frequency of contact:	1.000 1/week
Start of contact:	0.00e+00 min

Inhalation

Exposure

Scenario:	evaporation from mixture

Person uses product (room volume, ventilation and release area personal).

Personal volume:	5.000000 m³.
Mean event concentration (average case):	2.627e-03 mg/m³
Year average (average case):	7.911e-06 mg/m³
Mean event concentration (cumulative worst case):	2.627e-03 mg/m³
Year average (cumulative worst case):	7.911e-06 mg/m³

Exposure estimates based on the following parameters:

Release area:	0.500 m²
Temperature:	293.000 Kelvin
Ventilation rate:	1.000 m³/hr
Room volume:	5.000 m³
Weight fraction:	1.000 %
Molweight solvent:	18.000 g/mol

Uptake

Model: fraction model

Average case estimate:	1.003e-01 mg/year
	4.575e-06 mg/(kg.day)
Cumulative worst case estimate:	1.003e-01 mg/year
	4.575e-06 mg/(kg.day)

Uptake estimates based on the following parameters:

Absorbed fraction:	100.000%
Inhalation rate:	24100.000 cm³/min
Respirable fraction:	1.000 fraction

Dermal

Exposure

Scenario:	fixed volume of product
Mean event concentration during use (average case):	1.000e-02 mg/cm³
Year average (average case):	3.012e-05 mg/cm³
Mean event concentration during use (cumulative worst case):	1.000e-02 mg/cm³
Year average (cumulative worst case):	3.012e-05 mg/cm³

Exposure estimates based on the following parameters:

Product density:	1.000 g/cm³
Applied product volume:	1.000 cm³
Weight fraction of compound:	1.000%
Dilution before use:	1.000 times

Uptake

Model:	fraction model
Average case estimate:	5.280e-00 mg/year 2.409e-04 mg/(kg.day)
Cumulative worst case estimate:	5.280e-00 mg/year 2.409e-04 mg/(kg.day)

Uptake estimates based on the following parameters:

Absorbed fraction:	1.000%

Oral

No exposure

Total dose

Average case

(Semi) chronic dose 2.455e-04 mg/kg bw/day (year averaged)
Acute dose 1.698e-03 mg/kg bw/day of application

Cumulative worst case

(Semi) chronic dose 2.455e-04 mg/kg bw/day (year averaged)
Acute dose 1.698e-03 mg/kg bw/day of application

Descaling agents

Generated by CONSEXPO 3.0

Compound:	But-2-yne-1,4-diol (CAS: 110-65-6)
Subject:	person, female adult
Weight:	60.000 kg

Contact

Contact scenario:	House keeping, cleaning indoors
Parameter definition of scenario:	
Duration of contact per event:	2.000 hr
Duration of actual use per event:	10.000 min
Frequency of contact:	2.000 1/month
Start of contact:	0.00e+00 min

Inhalation

Exposure

Scenario:	evaporation from mixture

Person uses product (room volume, ventilation and release area personal).

Personal volume=	5.000000 m^3.
Mean event concentration (average case):	7.096e-03 mg/m^3
Year average (average case):	3.885e-05 mg/m^3
Mean event concentration (cumulative worst case):	7.096e-03 mg/m^3
Year average (cumulative worst case):	3.885e-05 mg/m^3

Exposure estimates based on the following parameters:

Release area:	2.000 m^2
Temperature:	293.000 Kelvin
Ventilation rate:	4.000 m^3/hr
Room volume:	20.000 m^3
Weight fraction:	1.000 %
Molweight solvent:	18.000 g/mol

Uptake

Model: fraction model

Average case estimate:	4.925e-01 mg/year
	2.247e-05 mg/(kg.day)
Cumulative worst case estimate:	4.925e-01 mg/year
	2.247e-05 mg/(kg.day)

Uptake estimates based on the following parameters:

Absorbed fraction:	1.000 fraction
Inhalation rate:	24100.000 cm^3/min
Respirable fraction:	1.000 fraction

Dermal

Exposure

Scenario:	fixed volume of product
Mean event concentration during use (average case):	1.000e-02 mg/cm³
Year average (average case):	5.476e-05 mg/cm³
Mean event concentration during use (cumulative worst case):	1.000e-02 mg/cm³
Year average (cumulative worst case):	5.476e-05 mg/cm³

Exposure estimates based on the following parameters:

Product density:	1.000 g/cm³
Applied product volume:	1.000 cm³
Weight fraction of compound:	1.000 %
Dilution before use:	1.000 times

Uptake

Model:	fraction model
Average case estimate:	2.400e-00 mg/year 1.095e-04 mg/(kg.day)
Cumulative worst case estimate:	2.400e-00 mg/year 1.095e-04 mg/(kg.day)

Uptake estimates based on the following parameters:

Absorbed fraction:	1.000%

Oral

No exposure

Total dose

Average case

(Semi)chronic dose 1.320e-04 mg/kg bw/day (year averaged)
Acute dose 2.009e-03 mg/kg bw/day of application

Cumulative worst case

(Semi)chronic dose 1.320e-04 mg/kg bw/day (year averaged)
Acute dose 2.009e-03 mg/kg bw/day of application

European Commission

EUR 21640 EN **European Union Risk Assessment Report**
but-2-yne-1,4-diol, Volume 54

Editors: S.J. Munn, R. Allanou, K. Aschberger, F. Berthault, O. Cosgrove, S. Pakalin, A. Paya-Perez, G. Pellegrini, B. Schwarz-Schulz, S. Vegro.

Luxembourg: Office for Official Publications of the European Communities

2005 – VIII pp., 117pp. – 17.0 x 24.0 cm

Environment and quality of life series

The report provides the comprehensive risk assessment of human health part of the substance but-2yne-1,4-diol. It has been prepared by Germany in the frame of Council Regulation (EEC) No. 793/93 on the evaluation and control of the risks of existing substances, following the principles for assessment of the risks to humans and the environment, laid down in Commission Regulation (EC) No. 1488/94.

The evaluation considers the emissions and the resulting exposure to the environment and the human populations in all life cycle steps. Following the exposure assessment, the environmental risk characterisation for each protection goal in the aquatic, terrestrial and atmospheric compartment has been determined. For human health the scenarios for occupational exposure, consumer exposure and humans exposed via the environment have been examined and the possible risks have been identified.

The environmental risk assessment for but-2yne-1,4-diol concludes that there is at present no concern for the aquatic ecosystem, the terrestrial ecosystem, the atmosphere or for microorganisms in the sewage treatment plant as well as for secondary poisoning.

The human health risk assessment for but-2yne-1,4-diol concludes that there is concern for workers regarding the local respiratory tract irritation as a consequence of single inhalation exposure arising from production and further processing of the solid substance in the large scale chemical industry and as a consequence of repeated exposure arising from manufacturing and further processing of the solid substance in the large scale chemical industry and in the preparation of formulations (in the absence of local exhaust ventilation).
In addition there is a concern for sensitisation as a consequence of dermal exposure arising from production and further processing of the substance in the large scale chemical industry and in the preparation of formulations.

For consumers and humans exposed via the environment, there is no concern.

The mission of the JRC is to provide customer-driven scientific and technical support for the conception, development, implementation and monitoring of EU policies. As a service of the European Commission, the JRC functions as a reference centre of science and technology for the Union. Close to the policy-making process, it serves the common interest of the Member States, while being independent of special interests, private or national.

European Commission – Joint Research Centre
Institute for Health and Consumer Protection
European Chemicals Bureau (ECB)

European Union Risk Assessment Report

but-2-yne-1,4-diol

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