European Chemicals Bureau

Institute for Health and Consumer Protection

European Chemicals Bureau

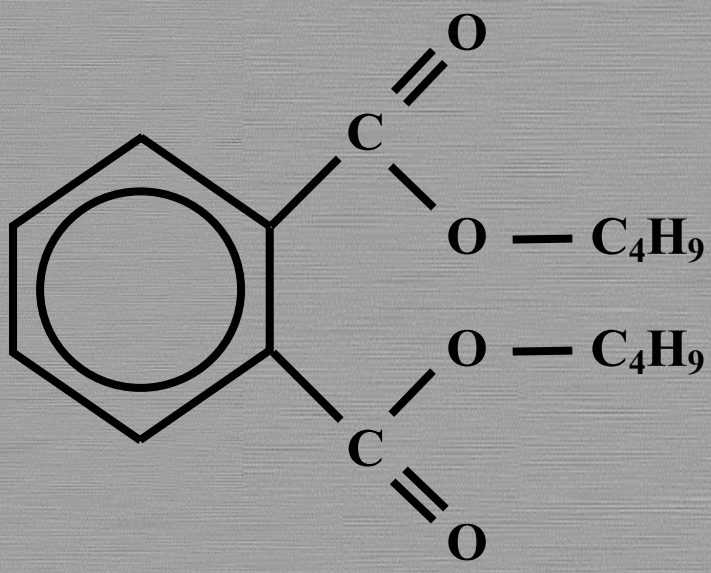
Existing Substances

European Union Risk Assessment Report

CAS No: 84-74-2

EINECS No: 201-557-4

dibutyl phthalate



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European Union Risk Assessment Report

DIBUTYL PHTHALATE

Addendum to the Environmental Section – 2004

CAS No: 84-74-2

EINECS No: 201-557-4

RISK ASSESSMENT

EXPLANATORY NOTE

This report is an addendum to the European Risk Assessment Report (RAR) on dibutyl phthalate, that has been prepared by the Netherlands in the context of Council Regulation (EEC) No. 793/93 on the evaluation and control of existing substances and published in 2003 on the European Chemicals Bureau website (European Risk Assessment Report Vol. 29, EUR 19840 EN) [1].

In the frame of this work, the initial environmental risk assessment for dibutyl phthalate was completed with a conclusion (i) for the atmospheric compartment. There was felt to be a need for further long-term plant testing (gas phase). Consequently, a long-term fumigation test has been conducted recently exposing six different plant species to various DBP concentrations. Results are presented in this report.

For detailed information on the risk assessment principles and procedures followed, the underlying data and the literature references the reader is referred to the comprehensive Final Risk Assessment Report (Final RAR).

[1] European Chemicals Bureau – Existing Chemicals – http://ecb.jrc.it

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TABLES

1 INTRODUCTION

The environmental risk assessment for dibutyl phthalate was completed with a **conclusion (i)** for the atmospheric compartment (EC, 2003a). There was felt to be a need for further long-term plant testing (gas phase). The reason behind was that with the derived $PNEC_{plant-air}$ of 0.01 μg/m^3 atmospheric PEC/PNEC ratios above 1 were found for all exposure scenarios, including recent measured regional concentrations in the Netherlands. This $PNEC_{plant-air}$ of 0.01 μg/m^3 was based on a NOEC estimate of 0.1 μg/m^3 in combination with an (arbitrary) assessment factor of 10. The NOEC estimate was, however, based on rather old experimental data showing a number of inconsistencies and limitations (a.o. analytics, exposure time, co-exposure with other phthalates, etc.). The validity of the derived PNEC was therefore debatable.

A long-term fumigation test has been conducted recently exposing six different plant species to various DBP concentrations for a period of 76 days (PRI, 2002). Mean measured concentrations amounted to 0.14 (control), 0.81, 1.37, 3.07 and 13.67 μg/m^3. The plant species chosen for the laboratory experiment were representative of the European flora and included plant species representative for crops, trees and natural vegetation: *Phaseolus vulgaris* (bean), *Brassica campestris* var. *chinensis* (cabbage), *Picea abies* (Norway spruce), *Trifolium repens* (white clover), *Plantago major* (plantain) and *Holcus lanatus* (common velvet grass). Cabbage was "automatically" selected, because this species was found to be the most sensitive one in the earlier DBP fumigation tests.

2 CHRONIC PLANT STUDY

Results

Visual injury was observed on all species, varying from chlorosis and necrosis, leaf crinkling to a total loss of colour in the leaves and needles. The variation in sensitivity between plant species was quantified on the basis of whole plant biomass (shoot plus root) in order to derive NOEC and EC10 values.

The EC10 values for total biomass, including lower and upper limits, for the six species are presented below:

Plant species	EC10 (µg/m^3)	EC10: lower and upper limit
Phaseolus vulgaris	2.32	1.20-4.48
Brassica campestris	0.77	0.36-1.67
*Picea abies**	-	-
Trifolium repens	0.33	0.12-0.91
Holcus lanatus	8.79	-
Plantago major	2.39	1.53-3.75

* No significant effects were observed even at highest tested concentration.

Interestingly, white clover was found to be more sensitive to DBP than cabbage. Further details can be found in the PRI (2002) report and IUCLID.

PNEC$_{plant-air}$ proposal

The PRI (2002) study is considered acceptable and useful for deriving a PNEC $_{plant-air}$. Two different routes can be used for deriving the PNEC$_{plant-air}$: 1) the standard method (lowest NOEC/EC10 divided by assessment factor, and 2) statistical extrapolation with an additional assessment factor.

Using the lowest EC10 value, i.e. 0.33 µg/m^3, and applying the standard factor of 10 would result in a PNEC$_{plant-air}$ of **0.03 µg/m^3**. Calculating the 5th percentile of the species sensitivity distribution (EC10 values for effects on total biomass) would result in a median (50% confidence interval) value of **0.2 µg/m^3** (ETX, 1993). The 5th percentile estimation meets the statistical goodness-of-fit requirements (Anderson-Darling test for normality). Calculating 5th percentile values for either root or shoot biomass, rather than total biomass, results in nearly the same 5th percentile.

The problem now is that there is no guidance yet on deriving a plant-air PNEC in the Technical Guidance Document (TGD) (EC, 2003b). The TGD focuses on the PNEC derivation for water, sediment and soil, but the assumptions etc. for those compartments may not directly hold for plants (airborne route). A number of considerations can be given here on the PNEC$_{plant-air}$ derivation for DBP:

1. the focus is only on deriving a PNEC air for plants. This means that other taxonomic groups of the atmospheric compartment (e.g. insects) will remain beyond the scope of the PNEC. This implies that assessment factors may cover 'less ecosystem' than normally for water, soil and sediment.

2. the TGD (2003b) criteria for using statistical extrapolation are not all met here (e.g. number of NOECs), but they may also not be relevant here as the focus is only on plants (see

point 1). There is a fairly well coverage of plant diversity in the selected plant species, and, in addition, an acceptable goodness-of-fit is shown. One may speculate then about the introduction of an additional assessment factor. Such additional assessment factor should still cover species diversity (see point 3). It is highly uncertain, however, whether a factor of 2, 3 or 4 should then be used. An arbitrary factor of 3 on the current 5th percentile would, for example, yield a PNEC of 0.07 µg/m^3.

3. the focus in the tiered testing program, of which the PRI (2002) test is the last part, has been on sensitive species (*Brassica* in particular). This is supported by literature data. It should be noted, however, that the PRI (2002) test showed that white clover was even more sensitive than *Brassica*. Some factor is needed therefore for possible other, even more sensitive species than clover.

4. according to plant experts, the conditions in greenhouses, are very unfavourable to plants with respect to their sensitivity to toxicants. This due to optimal light and feeding conditions which optimise the exposure and therefore the toxicity. Therefore the standard factor of 10 for extrapolating from laboratory tests to the field-situation may be argued here (lower factor).

Taking all these points into consideration, it is clear that a quantitative approach on the PNEC derivation would be very difficult in this case. The standard assessment factor of 10 is most probably too high, but should it then be 4, 6 or 7.5? The same is true for the additional assessment factor on the 5th percentile. It is pragmatically proposed therefore to use a **PNEC $_{plant\text{-}air}$ of 0.1 µg/m^3** for DBP in the revised risk assessment.

3 REVISED RISK CHARACTERISATION

The adjusted risk characterisation, based on the change in the $PNEC_{plant\text{-}air}$ from 0.01 µg/m^3 to 0.1 µg/m^3, is presented in **Table 3.1** (production sites) and **Table 3.2** (formulation/processing sites). Please note that the PEC/PNEC ratios for the compartments other than atmosphere remained unchanged.

Table 3.1 Local PEC/PNECs in the various compartments at production

PEC/PNEC	site-spec. A	site-spec. B	site-spec. C
STP	0.3	$3.4 \cdot 10^{-4}$	0.4
Surface water	0.4	0.1	0.6
Sediment	0.4	0.1	0.7
Soil	0.7	$3.3 \cdot 10^{-4}$	$3.2 \cdot 10^{-4}$
Oral, fish	$3.5 \cdot 10^{-5}$	$1.7 \cdot 10^{-5}$	$3 \cdot 10^{-5}$
Oral, worm	0.07	$6 \cdot 10^{-4}$	$6 \cdot 10^{-4}$
Plant (air)	0.2	0.2	0.2

Table 3.2 Local PEC/PNEC ratios at formulation/processing

PEC/PNEC for scenario	III-a	III-b1	III-b2	III-c1	III-c2	III-d	III-e
Type of application	plasticiser / softener in PVC	adhesive		printing inks		fibres	grouting agent
STP	0.08	0.4	0.09	0.05	0.002	0	-.
Surface water	0.3	0.9	0.3	0.2	0.1	0.1	0.7 (A) 0.1 (O)
Sediment	0.3	1	0.3	0.2	0.1	0.11	-
Soil	0.2	0.9	0.2	0.1	$5.9 \cdot 10^{-3}$	0.002	-
Oral, fish	$3 \cdot 10^{-5}$	$7.3 \cdot 10^{-5}$	$3 \cdot 10^{-5}$	$2.5 \cdot 10^{-3}$	$1.8 \cdot 10^{-5}$	$1.7 \cdot 10^{-5}$	-
Oral, worm	0.02	0.1	0.02	0.01	$1.2 \cdot 10^{-3}$	$7.4 \cdot 10^{-4}$	-
Plant (air)	23.6	3.4	0.1	0.5	2.0	10.0	-

On the basis of the new atmospheric PEC/PNEC ratios (>1) a **conclusion (iii*)** is drawn for the local DBP processing scenarios III-a (PVC production), III-b1 (adhesive production), III-c2 (printing ink usage) and III-d (glass fibre production). For the remaining scenarios, including the regional one, a **conclusion (ii)** seems to be most appropriate as the PEC/PNEC ratios are all below 1. The regional scenario also comprises the recent air monitoring data from the Netherlands.

4 RESULTS FOR THE ENVIRONMENT - ADDENDUM

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

This conclusion is reached because of anticipated risk for plants (atmospheric exposure) at a local scale for the DBP processing scenarios III-a (PVC production), III-b1 (adhesive production), III-c2 (printing ink usage) and III-d (glass fibre production).

5 REFERENCES

EC (2003a). Dibutyl Phthalate. European Union Risk Assessment Report, Vol.29. Hansen BG et al. (eds), European Commission (EC), Publication No. EUR 19840 EN (Internet publication at http://ecb.jrc.it/).

EC (2003b). Technical Guidance Document on Risk Assessment in support of Commission Directive 93/67/EEC on Risk assessment for new notified substances, Commission Regulation (EC) 1488/94 on Risk assessment for existing substances and Directive 98/8/EC of the European Parliament and of the Council concerning the placing of biocidal products on the market. Parts 1-4. 2nd edition. European Commission (EC), Publication No. EUR 20418/EN/1, 20418/EN/2, 20418/EN/3, 20418/EN/4 (Internet publication at http://ecb.jrc.it/).

ETX (1993). ETX1.3a. A program to calculate confidence limits for hazardous concentrations based on small samples of toxicity data. National Institute for Public Health and the Environment (RIVM). May 1993. Report no. 719102015, Bilthoven, The Netherlands.

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European Union Risk Assessment Report

DIBUTYL PHTHALATE

CAS No: 84-74-2

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RISK ASSESSMENT

Cataloguing data can be found at the end of this publication

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DIBUTYL PHTHALATE

CAS No: 84-74-2

EINECS No: 201-557-4

RISK ASSESSMENT

Final Report, 2003

The Netherlands

Rapporteur for the risk evaluation of dibutyl phthalate is the Ministry of Housing, Spatial Planning and the Environment (VROM) in consultation with the Ministry of Social Affairs and Employment (SZW) and the Ministry of Public Health, Welfare and Sport (VWS). Responsible for the risk evaluation and subsequently for the contents of this report is the rapporteur.

The scientific work on this report has been prepared by the Netherlands Organization for Applied Scientific Research (TNO) and the National Institute of Public Health and the Environment (RIVM).

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Date of Last Literature Search:	**1994**
Review of report by MS Technical Experts finalised:	**1999**
Final report:	**2003**

(The last full literature survey was carried out in 1994 - targeted searches were carried out subsequently).

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 Toxicity, Ecotoxicity and the Environment (CSTEE) 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.

Barry Mc Sweeney
Director-General
DG Joint Research Centre

Catherine Day
Director-General
DG Environment

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1 O.J. No L 084, 05/04/199 p.0001 – 0075

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.: 84-74-2
EINECS-No.: 201-557-4
IUPAC name: dibutyl phthalate

Environment

Conclusion (i) There is need for further information and/or testing.

This conclusion is reached because:

- there is a need for better information to adequately characterise the risks to plants exposed via the atmosphere (the airborne toxicity to plants).

The information requirement is a long-term plant toxicity test.

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

This conclusion applies to effects on the aquatic compartment (including sediment), soil and secondary poisoning.

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.

This conclusion is reached because of:

- concerns for general systemic toxicity as a consequence of repeated dermal exposure arising from aerosol forming activities.
- concerns for adverse local effects in the respiratory tract as a consequence of repeated inhalation exposure in all occupational exposure scenarios.

It is possible that in some industrial premises adequate worker protection measures are already being applied.

Consumers

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

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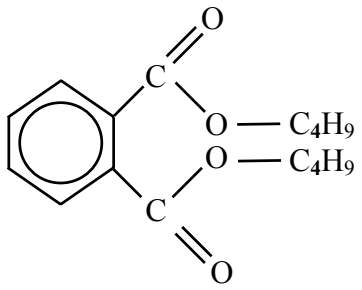
Euses Calculations can be viewed as part of the report at the website of the European Chemicals Bureau: http://ecb.jrc.it

TABLES

1 GENERAL SUBSTANCE INFORMATION

1.1 IDENTIFICATION OF THE SUBSTANCE

CAS-No.:	84-74-2
EINECS-No.:	201-557-4
IUPAC name:	Dibutyl phthalate
Synonyms:	Di-n-butylphthalat, 1,2-Benzenedicarboxylic acid, dibutyl ester (9CI), Phthalic acid, dibutyl ester (6CI, 8CI), Bis-n-butyl phthalate, Butyl phthalate, DBP, DBP (ester), Dibutyl o-phthalate, Di(n-butyl) 1,2-benzenedicarboxylate, n-Butyl phthalate, Palatinol C, Phthalic acid di-n-butyl ester
Molecular weight:	278.34
Molecular formula:	$C_{16}H_{22}O_4$
Structural formula:	



1.2 PURITY/IMPURITIES, ADDITIVES

Purity:	$\geq$99% (w/w)
Impurity:	ca. 0.01% (w/w) butan-1-ol ca. 0.01% (w/w) butyl benzoate
Additives:	none

1.3 PHYSICO-CHEMICAL PROPERTIES

Physical state:	oily liquid
Melting point:	- 69°C
Boiling point:	340°C at 1,013 hPa
Relative density:	1.045 g/cm^3 at 20°C
Vapour pressure:	$9.7 \pm 3.3 \cdot 10^{-5}$ hPa at 25°C
Water solubility:	10 mg/l at 20°C

Partition coefficient
n-octanol/water: log K_{ow} 4.57

Granulometry: not applicable
Flammability: negative
Explosive properties: negative
Oxidizing properties: negative

These data are mainly derived from Banerjee and Howard (1984), BASF (corporate data), BUA (1987), Hoyer and Pepperle (1958), Hüls (corporate data); Leyder and Boulanger (1983), Patty (1981). For an extended description see the IUCLID database.

1.4 CLASSIFICATION

Classification and labelling according to the 28th ATP of Directive 67/548/EEC[4]:

Classification:	Repr. Cat. 2; R61	May cause harm to the unborn child
	Repr. Cat. 3; R62	Possible risk of impaired fertility
	N; R50	Dangerous for the environment: very toxic to aquatic organisms
Labelling:	T; N	
	R: 61-50-62	
	S: 53-45-61	

No Note

Specific concentration limits: none

[4] The classification of the substance is established by Commission Directive 2001/59/EC of 6 August 2001 adapting to technical progress for the 28th time Council Directive 67/548/EEC on the approximation of the laws, regulations and administrative provisions relating to the classification, packaging and labelling of dangerous substances (OJ L 225, 21.8.2001, p.1).

2 GENERAL INFORMATION ON EXPOSURE

2.1 PRODUCTION

In 1998 the production volume of dibutyl phthalate (hereafter referred to as DBP) in the EU was estimated at 26,000 tonnes, of which 8,000 tonnes was thought to be exported outside the EU (Industry, 1999). This leads to a use volume of about 18,000 t/a. There is no import of DBP from outside the EU. There is a clear decreasing trend in the production of DBP: 49,000 t/a (1994) – 37,000 t/a (1997) – 26,000 t/a (1998).

The production (>1,000 tonnes) of DBP in 1998 was located at three production sites in the EU (**Table 2.1**).

Table 2.1 Production sites (>1,000 t/a) of DBP in 1998

Company	Location
BASF	Ludwigshafen, Germany
OXENO	Marl, Germany
BP	Hull, United Kingdom *
Lonza	Porto Marghera, Italy *
SISAS	Pioltello, Italy

* Stopped production since 1998

DBP is produced by the reaction of phthalic anhydride with n-butanol in the presence of concentrated sulphuric acid as a catalyst. Excess alcohol is recovered and recycled and the di-n-butyl phthalate is purified by vacuum distillation and/or activated charcoal.

2.2 USE PATTERN

Table 2.2 shows the industrial and use categories of DBP for the European market.

Table 2.2 Industrial and use categories of DBP

Industrial category	Use category
Polymers industry	softeners (plasticiser in PVC)
Others (adhesives)	softener (paper and packaging, wood building and automobile industry)
Pulp, Paper and Board industry	softener (printing inks)
Others	softener/solvent (e.g. sealants, nitrocellulose paints, film coatings, glass fibres and cosmetics)

The largest usage of DBP in general is as a plasticizer in resins and polymers such as polyvinyl chloride. Plasticizers are materials incorporated into a plastic in order to increase its workability and distendability. DBP is further used a.o. in printing inks, adhesives, sealants/grouting agents,

nitrocellulose paints, film coatings and glass fibres. The ubiquity of DBP in consumer products is demonstrated by its wide usage in cosmetics: a perfume solvent and fixative, a suspension agent for solids in aerosols, a lubricant for aerosol valves, an antifoamer, a skin emollient and a plasticizer in nail polish and fingernail elongators (IPCS/WHO, 1995).

In Denmark DBP has been found in 1,176 products accounting for 2,848 tonnes/year (Danish Product Register, 1995). In 94 products accounting for 388 tonnes/year the concentration of DBP is 80-100%. In Sweden DBP has been found in 343 products, 38 of which are available to consumers (KEMI, 1995).

A number of authors have given estimates of the quantitative usage distribution of DBP (Industry report, 1995; BUA, 1987; RIVM, 1991; Canadian EPA, 1994; Cadogan et al., 1994). Based on 1997 data, on average around 76% of DBP is used as a plasticizer in polymers, 14% in adhesives, 7% in printing inks and the remaining 3% of DBP is used in miscellaneous other applications.

3 ENVIRONMENT

3.1 ENVIRONMENTAL EXPOSURE

3.1.1 Environmental fate

DBP may be released into the environment during its production and subsequent life cycle stages, including disposal. Emissions to water and air are expected to be the most important entry routes of DBP. General characteristics of DBP which are relevant for the exposure assessment are discussed in the following subparagraphs.

3.1.1.1 Degradation

Hydrolysis

A test on the hydrolysis potential of DBP indicated that at pH 4.0 and 7.0 DBP was found to be stable, i.e. less than 10% hydrolysis after 5 days. At pH 9.0 and a temperature of 50°C a half-life time of 65.8 hours was reported. These results are in line with the RIVM-conclusion (RIVM, 1991) that the contribution of hydrolysis to the overall environmental degradation of phthalate esters, including DBP, is expected to be low.

Photodegradation

Photooxidation by OH radicals contributes to the elimination of DBP from the atmosphere. The experimental degradation rate constant amounts to about $18 \cdot 10^{-12}$ $cm^3/mol \cdot sec$ corresponding to a half-life of 21.4 hours at an average OH concentration of 500,000 molecules/cm^3. Vapour phase reactions of DBP with photochemically produced hydroxyl radicals were also estimated with a QSAR (Atkinson, 1985). The overall OH rate constant for DBP was estimated to be $8.7 \cdot 10^{-12}$ $cm^3/mol \cdot sec$. This value corresponds to an atmospheric half-life of about 1.8 days. Howard et al. (1991) estimated the photooxidation half-life of DBP in air to range from 7.4 hours to 3.1 days.

Biodegradation

The metabolic pathway of aerobic and anaerobic biodegradation of phthalates can be summarised as follows. First the di-ester is hydrolysed into the mono-ester by esterases with low substrate specificity. Subsequently the mono-ester is converted into phthalic acid. The hydrolysis of the mono-ester appears to be the crucial step which limits the rate of degradation. Further degradation differs according to the bacterial genus. There is ample evidence that DBP is ready biodegradable under aerobic conditions (a.o. ECETOC, 1985; BUA, 1987; RIVM, 1991). This is also concluded by a TemaNord report (1996), where it is stated that DBP may be considered to be readily biodegradable although several tests have been carried out under acclimated conditions. However, a BOD5:COD ratio of 0.63 obtained with a non-adapted inoculum “indicates that DBP may be regarded as readily biodegradable”. Recently it was also demonstrated that DBP is readily biodegradable in a modified Sturm test (Scholz et al., 1997).

The same literature sources indicate that biodegradation of DBP is much slower in the anaerobic environment, e.g. sediments or deeper soil or groundwater layers. This is an important conclusion as sediments are found to be an important "sink" for DBP (see below).

Recently, a thesis of Ejlertsson (1997) was published in which the anaerobic degradation of phthalic acid esters was studied under landfill conditions. With samples from a methanogenic landfill model working in the phase of stable methanogenesis, DBP was transformed to monobutyl phthalate (MBP), being the only product detected (Ejlertsson et al., 1996). Adding 230 µM DBP resulted in 130 µM MBP after 278 days. Using samples from a biogas reactor DBP was completely converted to methane and CO_2 after 30 days. The difference between both tests was explained by the longer acclimatisation period of the populations from the biogas reactor compared to the landfill model. This was confirmed by an experiment in which solid waste samples were taken from a depth of 16 m at the landfill at Filborna, Sweden (Ejlertsson, in press). DBP was completely degraded to methane and CO_2 after 91 days incubation. MBP was measured as a transient metabolite. The maximum concentration formed was not presented and a half-life of 4.2 days was derived (Ejlertsson, 1997).

It can be concluded that DBP can be degraded in landfills under anaerobic conditions. MBP appears to be the main metabolite, which can be degraded further. However, actual concentrations for MBP in water leachate from landfills have never been determined.

3.1.1.2 Distribution

The Henry's law constant of 0.27 $Pa \cdot m^3/mol$ indicates that DBP will only slowly volatilize from surface waters, i.e. virtually all of the DBP will remain in the water phase at equilibrium.

The octanol/water partition coefficient (K_{ow}) of DBP is high and consequently the equilibrium between water and organic carbon in soil or sediment will be very much in favour of the soil or sediment. Soil and sediment thus appear to be important sinks for DBP. Resuspension of DBP from the sediment to the water column may occur. Although DBP is only poorly soluble in water, it may be transported in water following the adsorption of DBP to humic substances.

Despite its low volatility, DBP has been reported as particulate and as a vapour in the atmosphere. In the air DBP is transported and removed by both wet and dry deposition.

Applying the QSAR $K_{oc} = 1.26\ K_{ow}^{0.81}$ from the Technical Guidance Document (EC, 1996) a K_{oc} of 6,340 l/kg can be calculated using the log K_{ow} of 4.57. The impact on the outcome of the risk assessment. This value is used to derive the following partition coefficients:

- Kp_{susp}: solids-water partition coefficient of suspended matter: 634 l/kg;
- $K_{susp,water}$: suspended matter-water partition coefficient: 159 m^3/m^3;
- $K_{sed,\ water}$: sediment-water partition coefficient: 159 m^3/m^3;
- $K_{soil,\ water}$: soil-water partition coefficient: 190 m^3/m^3.

Based on the above-cited physical chemical characteristics (log H = -0.6; log K_{ow}= 4.57) as well as the biodegradation rate of 1 h^{-1}, the removal of DBP in the STP is estimated (EUSES) as follows:

% to air	0.07
% to water	9
% to sludge	33
% degraded	58
% removal	91

3.1.1.3 Bioaccumulation

The high K_{ow} of DBP indicates that the substance has a potential for bioaccumulation. However, the actual degree of bioaccumulation *in vivo* will be determined by the metabolisation and the elimination rate of the substance. For phthalates it is known that an important biotransformation pathway is the formation of the mono-ester and the subsequent formation of phthalic acid. Especially the formation of the mono-ester is relevant from a toxicological point of view since this substance has been demonstrated to cause reproductive effects in mammals (see Section 4). On the other hand it should be noted that the log K_{ow} of the mono-ester is around 2.8 which does not indicate a high potential for bioaccumulation. The available BCF data demonstrate a relatively low bioconcentration but also indicate that higher BCF values are obtained when the BCF is calculated for the total amount of metabolites using ^{14}C-labelled material.

Reported BCFs for DBP for various organisms range from 2.9 for the brown shrimp (*Penaus aztecus*) to 2,125 for the fathead minnow (*Pimephales promelas*) (Canadian EPA, 1994). However, in both tests the criterion for bioaccumulation was the ^{14}C-content arising from a labelled material. This may give an overestimation of the BCF due to the fact that both ^{14}C-DBP and any ^{14}C-labelled metabolites of DBP were measured (including ^{14}C built into the tissue of the organism in e.g. fatty acids). The same is true for the studies of Mayer and Sanders (1973) in which very high BCFs (e.g. 5,000 and 6,700 for *Daphnia magna* and *Gammarus pseudolimnaeus*, respectively) were found. A much lower BCF of 11.7 was found in a fish study with *Cyprinidon variegatus* (Wofford et al., 1981). As in this study a static method was used, it may be an underestimation of "BCF".

Recently a bioaccumulation test according to international guidelines (OECD 305E) has been carried out under GLP by industry (Hüls, 1996). Carp (*Cyprinus carpio*) were exposed to 10 and 50 µg/l for 28 days. Based on measurements for the highest exposure concentration in water and fish a BCF value of 1.8 l/kg was found. It should be stated that this test showed some experimental shortcomings (e.g. rather weak recovery performance, unidentified background contamination and a remarkable (unclarified) drop in DBP levels during exposure period). Apart from these inconsistencies it should also be noted that also in this test the major metabolite, i.e. the mono-ester MBP, was not analysed. Hence the observed BCF only refers to the parent compound. A BCF that would include the mono-ester would probably be somewhat higher, but is expected to be lower than the BCF values measured with ^{14}C-labelled material. The experimental BCF of 1.8 l/kg for DBP from the recent study will be used in the further risk assessment for secondary poisoning. In the risk characterisation attention will be paid to the possible consequences of using a higher value. No experimental BCF data are available for terrestrial species. EUSES calculates a BCF worm of 13kg/kg.

Ray et al. (1983b) measured the concentration of DBP in marine sediment, clams and the bristle worm (Neanthes virens) from samples near Portland, Maine US. The concentrations in sediment were found to be higher than those in biota, 160 and 100 µg/kg, respectively (BCFs <1).

3.1.2 Environmental releases

3.1.2.1 Exposure scenarios

The environmental exposure assessment of DBP will be based on the expected releases of the substance during the following life cycle stages:

I.	Production
II.	Distribution (e.g. road transport)
IIIa.	Processing in polymers
IIIb-1.	Formulation in adhesives
IIIb-2.	Processing/use of adhesives
IIIc-1.	Formulation in printing inks
IIIc-2.	Processing/use of printing inks
IIId.	Processing of glass fibres
IIIe.	Processing of grouting agents
IV.	Exterior use of DBP containing products
V.	Incineration and disposal of DBP containing products.

Life cycle stage III (processing) consists of five subscenarios (a-e). Scenarios IIIa, IIIb and IIIc represent the major usages of DBP (about 97% of the total use). Scenario IIId and IIIe are examples of smaller applications of DBP. For life cycle stage III both site-specific and generic emission scenarios are used for calculating the local predicted environmental concentrations (PEC) values in the various compartments. Stages II, IV and V can be regarded as diffuse sources of DBP and will only be used for calculating the regional PEC.

Site-specific scenarios are based on actual data from industry on emission patterns etc., whereas generic scenarios are fully based on model calculations for a realistic worst-case situation. Generic scenarios are used if no data were obtained from either industry or other bodies.

The exposure assessment is based on the EU TGD in combination with the European System for the Evaluation of Substances, EUSES.

The background data of the various EUSES calculations can be viewed as part of the report at the website of the European Chemicals Bureau: http://ecb.jrc.it.

3.1.2.2 Local exposure assessment

3.1.2.2.1 Production (life cycle stage I)

Water and air

In Section 2.1 it is mentioned that there are three major DBP producers within the EU. For all plants (scenarios A, B, and C) site-specific data were submitted. **Table 3.1** contains the input data and the results for the local exposure assessment at production. For confidentiality reasons not all information is presented in this table. With the input data from **Table 3.1** local Predicted Environmental Concentrations (PECs) are calculated (**Table 3.2**). It is emphasized that the presented PECs in **Table 3.2** are the sum of the local concentration (C_{local}) and the regional background concentration ($PEC_{regional}$). The PEC regional is discussed in Section 3.1.2.3.

The EUSES model takes into account both the application of STP sludge on agricultural soil and the deposition from air for the calculations of DBP levels in the terrestrial compartment. All three companies stated that the sludge from their STP and also (solid) waste containing DBP is being incinerated. During incineration DBP, is thought to be completely combusted to carbon dioxide and water. Therefore for these scenarios the concentration in sludge was set at 0.

Table 3.1 Input data for the local exposure assessment for air and water at production (I). (Table A.1.1 TGD). Site-specific information is presented in bold

	Site-spec. A	**Site-spec. B**	**Site-spec. C**
Annual production tonnage	**confidential**	**confidential**	**confidential**
Main category	III	III	III
Number of days	300	300	104
Fraction of main source	1	1	1
Release air (%)	*0.001*	*0.001*	
Release water (%)	0.3	*0.3*	
Amounts released to air (kg/d)	**0.08** [a]	**0.07** [b]	**0.18**
Amounts released to water (kg/d)	47	0.377	0.41
Size of STP (m^3/d) [c]	**known**	**known**	**known**
Flow rec. water (m^3/s)	**known**	**known**	-
Dilution	**known**	**known**	10

a) According to official declaration of emission release
b) Emissions of DBP into air according to the governmental register
c) Sludge application is not relevant for all the site-specific scenarios due to incineration or landfilling of sludge

Table 3.2 Local PECs in the various environmental compartments at production

	Site-spec. A	Site-spec. B	Site-spec. C
$PEC_{effluent, STP}$ (mg/l)	0.06	0.074 *(in µg/l)* [a)]	0.09
$PEC_{surface, water}$ (µg/l)	3.6	1	6
PEC_{air} (µg/m³)	0.02	0.02	0.02
$PEC_{sediment}$ (mg/kg)	0.5	0.1	0.8
PEC_{soil} (mg/kg) 30 days; agri	1.3	$0.7 \cdot 10^{-3}$	$0.7 \cdot 10^{-3}$
PEC_{soil} (mg/kg) 180 days; agri	1.1	$0.7 \cdot 10^{-3}$	$0.7 \cdot 10^{-3}$
PEC oral, fish (µg/kg)	3.7	1.8	3.1
PEC oral, worm (mg/kg)	7.6	0.07	0.06

[a)] Measurement for 1988 indicated WWTP concentration of 1 µg/l (industry letter 26-3-1997)

3.1.2.2.2 Processing in polymers (life cycle stage IIIa)

In this context the term processing refers to the sequence of steps from the blending of raw materials, including DBP, to the final forming ("shaping") of the flexible end products (Cadogan et al., 1994). In Section 2.1, it was stated that about 18,000 tonnes are annually used in the EU. It is assumed that 76% of this amount, i.e. 13,500 tonnes, is used per annum as plasticizer in polymers. For one site site-specific information on releases was submitted. As the number of processing sites is known to be higher than 1 (estimate of 50 large processing sites in the EU according to Industry) a generic scenario was carried out as well. This scenario is based on the Use Category Document on Plastic additives (draft 1998). According to the UCD representative PVC processing sites are using 744 tonnes PVC in open processes, 3,990 tonnes in partially open processes and 341 tonnes in closed processes. The contents of plasticizer in PVC for these three mentioned types of processes are 50%, 50% and 30%, respectively. However, according to Industry DBP is no longer used on its own, but always in conjunction with other less volatile plasticizers. The assumption for this partitioning is 50% DBP and 50% other plasticizers. The amount of DBP in open processes therefore becomes $0.5 \cdot 0.5 \cdot 744 = 186$ t/a, in the partially open process $0.5 \cdot 0.5 \cdot 3{,}990 = 998$ t/a and in the closed process $0.3 \cdot 0.5 \cdot 341 = 51$ t/a. These DBP tonnages and the corresponding emission factors from the UCD lead to the daily emissions (**Table 3.3**). As a worst-case approach it is assumed that the three types of processes may occur within one site. Thus the sum of the emissions per process is used as the input for the local PEC calculations.

Table 3.3 Emissions from PVC processing

Process	Emission factor (%)	Annual release (kg/year)		Daily release (kg/day)	
		Air	Water	Air	Water
Open (186 tonnes/year)					
Raw materials handling	0.01		18.6		0.062
Compounding	0.05	93		0.31	
Conversion	0.25	465		1.55	
Partially open (998 tonnes/year)					
Raw materials handling	0.01		100		0.33
Compounding	0.05	499		1.7	
Conversion	0.15	1,500		5	
Closed (51 tonnes/year)					
Raw materials handling	0.01		5		0.017
Compounding	0.5 *	255		0.85	
Conversion	0.5 *	255		0.85	
Total				10.3	0.4

* Tonnage of PVC is below suggested threshold for presence of fume elimination equipment, so emission factors are increased by 10x

Table 3.4 contains the input data of the local exposure assessment at processing. The PECs are given in **Table 3.5**. It is emphasized that the presented PECs in **Table 3.5** are the sum of the local concentration (C_{local}) and the regional background concentration ($PEC_{regional}$). The PEC regional is discussed in Section 3.1.2.3.

Table 3.4 Input data for the local exposure assessment for air and water at formulation, processing/production (IIIa-d). Site-specific information is presented in bold

Scenario	**IIIa**	**IIIb-1**	**IIIb-2**	**IIIc-1**	**IIIc-2**	**IIId**
Type of application	**Polymers**	**Adhesive ..**		**Printing inks[3]**		**Production of fibres**
Industry and Use category	11 Polymer industry 47 Softeners (softener)	0 Others [2)] 0 Others		12 Pulp, Paper and Board Industry 48 Solvent [4)]		0 Others [2)] 0 Others
Life cycle step	Processing in polymers	formulation in adhesives	processing/ use in adhesives	formulation in printing inks	processing/use of printing inks	production of glass fibres
Application (% use)	76	14	14	7	7	*?(0.005)*
EU tonnage (T/y)	13,500	2,500	2,500	1,250	1,250	***conf.***
Main category	Processing: MC: inclusion into or onto a matrix Category Polymer processing: A Processing of thermoplastics Type of chemical: II Plasticizers	III multi-purpose equipment	II	III multi-purpose equipment	III non-dispersive use	III non-dispersive use
% in formulation	-	10		5		10

Table 3.4 continued overleaf

Table 3.4 continued Input data for the local exposure assessment for air and water at formulation, processing/production (IIIa-d). Site-specific information is presented in bold

Scenario	IIIa	IIIb-1	IIIb-2	IIIc-1	IIIc-2	IIId
Number of days (B-table)		300 (Table B2.2)	300 (Table B3.13)	300 (B2.3)	300 (B3.10)	300
Fraction of main source (B-table)	UCD	**f = 0.07** [1)]	f = 0.05 [5)]	**f = 0.02** [1)]	**f = 0.005** [1)]	f = 0.2 [D)]
Release air (%) (A-table)	UCD	0.25 (table A 2.1)	0.01 (table A 3.16)	0.25 (table A 2.1)	5 (table A 3.12)	0.07 [D)]
Release water (%) (A-table)	UCD	0.3 (table A 2.1)	0.1 [5)] (table A 3.16)	0.3 (table A 2.1)	0.05 (table A 3.12)	0.33 [D)]
Amounts released to air (kg/d)	10.3	1.5	0.04	0.25	1.2	**4.7**
Amounts released to water (kg/d)	0.4	1.8	4	0.3	0.01	**measured effluent concentration < 2 µg/l**
Size of STP (m^3/d)	2,000	2,000	2,000	2,000	2,000	
Flow rec. water (m^3/s)	-	-	-	-	-	-
Dilution	10	10	10	10	10	

1) Number of sources in one country or in EU is known
2) No specific Industry and Use Category available for the application
3) Source: Baumann W and Herberg-Liedtke B (1991). Druckerei-chemikalien.Springer-Verlag
4) For selecting a relevant Use category DBP is considered as a solvent. However, it should be noted that it is not a typical solvent
5) Deviation from TGD
D) Deduced. Although site-specific release data were available, some parameters had to deduced in order to carry out the regional (and continental) calculations

Table 3.5 Local PECs in the various environmental compartments at formulation/processing (output of EUSES calculations)

Scenario	IIIa	IIIb-1	III-b2	III-c1	III-c2	III-d
Type of application	Plasticizer in PVC	Adhesive		Printing inks		Fibres
PEC effluent STP (mg/l)	0.02	0.08	0.02	0.01	$4.7 \cdot 10^{-4}$	< 2 μg/l
PEC surface water (μg/l)	2.8	8.9	2.9	2.1	1.1	1
PEC air (μg/m^3)	2.4	0.3	0.02	0.05	0.2	1
PEC sediment (mg/kg)	0.4	1.2	0.4	0.3	0.15	0.1
PEC soil (mg/kg) 30 days; agri	0.4	1.8	0.4	0.3	0.01	0.003
PEC soil (mg/kg) 180 days; agri	0.4	1.5	0.4	0.2	0.01	0.003
PEC oral, fish (mg/kg)	0.003	0.008	0.003	0.003	0.002	0.002
PEC oral, worm (mg/kg)	2.5	10.2	2.5	1.5	0.1	0.1

3.1.2.2.3 Formulation in adhesives (life cycle stage IIIb-1) and processing of adhesives (life cycle stage IIIb-2)

DBP is used together with other softeners at the production of dispersion adhesives. These phthalate-containing adhesives are applied for paper and packaging, wood, building industry and automobile industry purposes (German Association of Adhesives Manufacturers, 1998). According to Industry the most important application is for paper and packaging. The use of DBP in adhesives is stated to be decreasing. In Section 2.1 it was stated that about 18,000 tonnes is annually used in the EU. It is assumed that 14% of this amount, i.e. 2,500 tonnes, is used per annum in adhesives. There is site-specific information on actual releases for one adhesive formulation site. As there are only data for one formulation site, a generic scenario is still needed for this life cycle stage. The number of adhesive producers (formulation) in Germany is known (23). There is no reason to assume that formulation of adhesives is specifically related to Germany. And thus using the number of German sites directly as being representative for the whole EU would most probably be an underestimation for the total number of EU sites. Therefore for the EU, the number of sites in Germany is multiplied by a factor 3. This figure ($3 \cdot 23 = 69$) is then used in combination with the factor 5 that takes into account the spread in site size, in order to derive the local input tonnage (fraction of main source is 0.07). For scenario IIIb-2 (use of DBP-containing adhesives)) it was felt that the TGD fraction of main source of 0.3 is over-conservative in combination with the total EU tonnage as input for the local exposure assessment. For this reason a fraction of main source of 0.05 is chosen. In addition, for this particular kind of process (glueing), Main category II (matrix) seems to be most appropriate. The emission factor to water according Table A3.16 of the TGD is 1%. This is considered overconservative in comparison with the emission factor for air of 0.01% in the same A-Table. This because releases to air are more likely for this type of process than those to water. In addition the aquatic emission factor of 1% is much higher than the emission factors in all other scenarios used in the current risk assessment without any rationale. For these reasons, an emission factor of 0.1% is proposed, although it is realised that it will probably still be rather conservative.

Apart from some site-specific information (see above) the exposure assessment for scenario IIIb is based on generic defaults.

Table 3.4 contains the input data of the local exposure assessment at formulation and processing. The PECs are given in **Table 3.5**. It is emphasized that the presented PECs in **Table 3.4** are the sum of the local concentration (C_{local}) and the regional background concentration ($PEC_{regional}$). The $PEC_{regional}$ is discussed in Section 3.1.2.3.

3.1.2.2.4 Formulation in printing inks (life cycle stage IIIc-1) and processing of printing inks (life cycle stage IIIc-2)

DBP is used as softener in the production of photopolymer plates and printing inks, which are mainly used in printing processes for packaging products (paper, film and foil). In Section 2.1 it was stated that about 18,000 tonnes of DBP is annually used in the EU. It is assumed that 7 % of this amount, i.e. 1,250 tonnes, is used per annum in printing inks. There is no site-specific information on actual releases from printing ink formulation or processing sites. Only the number of printing ink producers (formulation) and users in the EU are known (250 and 1,000, respectively). These figures are used in combination with the factor 5 that takes into account the spread in site size, in order to derive the local input tonnage (fractions of main source are 0.02 and 0.005, respectively). Apart from this site-specific fraction of main source the exposure assessment for scenario IIIc is based on generic defaults.

Table 3.4 contains the input data of the local exposure assessment at formulation and processing. The PECs are given in **Table 3.5.** It is emphasized that the presented PECs in **Table 3.5** are the sum of the local concentration (C_{local}) and the regional background concentration ($PEC_{regional}$). The $PEC_{regional}$ is discussed in Section 3.1.2.3.

3.1.2.2.5 Production of glass fibres (scenario IIId)

Recently it has become clear that DBP is also used as a solvent in the production of fiber glass. Site-specific release data are available for one fiber glass producer in a EU member state, showing emissions to air and water. These site-specific data are used in combination with generic defaults for calculating the PECs. **Table 3.4** contains the input data of the local exposure assessment at fiber glass production. The PECs are given in **Table 3.5**. It is emphasized that the presented PECs in **Table 3.5** are the sum of the local concentration (C_{local}) and the regional background concentration ($PEC_{regional}$). The PEC regional is discussed in Section 3.1.2.3.

3.1.2.2.6 Processing of grouting agents (scenario IIIe)

DBP contents as high as 30-60% are found in polyurethane foams used in grouting applications for water control in tunnels, sewer systems, buildings etc. The grouting agents are used to reduce water leakages in such construction works. The polyurethane foam is injected into occuring point leakages in the cement, where it is expected to polymerise and expand rapidly. Although the total amount of DBP in this category is relatively low (<200 tpa), this usage may lead to rather direct releases into the (aquatic) environment. This because DBP is not covalently bound in the polyurethane foams and therefore releases may occur if the injected foam gets into contact with flowing water. DBP leakage rates of 0.16% (based on the injected product) have been found (Aquateam, 1999). An extensive monitoring program has been carried out in Norway for DBP

releases during a tunnel (Romeriksporten) construction period. DBP concentrations in the drainage water of the tunnel have been measured (Aquateam, 1999). In this construction project a total amount of 117 tonnes grouting agent has been used, corresponding to a total DBP amount of 35-70 tonnes DBP (30-60% DBP in grouting agent). With the measured levels in the drainage water of the tunnel PECs have been calculated in the receiving waters (river and fjord (sea)) using the US EPA dilution model "PLUMES". Data are presented in the next Section (3.1.2.2.7).

3.1.2.2.7 Measured local data in the environment

I Production

At present there are no measured data available of local water concentrations of DBP around DBP production sites.

IIIa Processing of PVC

Monitoring data became available from a site producing plasticized PVC imitation leather (Industry, 1999). Samples were taken in January 1999. Concentrations in soil (150 meters from stack emissions) were found to be 0.02 and 0.09 mg/kg dwt. An air level (100 meters from the emission source) of 0.18 μg/m^3 was measured. There is no discharge of process water. Water is stated to be only used as a cooling medium for the calendar.

Fatoki and Vernon (1990) concluded in their study on the presence of phthalate esters in rivers of the greater Manchester area, UK: "The concentration of DBP (average 25.38 ± 10.70 μg/l) was very high in both rivers and was a major component in all samples analyzed. The presence of phthalate esters in the rivers is not unexpected because some factories which make plastic products are located near the banks of these rivers, and discharge their wastewater either directly or indirectly into the rivers". The geographical relation between emission sources and sampling sites in this UK study is not exactly known, but these data may be indicative for a local situation.

Kördel and Müller (1992) analyzed the DBP content of soil samples taken close to a PVC coating plant with no waste air scrubbing facilities. A large number of soil samples of corn plantations and meadows within a radius of 1,000 m were analyzed. No DBP was detected in the soil samples from the corn plantation (detection limit: 0.025 mg/kg dry substance). The maximum concentration in the meadow soil samples was 0.170 mg/kg ds, but no DBP was detected in most samples.

IIIb-1 Adhesives production (formulation)

Monitoring data became available from an adhesives production site (emulsion polymerisation basis). Samples were taken in January 1999. Concentrations in soil (70 meters from stack) were found to be 0.03 and 0.85 mg/kg dwt. An air level (70 meters from stack) of 0.04 μg/m^3 was measured. Water concentrations of 0.3 and 0.5 μg/l were detected in the effluent from the company's purification system. This water is discharged to a municipal WWTP. Surface water samples were not taken, but they should be theoretically <0.5 μg/l (ignoring background).

IIIb-2 Adhesives processing, IIIc-1 printing ink formulation and IIIc-2 printing ink usage

No monitoring data available.

IIId Glass fibre production

DBP concentrations were analysed in 1999 in the effluent of a Dutch glass fibre production plant (Industry, 1999). DBP-levels of 1,400, 43 and <2 μg/l (detection limit) were found in, respectively, untreated effluent, treated (first step) effluent and treated (second step) effluent.

IIIe Grouting agent usage

DBP concentrations were measured in drainage water of a Norwegian tunnel where a DBP containing grouting agent was used (see section above). Near every week samples were taken during almost a year. The mean, 90-percentile and maximum concentration in the drainage water were found to be, respectively, 119, 197 and 432 μg/l. The drainage water is leading to the river Alna and further to the Oslofjord (marine ecosystem). With the measured drainage water levels, concentrations in the river Alna and Oslofjord (400 meters from Alna outlet) were estimated with the US EPA PLUMES dilution model. Mean, 90-percentile and maximum PECs in the Alna river are calculated to be, respectively, 4.1, 7 and 15 μg/l. For the Oslofjord the levels are 0.8, 1.4 and 3 μg/l.

3.1.2.2.8 Comparison of measured and calculated data

For some general aspects on DBP analytics: see Section 3.1.2.3. Section 3.1.2.3 also contains some local data that are not specifically related to DBP production or using sites (e.g. DBP levels in municipal WWTPs).

Only a limited comparison between local calculated and measured data is possible as measured data are available for two scenarios. **Table 3.6** presents both calculated and measured concentration for these scenarios, i.e. IIIa Processing PVC and IIIb-1 Formulation of adhesives. Measured data were found to be lower, but the difference is in general around one order of magnitude. It should be borne in mind that the calculated concentrations are not from "full generic" TGD scenarios, but that some site-specific information is already included (UCD for IIIa and fraction of main source for IIIb-1). Both measured and calculated data will be used in the risk characterisation for these scenarios.

Table 3.6 Comparison of local calculated and measured data

Scenario	Calculated (default scenario UCD/TGD)	Measured (site specific)
IIIa PVC		
Water (μg/l)	2.8 (incl. 1 μg/l background)	No discharge
Soil (mg/kg)	0.4 (wwt)	0.02, 0.09 and 0.17 (dwt)
Air (μg/m^3)	2.4	0.18
IIIb-1 formulation adhesives		
Water (μg/l)	8.9	<0.5
Soil (mg/kg)	1.8 (wwt)	0.03 and 0.85 (dwt)
Air (μg/m^3)	0.3	0.04

3.1.2.3 Regional and continental exposure assessment

3.1.2.3.1 Releases from diffuse sources

In the previous paragraphs the releases of DBP to the environment during production (life cycle stage I), processing in polymers (IIIa) and formulation and processing of adhesives (IIIb), formulation and processing of printing inks (IIIc), production of glass fibres (III-d) and processing of grouting agents (III-e) were investigated. A local exposure assessment was carried out for these life cycle stages (point sources).

This section will be focused on the releases from diffuse sources of DBP, i.e. the life cycle stages distribution (II), exterior end use (IV) and incineration/disposal (V). The results will be used in combination with the regional and continental data for life cycle stages I and IIIa/IIIb/IIIc/IIId for calculating the regional and continental PECs in the various environmental compartments. Emissions from scenario IIIe grouting agents were not used at a regional/continental scale as they are negligible at those scales.

Distribution (life cycle stage II)

Almost all phthalates, including DBP, consumed in the EU are distributed via road tankers (Cadogan et al., 1994). During distribution, losses may occur during the cleaning of the tanks. There are two estimates available for the losses of DBP to the aquatic environment from tank cleaning activities: 0.05% of total production (ECETOC, 1985) and 0.01 % of total consumption (Cadogan et al., 1994). The highest figure is chosen (worst-case approach) for an estimation of the aquatic releases of DBP from distribution activities in the EU:

$0.0005 \cdot 26{,}000$ = **13 tonnes per year in the EU**

Exterior end use (life cycle stage IV)

Losses of DBP during its exterior use in several products may occur due to a number of processes which include evaporation, microbial attack, hydrolysis, degradation, exudation and extraction (Cadogan et al., 1994). There are several release estimates available for these exterior end use losses of DBP which all have in common that they are high compared to those for the other life cycle stages (ECETOC, 1985; BUA, 1987; RIVM, 1991 and Cadogan et al., 1994).

For the DBP releases from plasticized PVC a figure of 5% of the annual consumption of DBP is used for the release estimation to water (Cadogan et al., 1994). The figure of 5% is based on an assumed product life of 7.5 years. For paint the losses to air are likely to be about 15% of the annual consumption (ECETOC, 1985). The ECETOC report does not give any further rationale for this estimate. The estimate for the losses from paint are assumed to be representative for adhesives as well.

PVC products:
$0.05 \cdot 11{,}000$ = **550 tonnes per year in the EU**

DBP in adhesives:
$0.15 \cdot 2{,}000$ = **300 tonnes per year in the EU**

Incineration/disposal (life cycle stage V)

About 35% of all the waste, including DBP containing products, is assumed to be incinerated in the EU. Modern incineration techniques result in complete combustion of DBP to carbon dioxide and water. This means that there will be virtually no DBP release for the incinerated fraction of DBP containing products.

The situation is different for DBP containing products that are landfilled. After dumping in landfills the plasticiser will be slowly leached from the product to groundwater. Cadogan et al. (1994) give an estimate of 0.25% of the total annual consumption for the plasticizer amount annually released from disposal of PVC products. This estimate is based on data for the phthalate ester DEHP. It should be borne in mind, however, that the water solubility of DBP is much larger than for DEHP, and thus the figure of 0.25% may underestimate the situation for DBP. As there are currently no better data available, the figure of 0.25% will be used:

$0.0025 \cdot 7{,}150 =$ **18 tonnes per year in the EU**
(7,150 (= $0.65 \cdot 11{,}000$) tonnes is the annual amount of DBP used in polymers in the EU that is landfilled (not incinerated)).

3.1.2.3.2 Regional and continental PECs

The calculations of PECs at a regional and continental scale were done using the EUSES model. The regional and continental input data are presented in **Table 3.7**.

The regional production data are based on the sum of the releases of producers A and B as they are known to be situated within the same region. For scenario IIIa the local assessment is carried out with default tonnages from the UCD on plastics. This default figure (1,235 t/a) is about 10% of the total EU tonnage for this application (13,500 t/a). For the continental input the local emissions are therefore multiplied with a factor 10. For the regional input local emissions are multiplied with a factor 5. This factor 5 (50/10) is deduced from the number of PVC processing sites (50) and the extrapolation factor from continent to region (10). For exterior end use and incineration/disposal it is assumed that 10% of the EU releases takes place in the region. All distribution activities of DBP are assumed to take place within one region (worst-case approach).

Table 3.7 Input data (daily release in kg) for calculating the regional and continental PECs

	Regional		Continental	
	Air	**Water**	**Air**	**Water**
I Production	0.15	47	0.33	47.8
II Distribution	0	36	0	36
IIIa Processing of polymers	51.3	2.1	102.6	4.1
IIIb-1 Formulation in adhesives	17.1	20.5	17.1	20.5
IIIb-2 Processing of adhesives	0.7	6.8	0.7	6.8
IIIc-1 Formulation in printing inks	8.6	10.3	8.6	10.3
IIIc-2 Processing/use of printing inks	170	1.7	170	1.7
IIId Production of glass fibres	19	0	19	0
IV Exterior end use	102.7	184.9	1,027	1,849
V incineration/disposal	0	6	0	60
Total	**370**	**315**	**1,345**	**2,036**

The results of the PEC calculations at a regional scale are shown in **Table 3.8**.

Table 3.8 Calculated regional PECs

	Regional
PEC in water (µg/l)	0.4
PEC in sediment (µg/kg)	89
PEC in air (µg/m^3)	0.006
PEC in soil (mg/kg)	0.01

3.1.2.3.3 Measured regional data in the environment

Phthalates frequently occur as plasticizers in analytical equipment and as contaminants in laboratory air and solvents. This can result in an overestimation of their concentration in environmental samples. Steps taken to avoid contamination are rarely described in the reports published before 1980 and, consequently the reliability of those data can often not be assessed (IPCS/WHO, 1995). Where available, therefore, only the more recent data are presented in this report. A compilation of measured concentrations (ranges) for DBP in the environment is presented in the following tables.

Table 3.9 Measured DBP concentrations in STPs

Location	Concentration	Source
Three STPs, Norway	influent range: 0.115- 0.827 (µg/l) effluent range: <0.06-1.54 (µg/l) sludge: 135-670 (µg/kg dw.)	Braaten et al. (1996)
Two STPs, Denmark	sludge: 340-350 (µg/kg dw.)	Krogh and Petersen (1997)
Five STPs, The Netherlands	influent range: <0.09-6.0 (µg/l) effluent range: <0.09-4.6 (µg/l)	Belfroid et al. (1998)
STP, Sweden	influent: 10-200 (µg/l) effluent: 0.1-2.0 (µg/l)	Paxéus (1996)
Five urban STPs, France, 1998	Effluent < 2 (µg/l) Sludge < 100 mg/kg suspended matter	Agence de l'eau (1999)
Effluent STP, UK, 1984	6.0 (µg/l)	Fatoki and Vernon (1990)

Table 3.10 Measured DBP concentrations in water

Location	Concentration (µg/l)	Source
Rhine (Lobith), 1988-1990	0.1-0.4	RIZA (1991)
Rhine (Lobith), 1996	0.3-0.4	RIVM (1996)
Rhine (Lobith), 1986	0.1-1.2	Ritsema et al. (1989)
Rhine (Lobith), 1997	0.4	Belfroid et al. (1998)
Lake IJssel, 1980-1988	0.3 - 1.2	idem
Lake IJssel (Andijk), 1992	6.9	RIVM (1996)
Meuse (Eijsden), 1988-1990	0.1-10.0	RIZA (1991)
Meuse (Eijsden), year unknown	0.5	Ritsema et al. (1989)
Meuse (Eijsden), 1996	0.2	RIVM (1996)
Meuse (Eijsden)	0.5	Belfroid et al. (1998)
Meuse (Keizerveer), 1996	0.5	idem
Lek (Hagestein), 1992	0.1-0.4	idem
Westerscheldt, year unknown	0.2	Ritsema et al. (1989)
38 samples in Noord Brabant, 1987/88	1-6	Zwalijs (1989)
Reeuwijk, 1996	0.7	RIVM (1996)
Marine/estuarine areas	0.007-3.4	BUA (1987); Renner et al. (1990)
Weser and tributaries 91/92	0.12-0.29	Furtmann (1993)
Rhine 91/92	<0.03-1.3	Furtmann (1993)
Rhine tributaries 91/92	<0.03-1.1	Furtmann (1993)
Lippe (2.5 km downstream Huls STP) 91/92	0.45	Furtmann (1993)
Elbe, 1986	<0.2-0.9	Jacobs and Mofid (1986)
Surface waters UK, 1984	12.1-33.5	Fatoki and Vernon (1990)
Groundwater close to dumping site	0.17-3.9	Furtmann (1993)
Four lakes, Norway, 1995/96	<0.060	Braaten et al. (1996)
Oslofjord, Drammensfjord, Grenlandsfjords, Iddefjord (seawater), Norway, 1995/96	<0.060	Braaten et al. (1996)
French rivers (La Moselle, La Sarre and Le Rhin), 1998	< 2	Agence de l'eau (1999)

Table 3.11 Measured DBP concentrations in sediment

Location	Concentration (mg/kg d.s.)	Source
Great rivers in NL, 1992	<0.1	RIVM (1993)
Small rivers in NL, 1992	≤0.1 (0.6 in Ketelmeer)	RIVM (1993)
Close to phthalate producers/users NL, 1993	≤0.1	RIVM (1993)
Ditches alongside highways NL, 1992/1993	<0.1	RIVM (1993)
Sediments	0.2-1.7	Jacobs and Mofid (1986)
STP sludge, 1992/1993	<2-9.1 (µg/l)	RIVM (1993)
Lake Constance	0.1-0.3	Giam and Atlas (1980)
Sediments in monitoring program, Sweden	0.001-0.182	Parkman and Remberger (1995)
Lake Mjosa, Norway, 1995/96	<0.020 (surface) 0.330 (15 cm deep)	Braaten et al. (1996)
3 lakes, Norway, 1995/96	<0.020 (surface and 15 cm deep)	Braaten et al. (1996)
Oslofjord, Drammensfjord, Grenlandsfjords, Iddefjord (seawater), Norway, 1995/96	<0.020- 0.102 (surface and 15 cm deep)	Braaten et al. (1996)
Rhine	0.14-2.2	Furtmann (1993)
Industrial harbours	0.05-0.42	Furtmann (1993)
Weser and tributaries	0.03-9.1	Furtmann (1993)
River Lippe, 1988-1990	1	Furtmann (1993)
Marine sediments Denmark, 1996-1997	0.1 to 2.4	Aagard (1998)

Table 3.12 Measured DBP concentrations in soil (not EU)

Location	Concentration (mg/kg)	Source
Port Credit/Oakville, Canada	<0.1-1.4	Golder Associates (1987) (in: IPCS/WHO, 1997)
Industrial site Quebec	0.027-0.175	MENVIQ (1989)

Table 3.13 Measured DBP concentrations in air

Location	Concentration (ng/m^3)	Source
Along Niagara river (Can.), 1982	1.9 ± 1.3 (gas phase) 4.0 ± 2.2 (part. phase)	Hoff and Chan (1987) (in: Canadian EPA, 1994)
idem, 1983	4.5 ± 3.5 (gas) 6.2 ± 2.6 (particulate)	Hoff and Chan (1987) (in: Canadian EPA, 1994)
Great Lakes area	0.5-5	Giam et al. (1978, 1980) Eisenrich et al. (1981)
Residential area Antwerp, 1976	24-74 (part.)	Cautreels et al. (1977)
Nordrhein-Westfalen	56	Furtmann (1993)
Sweden, 1984-1985	0.23-50	Thuren et al. (1990)
The Netherlands, 2000	9-77 (total range; 4 locations)	RIVM/ECPI (2000)

Table 3.14 Measured DBP concentrations in biota

Organism	Concentration (mg/kg)	Source
Fresh water fish (Canada)	0.5	NHW (1992)
Fresh water fish (USA)	<0.02 - 35 (wet weight)	De Vault (1985)
Aquatic invertebrates (Elbe)	0.3 - 0.8 (dry weight)	Jacobs and Mofid (1986)
Bream (Elbe)	0.2-0.5 (dry weight)	Jacobs and Mofid (1986)
Aquatic biota (Canada)	<10 (wet weight)	Canadian EPA (1994)
Egg yolk of cormorant/herring gull (Canada)	14.1/19.1 (lipid basis)	Zitko (1972)

3.1.2.3.4 Comparison of measured and calculated data

The risk characterisation should be based on the most realistic exposure information. Therefore, it has to be decided whether the available monitoring data can overwrite the calculated concentrations and thus be used in the risk characterisation. For this, a comparison is made between measured concentrations of DBP in the various environmental compartments and the corresponding calculated PECs.

Water

The regional surface water concentration of DBP based on EUSES calculations is 0.4 µg/l. **Table 3.10** shows that the mean regional measured DBP concentrations in surface waters range from 0.1 to 1 µg/l. From the comparison of measured and calculated data it can be concluded that the most relevant sources of exposure were likely taken into account.

The set of regional measured data of DBP in surface waters is considered as reliable and representative. Therefore a concentration of 1 µg/l, i.e. the upper limit of the range of average measured data, will be used for the risk characterisation at a regional scale.

Sediment

Table 3.11 shows that the mean measured concentrations of DBP range from 0.001 to 2.4 mg/kg (dry weight basis). The calculated regional sediment concentration of 0.09 mg/kg (wet weight basis) fits quite well within the measured range applying a correction factor of 2.6 for the conversion of dry weight to wet weight.

The concentration of 0.09 mg/kg will be used for the risk characterisation at a regional scale. As there are no monitoring data for the local situation, the calculated concentrations will be used for the risk characterisation at a local scale.

Soil

Calculated soil concentrations will be used for the risk characterisation of the terrestrial compartment, because of the very limited and not representative (not EU) set of monitoring data for soil.

Air

The limited data in **Table 3.13** indicate that the regional DBP concentrations in the EU range from 0.00023-0.077 µg/m^3. The calculated regional PEC of 0.006 µg/m^3 (**Table 3.8**) is found to be of the same order of magnitude, although it is below recent monitoring data in the Netherlands (RIVM/ECPI, 2000). Monitoring data for the local situation are lacking.

The set of regional measured data of DBP in air is considered to be too limited to overwrite the predicted concentrations. Therefore calculated air concentrations (local and regional) will be used for the risk characterisation. In the risk characterisation attention will be paid to the recent monitoring data.

Biota

Table 3.14 presents the measured DBP concentrations in various aquatic biota. Strictly speaking, there is only one figure that can be used for a comparison with the calculated concentrations in fish: 2-5 mg/kg DBP for bream in the river Elbe. (A conversion factor of 10 is used for extrapolating dry weight to fresh weight data.) Other data refer to non-EU situations or other aquatic organisms. The calculated regional PEC in fish amounts to 1.8 µg/kg. It would be speculative to discuss the difference. Local monitoring data are lacking.

Calculated fish concentrations (local and regional) will be used for the risk characterisation.

There are no monitoring data for DBP concentrations in worm.

3.2 EFFECTS ASSESSMENT

The subsequent paragraphs only contain the summary results of the ecotoxicity studies with DBP. The tests are discussed in more detail in the validated IUCLID HEDSET prepared by RIVM/TNO. In most cases the effect concentrations refer to nominal DBP concentrations.

3.2.1 Aquatic compartment

3.2.1.1 Toxicity to fish

The DBP short-term toxicity studies with fish are summarised in **Table 3.15**.

Table 3.15 Short-term toxicity data of DBP for fish

No.	Species	96h LC_{50} (mg/l) 95% C.I.	Method	Reference
1	*Brachydanio rerio*	2.2 (1.3-2.5)	semi static (EEC 92/69 C1)	Hüls (1994a)
2	*Pimephales promelas*	0.9 (0.7-1.2)	flow through (EG&G Bionomics, 1981)	CMA (1984)
3	*Pimephales promelas*	2.0 (1.3-2.9)	flow through (EPA-60018-81-011)	McCarthy and Whitmore (1985)
4	*Pimephales promelas*	1.3	static (APHA, 1971)	Mayer and Sanders (1973)
5	*Pimephales promelas*	3.0 (2.6-3.4)	static (EG&G Bionomics, 1982)	CMA (1984)
6	*Pimephales promelas*	1.1 (1.0-1.2)	static	Geiger et al. (1985)
7	*Oncorhynchus mykiss*	1.6 (1.1-2.2)	flow through (EG&G Bionomics, 1981)	CMA (1984)
8	*Oncorhynchus mykiss*	6.5	static (APHA, 1971)	Hudson et al. (1981)
9	*Ictalurus punctatus*	0.46	flow through	Mayer and Ellersieck (1986)
10	*Ictalurus punctatus*	2.9	static (APHA, 1971)	Mayer and Sanders (1973)
11	*Lepomis macrochirus*	0.9 (0.7-1.0)	static (EG&G Bionomics, 1982)	CMA (1984)
12	*Lepomis macrochirus*	0.7	static (APHA, 1971)	Mayer and Sanders (1973)
13	*Lepomis macrochirus*	1.2 (1.0-1.4)	static (EPA, 1975)	CMA (1984)
14	*Lepomis macrochirus*	1.2 (1.0-1.4)	static	Buccafusco et al. (1981)
15	*Perca flavescens*	0.35	flow through	Mayer and Ellersieck (1986)
16	*Leuciscus idus*	7.3 (4.6-10)	static (DIN 38 412, 1982)	CMA (1984)

The IPCS document on DBP contains a few long-term toxicity studies with fish (IPCS/WHO, 1997). The lowest NOEC was observed in a 99-day test (60 days posthatch) with *Oncorhynchus mykiss* (Ward and Boerie, 1991). A measured value of 100 µg/l was established based on growth as the most sensitive endpoint.

3.2.1.2 Toxicity to aquatic invertebrates

The short-term toxicity data of DBP for aquatic and marine invertebrates are presented in **Table 3.16**.

Table 3.16 Short-term toxicity of DBP to aquatic invertebrates

No.	Species	Result (mg/l) 95% C.I.	Method	Reference
1	*Daphnia magna*	3.4 (48 h EC_{50})	EE92/69	Hüls (1994b)
2	*Daphnia magna*	5.2 (4.7-5.6) - (48 h EC_{50})	Other	McCarthy and Whitmore (1985)
3	*Daphnia magna*	17 (24 h EC_{50})	Other	Kühn et al. (1989)
4	*Daphnia magna*	3.4 (3.1-3.8) - (48 h EC_{50})	EG&G Bionomics (1982)	CMA (1984)
5	*Chironomus plumosus*	0.76 (48 h EC_{50})	Other	Streufert et al. (1980)
6	*Mysidopsis bahia*	0.8 (0.6-0.9) - (96 h $LC(I)_{50}$)	Other	EG&G Bionomics (1984a)
7	*Nitocra spinipes*	1.7 (1.3-2.2) - (96 h $LC(I)_{50}$)	Other; brackish water	Lindén et al. (1979)
8	*Gammarus pseudolimnaeus*	2.1 (96 h LC_{50})	APHA (1971)	Mayer and Sanders (1973)
9	*Paratanytarsus parthenogenetica*	5.8 (96 h EC_{50})	Other	EG&G Bionomics (1984b)
10	*Artemia salina*	8 (24 h LC_{50})	Other; seawater	Hudson et al. (1981)

Table 3.17 Long-term toxicity of DBP for aquatic invertebrates

No.	Species	Result (mg/l)	Method	Reference
1	*Daphnia magna*	1 (21 d NOEC)	Other	Kuhn et al. (1989)
2	*Daphnia magna*	0.56 (16 d NOEC)	OECD202	McCarthy and Whitmore (1985)
3	*Daphnia magna*	1.05 (21 d EC_{50})	EPA 600/8-87/011	DeFoe et al. (1990)
4	*Dugesia japonica*	0.54 (7 d EC_{50})	Other	Yoshioka et al. (1986)
5	*Gammarus pulex*	0.10 (10 d NOEC)	Other, flow through	Thurén and Woin (1991)

The IPCS document on DBP (IPCS/WHO, 1997) contains some other long-term toxicity studies with aquatic invertebrates. The effect concentrations in these tests were all larger than 100 µg/l.

3.2.1.3 Toxicity to algae

The short-term toxicity studies with DBP for freshwater and marine algae are summarised in **Table 3.18**.

Table 3.18 Short-term toxicity of DBP to algae

No.	Species	Result (mg/l)	Method	Reference
1	*Scenedesmus subspicatus*	1.2 (72 h EC_{50})	92/69/EEC	Hüls (1995)
2	*Scenedesmus subspicatus*	3.5 (48 h EC_{50}; biomass)	DIN 38412/9	Kühn and Pattard (1990)
3	*Scenedesmus subspicatus*	9.0 (48 h EC_{50}; growth rate)	DIN 38412/9	Kühn and Pattard (1990)
4	*Gymnodium breve*	0.0034 - 0.2 (96 h EC_{50})	Other	Wilson et al. (1978)

The test with the marine *dinoflagellate Gymnodium breve* showed a very poor reproducibility. In the first assay an EC_{50} of 0.0034 mg/l was established, whereas in the second, a value of 0.2 mg/l was found. It is doubtful whether such a large difference can be attributed to biological variation. This is supported by the fact that the variation between the replicates was much smaller in the tests with other phthalate esters in the same study. The BUA report (BUA, 1987) revealed some more, technical shortcomings of the Gymnodium test. For these reasons the test results will not be used for the derivation of the PNEC for the aquatic compartment.

The NOEC values for both freshwater and marine algae are presented in **Table 3.19**.

Table 3.19 NOEC values of DBP for algae

No.	Species	Result (NOEC in mg/l)	Method	Reference
1	*Selenastrum capricornutum*	2.8 (7 d)	Other	Melin and Egnéus (1983)
2	*Selenastrum capricornutum*	0.8 (10 d)	EGG-CMA-002	CMA (1984)
3	*Skeletenoma costatum*	0.6-0.7 (? d)	Other (marine)	Medlin (1980)
4	*Dunaliella parva*	0.2 (8 d)	Other (marine)	Acey et al. (1987)
5	*Thalassiosira pseudomona*	2.0 (4 d)	Other (marine)	Acey et al. (1987)
6	*Synecchococcus lividus*	0.002 (14 d LOEC)	Other (marine)	Acey et al. (1987)

It is necessary to discuss the 14-day LOEC of 0.002 mg/l for the blue-green algae *Synecchococcus lividus* in more detail. At DBP concentrations of 0.002 mg/l and higher, the number of monodispersed (i.e. non-aggregated) cells of the blue-green algae was found to be significantly decreased. This effect, however, can be fully attributed to a DBP induced shift from non-aggregated towards aggregated cells. At each concentration of DBP tested namely, the percentage of aggregated *S. lividus* was found to be increased: at 0.002 mg/l about 95% of the algae were in aggregated form as opposed to 22% in the control group. In addition, when counting the total number of *S. lividus*, i.e. both aggregated and non-aggregated organisms, a significant increase was found at all test concentrations. In conclusion it can be said that DBP caused a decrease only in the number of non-aggregated *S. lividus*. Nevertheless, very low concentrations of DBP seem to affect the growth behaviour of these blue-green algae. At present,

however, the ecological significance of this effect is unknown and therefore the value will not be used for the PNEC derivation.

3.2.1.4 PNEC for the aquatic compartment (incl. sediment)

The PNEC for the aquatic compartment is derived from the 99-day NOEC of 100 µg/l for *Onchorhynchus mykiss*. This key study is supported by the *Gammarus pulex* study in which a similar value was found based on a decrease in the locomotor activity. An assessment factor of 10 will be used for the extrapolation. This factor is used because long-term NOECs for three trophic levels are available.

$PNEC_{aquatic}$ = 10 µg/l

As there are no laboratory data for the toxicity of DBP to sediment-dwelling organisms, the equilibrium method is used for the derivation of a PNEC in sediment:

$$\begin{aligned} \mathbf{PNEC_{sediment}} &= K_{sed,\ water}/RHO_{sed} \cdot PNEC_{aquatic} \cdot 1{,}000 \\ &= 159/1{,}300 \cdot PNEC_{aquatic} \cdot 1{,}000 \\ &= 122 \cdot PNEC_{aquatic} \\ &= 122 \cdot 0.010 \\ &= \mathbf{1.2\ mg/kg}\ \text{(wet weight)} \\ &= \mathbf{3.1\ mg/kg}\ \text{(dry weight)} \end{aligned}$$

A - poorly reported - multi-species experiment was carried out, in which effects of DBP on benthic estuarine communities was studied at concentrations of 10, 100 and 1,000 mg/kg (Tagatz et al., 1986). Laboratory and field colonized sand-filled (no characteristics given) boxes containing 40-58 species from 7-9 phyla were exposed for 8 weeks. Measured concentration in sediments were 4-48% of nominal at the end of the experiment, while water samples contained 30-53 µg/l on day 2, while no DBP was detected after 7 days. Only at the highest concentration effects on the community structure was observed, in the field as well as in the laboratory exposed sediments. As the study is poorly reported and only sum parameters could be studied (low number per species), the $PNEC_{sed}$ of 1.2 mg/kg ww based on equilibrium partitioning is preferred over a $PNEC_{sed}$ based on this multi-species study

3.2.1.5 Toxicity to microorganisms

The toxicity studies with microorganisms are summarised in **Table 3.20**. The table contains both data for bacteria and protozoa.

Table 3.20 Toxicity of DBP to microorganisms

No.	Species	Result (mg/l)	Method	Reference
1	*Pseudomonas putida*	>10 (30 min NOEC)	DIN 38412/27	BASF (1989)
2	*Pseudomonas putida*	>10 (6 h EC_{10})	Other	Hüls (1995)
3	*Tetrahymena pyriformis*	2.2 (24 h EC_{50})	Other	Yoshioka et al. (1985)
4	*Photobacterium phosphoreum*	10.9 (30 min EC_{50})	Microtox	Tarkpea et al. (1986)

In both *Pseudomonas putida* tests no effects of DBP were found even at concentrations above the water solubility of the substance. The low toxicity of DBP to bacteria is supported by the results of the biodegradability test (Huls study, 1995; modified Sturm test). In this test, showing ready biodegradability of DBP, a test concentration of 21.7 mg/l was used.

The MICROTOX test cannot be used for the derivation of a $PNEC_{microorganisms}$ that is relevant for a STP situation, as a saltwater species is used.

3.2.1.6 PNEC for microorganisms

The test with *Tetrahymena pyriformis* can be used to derive a $PNEC_{protozoa}$: applying a factor 10 on the EC50 leads to a value of 0.22 mg/l. For DBP: **$PNEC_{STP}$ =0.22 mg/l**

It is realised that this PNEC is low compared to the fact that no biodegradation impairment of DBP was found at concentrations far above the water solubility (see above).

3.2.2 Terrestrial compartment

Invertebrates

For the earthworm *Eisenia fetida* a 48-hour LC_{50} of 1.4 mg/cm^2 was found in a contact test in which DBP was applied to filter paper. The toxic unit refers to the amount of chemical per cm^2 of paper (Neuhauser et al., 1986).

DBP applied to female house flies topically or by injection at a concentration of 20 µg/fly (1,000 µg/g) was not toxic, causing a mortality of less than 16% after 24 hours (Al-Badry and Knowles, 1980).

Both invertebrate tests are considered not to be useful for deriving a PNEC for the terrestrial environment.

Plants

In a limited greenhouse experiment in which seeds of corn *Zea mays* were planted in a sandy soil containing 0 to 20,000 mg DBP/kg, germination was not affected at any concentration. After 3 weeks of exposure, plant height and shoot fresh weight were reduced significantly at 2,000 mg/kg (17% and 25%, respectively); a concentration of 200 mg/kg was without effect (NOEC). After planting a second group of seeds in the soils, plant growth was only reduced at 20,000 mg/kg, while concentrations <2,000 mg/kg were without effect. These results indicate that plant-available DBP levels have decreased through complex formation with soil components and/or by degradation (Shea et al., 1982).

In laboratory tests in which spinach and pea seeds were planted in potting soil, the effects of DBP and three other phthalate esters on plant height were investigated. No effects were found after 2 weeks of exposure to concentrations up to 1,000 mg/kg DBP. The test substance was added to the soil as aqueous solution. The effect of germination was studied with tap water to which a methanol solution of DBP was added at concentrations of 100 to 1,000 mg/l. DBP inhibited germination at 1,000 mg/l, especially that of pea seeds. No effects were found on the subsequent development of the seeds that did germinate (Herring and Bering, 1988). It should be

noted, however, that this test concentration was much higher than the saturation concentration of DBP in water.

PNEC for terrestrial compartment

The NOEC of 200 mg DBP/kg for *Zea mays* can be used for the derivation of the PNEC for the terrestrial compartment. According to the TGD, an assessment factor of 100 should be used:

$PNEC_{terrestrial}$ = 2 mg/kg dw

For comparison also a $PNEC_{terrestrial}$ is derived based on equilibrium partitioning. This gives a value of 1.24 mg/kg dw using a $K_{soil\text{-}water}$ of 190 m^3/m^3, which is in agreement with the $PNEC_{terrestrial}$ derived above.

3.2.3 Atmospheric compartment

Plants

There are a number of studies on the airborne toxicity of butyl phthalates to plants. In these studies, plants were exposed in a growth chamber or in a glasshouse to DBP vapour originating from plastics which contained DBP as a plasticizer or from substrates moistened with DBP. In most studies, the test compound DBP is di-n-butyl phthalate. However, in the study by Hardwick et al. (1984), "total DBP" includes DIBP and INBP.

The results of the studies summarised in **Table 3.21** show a wide range of effect levels of butyl phthalates, ranging from 1.2 µg/m^3 (Hardwick et al., 1984) to 1,000 µg/m^3 (Virgin et al., 1981). This wide range of effect levels is partly due to limitations of the studies, namely the use of only one test concentration and the unquantified or poorly quantified response with respect to chlorosis, growth and/or mortality. This is clearly demonstrated by the data for seedlings of radish *Raphanus sativus cv. Cherry Belle*, which show effect levels in the range of <100 to 1,000 µg DBP/m^3, with respect to chlorosis. However, the wide range of effect levels is also partly due to real differences in sensitivity among plant species. The large interspecies variation in sensitivity to butyl phthalates is confirmed by data on phytotoxic effects observed in the horticulture in glasshouses and confirmed by bioassays. Some species of *Cruciferae*, notably summer cabbage *Brassica oleracea* and radish *Raphanus sativus*, are (among) the most sensitive plant species, followed by tomato and spinach. Lettuce, pea, grasses, nettle and yarrow are relatively resistant. There may also be a large variation in sensitivity among different varieties of single species. For example, seedlings of sixteen Brassica varieties tested in a study by Fyfield et al. (1984) varied in response to DBP from "highly sensitive" (summer cabbage B. *oleracea var. capitata cv. Derby Day*; see also **Table 3.21**) to "comparatively resistant" (Brussels sprout B. *oleracea var. gemmifera cv.* Asmer Leander).

Table 3.21 Toxicity of airborne butyl phthalates to plants

Plant species & life stage	Exposure time (d)	Criterion	Endpoint	Result * (µg/m³)	Compound **	Ref.
Brassica oleraca; seedlings	30	EC	chlorosis; growth inh.; mortality	1.2 (0.6-2.0)	DBP + DIBP + INBP	Hardwick et al. (1984)
Brassica oleraca; seedlings	14	NOEC	chlorosis; growth inh.; mortality	0.12 (0.11-0.14)	DBP + DIBP	Hardwick et al. (1984)
Brassica oleraca; seedlings	30	EC	chlorosis; growth inh.; cotyledon mortality	360	DBP + DIBP + INBP	Hardwick et al. (1984)
Raphanus sativus; seedlings	>7	EC	chlorosis; mortality	10 --> 150	DBP	Virgin et al. (1981)
Raphanus sativus; seedlings	10	EC	chlorosis	63 (40-88)	DBP	Virgin (1988)
Raphanus sativus; seedlings	7	EC	chlorosis	1,000	DBP	Virgin et al. (1981)
Raphanus sativus; seedlings	12	EC	chlorosis; mortality	170 (160-180)	DBP or DIBP	Hannay and Millar, (1986)
Raphanus sativus; 15-d old plants	13	EC	photosynth.	120	DBP	Hannay and Millar, (1986)
Triticum aestivum; seedlings	10	NOEC	chlorosis	>65 (31-91)	DBP	Virgin (1988)
Browalia speciosa; rooted sprouts	7	EC	chlorosis	1,000	DBP	Virgin et al. (1981)
Browalia speciosa; rooted sprouts	>7	EC	chlorosis; mortality	10 --> 150	DBP	Virgin et al. (1981)

* Average exposure concentration (between brackets: total range of concentrations)
** DBP = di-n-butyl phthalate; DIBP = diisobutyl phthalate; INBP = iso-n-butyl phthalate

The main effect of butyl phthalates observed in the studies summarised in **Table 3.21** is chlorosis (i.e. the absence or disappearance of chlorophylls, the green pigments in the leaves of green plants, resulting in inhibition of photosynthesis). Leaves of affected plants also lack yellow pigments such as carotenoids and show accumulation of the carotenoid precursor phytoene. Therefore, the lack of chlorophylls is considered to be a secondary effect caused by the lack of yellow pigments. Mature, fully expanded leaves are less sensitive to chlorosis as they already possess a full complement of carotenoids and chlorophylls, while developing leaves lack these pigments. Hence, seedlings are more sensitive than mature plants. In severe cases, exposure to butyl phthalates results in necrotic leaves, growth inhibition and mortality of plants. The effects of butyl phthalates are inversely related to light intensity, as shown by Virgin et al. (1981) and Virgin (1988). The latter study shows complete chlorosis in radish, but no chlorosis in wheat, although external (in air) and internal (in plants) DBP levels were very similar. This study confirms the differences in sensitivity among species.

The study of Hardwick et al. (1984) with seedlings of summer cabbage *B. oleracea cv*. Derby Day resulted in severe effects, including mortality, at an average concentration of total butyl phthalates (DBP, DIBP and INBP) of 1.2 µg/m^3 (range 0.57 to 2.01 µg.m^{-3}), while no effects were observed at 0.12 µg/m^3 (range 0.11 to 0.14 µg/m^3). This study does not allow an evaluation

of the phytotoxic effects of butyl phthalates on a compound by compound basis. However, *in vitro* tests with isolated chloroplasts of spinach (Millar and Hannay, 1986) showed equitoxic responses for DBP and DIBP with respect to the inhibition of photosynthesis, suggesting that the butyl phthalates are equitoxic to plants. Effect concentrations observed in other studies, mostly conducted with DBP, are at least one order of magnitude higher. The effect concentration of 0.2 µg DBP.m^{-3} mentioned by Hardwick and Cole (1986) cannot be evaluated. Therefore, and because of the high sensitivity of *B. oleracea cv*. Derby Day to butyl phthalates, an average concentration of (rounded) 1 µg/m^3, range 0.5 to 2.0 µg/m^3, is considered to be the LOEC for butyl phthalates. It has to be borne in mind that the climate in glasshouses (high temperature, humidity and light intensity) usually results in a higher sensitivity of plants to air pollution. With respect to butyl phthalates, at least light intensity is a factor that increases the phytotoxic effects. The study of Hardwick et al. (1984) does not allow the derivation of a reliable NOEC, because the exact exposure time and exposure concentration in the control compartment of the glasshouse are not known (In the 10 days preceding the relatively short 2-w "exposure" period that butyl phthalates were detected in this compartment, no measurements were made). Nevertheless, an average concentration of (rounded) 0.1 µg/m^3 is considered to be a fairly good estimate of the plant NOEC for butyl phthalates.

PNEC for plants

The NOEC of 0.1 µg/m^3 DBP will be used for the derivation of the PNEC for plants. The TGD does not give any guidance for the derivation of a $PNEC_{plants}$. Although the experiments were carried out under unfavourable greenhouse conditions and, additionally, the NOEC seems to be based on a very sensitive species, from a consistency point of view a factor of 10 is applied on the NOEC. This leads to the provisional value given below.

$PNEC_{plants\text{-}air}$ = 0.01 µg/m^3

It was decided that for the final risk characterisation of DBP a more reliable $PNEC_{plants,\ air}$ should be derived by additional testing (see Risk characterisation). A follow-up test with three plant species was already conducted in the meantime (Infracor, 2000). The results of this 15-day exposure test are unequivocal: very distinct effects were found on Chinese cabbage at all tested concentrations (range actual concentrations: 11.8-15.2 µg/m^3). No or less severe effects were found on oat and cress. Cabbage was found to be the most sensitive species which is in accordance with available literature data (see above). The current EC100 result of 11.8 µg/m^3 for Brassica seems also to be in line, at least not contradicting, with literature data: (L)NOECs around 0.1- 2 µg/m^3 were reported. As no NOEC could be derived from this study it was concluded that further, chronic testing has to be carried out. It was agreed to perform a 3-4 months fumigation test with seven plant species (including Brassica).

Following the establishment of criteria for R54 (toxic to flora), application to DBP could also be considered.

3.2.4 Secondary poisoning

The effects of a diet of 10 mg DBP/kg on egg shell thickness, breaking strength, permeability and shell structure of ring dove (*Streptophelia risoria*) eggs were examined in a 3-week experiment (Peakall, 1974). Egg shell thickness was found to be decreased (10%), whereas the water permeability increased (23%). A 15% decrease in shell thickness is considered significant for reproductive effects. Rapid recovery occurred upon cessation of exposure.

An ED_{50} of 33 µmol (9.19 mg) per egg was calculated for DBP in a chicken embryo toxicity study (Korhonen et al., 1983).

As no more information is available on the effects of DBP on higher organisms other than laboratory mammals, the overall oral LOAEL of 52 mg/kg bw (see Section 4.1.2.9) will be used for the derivation of the PNEC for predators (conversion factor = 20, assessment factor = 10), resulting in a:

$PNEC_{oral}$ = 104 mg/kg in food

It has to be borne in mind that this PNEC is derived from a LOAEL. The TGD does not give assessment factors for LOAELs. The assessment factor for NOAELs is used now, but this may have resulted in an underestimation (an extra factor of 3-10) of the $PNEC_{oral}$.

3.2.5 Estrogenic activity

DBP reduced the binding of 17β-estradiol to the receptor in an assay with cytosolic liver extracts of rainbow trout at concentrations of approximately 10^{-5} to 10^{-7} M (Jobling et al., 1995). According to the authors these figures cannot be used to predict estrogenic activity *in vivo*. Ankley et al. (1997) state that there is a need for standard operating procedures for these types of tests. One of the issues that needs to be addressed is whether the estrogen or androgen receptor binding affinity varies widely among fish species.

In vivo testing, in which endpoints have been studied relevant to estrogenic activity, have been carried out with invertebrates and fish. With respect to invertebrates it is still unclear what the actual role of androgens and estrogens is in invertebrate development and reproduction (Ankley et al., 1997). The long-term test with *D. magna* is carried out with the parthenogenic stage of this species, which limits the ability to detect a substance affecting sexual reproduction. It has been concluded in various international workshops that test methods still have to be developed for invertebrates to assess estrogenic activity (EDSTAC, 1998).

Several long-term tests have been carried out with fish. The critical study is an early life-stage test with rainbow trout by Ward and Boerie (1991). Endpoints studied were egg hatchability and survival, fry survival and growth measured as length and weight. At the moment it is discussed - for example by the OECD (EDTA, 1998) and US EPA (EDSTAC, 1998) - whether the current guidelines should be enhanced to make them suitable to identify whether a substance is an endocrine disrupter. Enhancement may include several biochemical - for example vitellogenin analysis- and histological analyses of the gonads.

Summarising, DBP showed estrogen receptor affinity *in vitro*. Several long-term tests with fish and invertebrates are available, but specific endpoints with respect to estrogenic activity were not studied in these tests. However, internationally accepted guidelines for such a test are not available at the moment.

3.3 RISK CHARACTERISATION

Table 3.22 Local PEC/PNECs in the various compartments at production

PEC/PNEC	Site-spec. A	Site-spec. B	Site-spec. C
STP	0.3	$3.4 \cdot 10^{-4}$	0.4
Surface water	0.4	0.1	0.6
Sediment	0.4	0.1	0.7
Soil	0.7	$3.3 \cdot 10^{-4}$	$3.2 \cdot 10^{-4}$
Oral, fish	$3.5 \cdot 10^{-5}$	$1.7 \cdot 10^{-5}$	$3 \cdot 10^{-5}$
Oral, worm	0.07	$6 \cdot 10^{-4}$	$6 \cdot 10^{-4}$
Pant (air)	2	2	2

Table 3.23 Local PEC/PNEC ratios at formulation/processing

PEC/PNEC for Scenario	IIIa	IIIb-1	III-b2	III-c1	III-c2	III-d	IIIe
Type of application	Plasticizer softener in PVC	adhesive		printing inks		fibres	grouting agent
STP	0.08	0.4	0.09	0.05	0.002	0	-.
Surface water	0.3	0.9	0.3	0.2	0.1	0.1	0.7 (A) [1] 0.1 (O)
Sediment	0.3	1	0.3	0.2	0.1	0.11	-
Soil	0.2	0.9	0.2	0.1	$5.9 \cdot 10^{-3}$	0.002	-
Oral, fish	$3 \cdot 10^{-5}$	$7.3 \cdot 10^{-5}$	$3 \cdot 10^{-5}$	$2.5 \cdot 10^{-3}$	$1.8 \cdot 10^{-5}$	$1.7 \cdot 10^{-5}$	-
Oral, worm	0.02	0.1	0.02	0.01	$1.2 \cdot 10^{-3}$	$7.4 \cdot 10^{-4}$	-
Plant (air)	236	34	1	5	20	100	-

[1] A= Alna river; O=Oslofjord
PEC/PNEC based on 90-percentile PEC

3.3.1 Aquatic compartment (incl. sediment)

STP

The $PNEC_{microorganisms}$ for DBP was set at 220 µg/l. (see Section 3.2.1.5). For the risk characterisation this value is compared with the PEC_{STP} for the various exposure scenarios. The PEC/PNEC ratios for production and formulation/processing are shown in **Tables 3.22** and **3.23**, respectively. For production and processing all PEC/PNEC ratios were found to be below 1 **(conclusion (ii)).**

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

Surface water

The PNEC for surface water was set at 10 µg/l (see Section 3.2.1.4). For the risk characterisation this value is compared with the PEC in surface water for the various exposure scenarios. The PEC/PNEC ratios for production and formulation/processing are shown in **Tables 3.22** and **3.23**, respectively. For production and processing all aquatic PEC/PNEC ratios were found to be below 1 **(conclusion (ii)).** It should be noted that for scenario IIIe grouting agent the PEC/PNEC based on the maximum (rather than 90 percentile) estimated PEC would amount to 1.5. The current scenario IIIe is based on a Norwegian case and extrapolation to other EU situations is difficult. The general conclusion, however, is that environmental releases of DBP during grouting activities may reach high levels in surface water. Therefore the environmental impact of these kinds of operations should be carefully assessed/monitored. Apart from a few rather old monotoring data (1984) the local and regional measured surface water concentrations were found to be below the PNEC **(conclusion (ii)).** The same is true for the calculated regional water concentration.

Sediment

The PNEC for sediment is 1.2 mg/kg wwt/3.1 mg/kg dwt (see Section 3.2.1.4). As both the PNEC and the PEC were calculated with the equilibrium partitioning method from the water data, the same conclusions as for water can be drawn. In addition, most of the available monitoring data as presented in Table 3.1.1.9 are lower than the PNEC for sediment-dwelling organisms. Only the upper limit of the Furtmann data (1993) for the river Lippe is higher than the PNEC (PEC/PNEC = 3). Recent marine sediment data (1997) in Denmark indicated that levels (maximum 2.4 mg/kg dwt) very close to the PNEC (fresh water based) could be found. Additional monitoring in marine sediments and identification of emission sources could be relevant. The PEC/PNEC ratio based on a calculated regional PEC sediment is 0.3 **(conclusion (ii))**.

3.3.2 Terrestrial compartment

The PNEC for the terrestrial compartment is 2 mg/kg dw (1.8 mg/kg wwt) (see Section 3.2.2). For the risk characterisation this value is compared with the PEC in soil for the various exposure scenarios. The PEC/PNEC ratios for production and formulation/processing are shown in **Tables 3.22** and **3.23**, respectively. For production and processing all PEC/PNEC ratios were found to be below 1 **(conclusion (ii))**. Measured local data and the calculated regional PEC were found to be below the PNEC **(conclusion (ii))**.

3.3.3 Atmospheric compartment

The provisional PNEC for the atmospheric compartment is 0.01 µg/m^3 (see Section 3.2.3). A comparison of this PNEC with the calculated PECs (production and formulation/processing), including the calculated regional PEC and measured local data, shows that all PEC/PNEC ratios are above 1 **(conclusion (i)).** The same is true for the recent (2000) air monitoring data from the Netherlands. As for the production scenarios the local PECs are already based on site-specific data, a chronic fumigation test with plants has to be conducted.

Conclusion (i) There is need for further information and/or testing.

3.3.4 Secondary poisoning

The PNEC $_{oral}$ is 104 mg/kg (see Section 3.2.4). For the risk characterisation this value is compared with the PECs in fish and worm for the various exposure scenarios. The PEC/PNEC ratios for production and formulation/processing are shown in **Tables 3.22** and **3.23**, respectively. All PEC/PNEC ratios were found to be far below 1 **(conclusion (ii)).** It should be noted that with the application of a higher BCF-value based on tests with ^{14}C-labelled DBP (see Section 3.1.1) the risks for secondary poisoning would still be low.

4 HUMAN HEALTH

4.1 HUMAN HEALTH (TOXICITY)

4.1.1 Exposure assessment

4.1.1.1 General discussion

The human population may be exposed to dibutyl phthalate (DBP) at 1) the workplace, 2) from use of consumer products, and 3) indirectly via the environment. An overview of the uses of DBP (industrial and use categories) is given in **Table 2.2**.

The human population can be exposed to DBP by inhalation and ingestion as well as after dermal contact.

DBP is or may be produced in the following chemical industries with the mentioned purposes (see also Section 2):

- basic chemicals: production of dibutyl phthalate;
- polymer industry:
  - plasticizer in Poly Vinyl Alcohol (PVA);
  - plasticizer in Poly Vinyl Chloride (PVC);
  - plasticizer in rubber industry; polychloroprene rubber acrylonitrile-butadiene copolymer(nitrile) rubber;
  - solvents for nitrocellulose esters, colours, oils, natural resins;
- lacquers and varnishes industry: softener;
- printing ink industry: use as a softener;
- additive in textile industry;
- additive in insecticides;
- polymethylmethacrylate for the purpose of pigment- and additive pastes.

Because of its relatively high volatility, compared to other plasticizers, DBP is only used in combination with other plasticizers, mostly high molecular phthalates. DBP has a better low temperature flexibility in soft PVC than for example diisobutyl phthalate (DIBP).

DBP has been used in making flexible plastics that are part of many consumer products, including home furnishing, paints, clothing and cosmetic products. In Denmark DBP has been found in 1,176 products accounting for 2,848 tonnes/year (Danish Product Register, 1995). In 94 products accounting for 388 tonnes/year the concentration of DBP is 80-100%. In Sweden DBP has been found in 343 products, 38 of which are available to consumers (KEMI, 1995).

Because of its diverse uses dibutyl phthalate is widespread in the environment and has been identified in air, water and soil (ATSDR, 1990). Human exposure via the environment may occur through contact with contaminated air, water, soil or food.

4.1.1.2 Occupational exposure

4.1.1.2.1 Exposure scenarios

During the production of DBP, in the polymer industry and in the paint and printing industry worker may be exposed to DBP. Possible exposure patterns are given below.

Production of dibutyl phthalate:
- the production of DBP takes place in closed systems; exposure may occur through system leaks;
- cleaning the tanks in which dibutyl phthalate has been produced;
- drumming of the dibutyl phthalate.

Polymer industry:
- adding (manual handling of the agent);
- mixing the agent;
- removing the batch and afterwards forming into shapes:
- extruding
- calendering
- spray moulding
- confectionating.

Paint/printing ink industry:
- mixing of the product;
- drumming.

The use of products may include the following activities.

Dibutyl phthalate is used as a plasticizer in the polymer industry (FIOH, 1995; Morton, 1987). Below the uses of DBP as plasticizer are given.

DBP is used in gels like PVC used for customer purposes such as garden hoses. It is also used in polychloroprene rubber and nitrile rubber. Phthalates improve low temperature serviceability of the product. It is not used in all polychloroprene (neoprene) or nitrile rubbers.

Next to this purpose it is used as a softener in PVA adhesives, lacquers, varnishes and printing inks. The main uses of PVA are in textile and paper sizing, as adhesives and as an emulsion-polymerization aid.

Exposure is possible due to inhalation of vapours as well as due to skin contact.

Workers in the polymer industry are potentially exposed especially those workers that may have more or less direct contact with the substance. It concerns workers drumming the (pure) substance or products containing the substance and workers transferring the substance or products to other systems in the chemical industries.

Workers active in the mixing step and the forming step (calendering, spray coating, extruding, moulding) of the process in the rubber industry are also potentially exposed. This also holds for workers using products in the paint industry.

The following data are used for occupational exposure assessments:

- physico-chemical data of dibutyl phthalate, physical appearance, vapour pressure at different temperatures;
- data regarding methods and use pattern of the product; temperature at which production processes take place; amount of dibutyl phthalate used in the different products;
- exposure data from the HEDSET;
- measured data from DBP or analogues;
- results from exposure models (EASE model, EPA transfer model).

The exposure is assessed using the available information on substance, processes and work tasks. More detailed information on these parameters may lead to a more accurate exposure assessment.

In this part of the assessment, external (potential) exposure is assessed using relevant models and other available methods in accordance with the TGD and agreements made at official Meetings of Competent Authorities. Internal dose depends on external exposure and the percentage of the substance that is absorbed (either through the skin or through the respiratory system).

The exposure is assessed without taking account of the possible influence of personal protective equipment (PPE). If the assessment as based on potential exposure indicates that risks are to be expected, the use of personal protective equipment may be one of the methods to decrease actual risks, although other methods (technical and organisational) are to be preferred. This is in fact obligatory following harmonized European legislation.

Knowledge of effectivity of PPE in practical situations is very limited. Furthermore, the effectivity is largely dependent on site-specific aspects of management, procedures and training of workers. A reasonably effective use of proper PPE is tentatively assumed to reduce the external exposure with 85%. This estimate of reduction is not a generally applicable “reasonable worst-case” estimate, but an indicative value based on very limited data. Furthermore, this reduction of external exposure does not necessarily reflect the reduction of absorbed dose. It has to be noted, that the use of PPE can result in a relatively increased absorption through the skin (effect of occlusion), even if the skin exposure is decreased. This effect is very substance-specific. Therefore, in the risk assessment it is not possible to use default factors for reduction of exposure as a result of the use of PPE.

In some specific situations a preliminary assessment of the possible influence of PPE exposure will be made. This regards situations in which the failure to use adequate protective equipment properly will often lead to acute adverse effects on the worker. Examples of such situations are manual handling of very corrosive substances and handling materials with high temperatures.

There are several industries in which dibutyl phthalate is used or produced. In some cases, the processes and activities may lead to emission of dibutyl phthalate into the workplace. The exposure of the workers may be similar in the different industries. The industries can be clustered in similar exposure scenarios based upon the type of process and activity and the possibilities for exposure that relate to that process and activity.

The following exposure scenarios are considered:

1. production of dibutyl phthalate;
2. production of products containing dibutyl phthalate;
3. use of products containing DBP.

Some weight and volume percentages of DBP have been found in the literature, and information is obtained from TNO (1995).

In this report for each scenario the general description of exposure data will be followed by suitable inhalation models. The methods used will be compared using expert judgement and a choice for the best applicable estimators will be made. Dermal exposure will be described and assessed by means of EASE.

4.1.1.2.2 Scenario 1: Production of dibutyl phthalate

The production of dibutyl phthalate usually takes place in closed systems. After it has been produced it is pumped into tanks. Exposure can occur:

- via "breathing" of the system (through valves, pumps, etc.);
- via displacement emission during pumping of the dibutyl phthalate into tanks;
- during drumming of dibutyl phthalate in drums;
- during cleaning/maintenance.

The process temperature during the production varies between 140^{o}C and 165^{o}C (BUA, 1987). It is expected that the drumming is performed at 20^{o}C in the presence of LEV, although the absence of LEV cannot be excluded. Drumming of dibutyl phthalate in drums occurs only occasionally; most of the amount of dibutyl phthalate produced is pumped into tanks.

Inhalation exposure data

Exposure data regarding production of DBP and other phthalates are available. Measurements were carried out at different parts of a number of production sites. Not for all reported data all relevant details regarding number of measurements, duration of measurements and tasks of workers have been provided. In the data of one producer, details regarding activities of exposed workers and regarding frequency of exposure are given. Activities possibly leading to exposure are: supervision, filling of tankers or drums, after treatment (disposal of filters), esterification (sampling), maintenance and decocting of the distant receiver. Most of the activities are in the open air, except for drum filling. Drum filling stations are largely automated and LEV is used during drumming. Where exposure is considered to be possible, the use of PPE (working clothes, gloves and goggles) is mandatory (Producer A, 1996). Exposure levels of DBP in 1993 to 1995 were up to 0.5 mg/m^3 for most activities (20 samples). For emptying and decocting of the distant receiver the maximum was 1.1 mg/m^3 (8 samples) and for filling station work (5 samples) and sampling (4 samples) exposure levels up to approximately 5 mg/m^3 were measured (Producer A, 1996). No details regarding duration of exposure are given. Earlier data from the same producer are more limited in detail. The mean 8-hour DBP concentration was reported to be less than 0.5 mg/m^3. Short-term exposure was measured in several sensitive areas for 5 minutes per sample. The DBP concentration never exceeded 1.0 mg/m^3 (OSPA, 1995; Producer A, 1994). For the above-mentioned measurements, the number of samples is not given. Another producer presented data showing a mean exposure during the production of DBP is 0.04 mg/m^3 (Producer B, 1992). During this measurement 114 samples were taken. The duration of the measurements was not given. Measurements carried out at a production site of producer B, presented in 1995, showed a mean concentration of DBP of 0.7 mg/m^3. Long-term exposures were measured in several sensitive areas for several hours and the results are directly comparable with 8-hour time weighted averages (Producer B, in: OSPA, 1995). Number of measurements was not given. It is not clear whether the data presented above are part of the data presented by King (1996) and by Producer A (1996).

Exposure data are also available on exposure to a number of analogues. Of fifty measurements of DEHP six levels were above the analytical detection limit of 10 µg/m^3. The time-weighted average concentrations of these six ranged from 20 to 4,110 µg/m^3 (mean 71 µg/m^3). It probably concerns time-weighted average values over 8 hours. The high levels were obtained from one maintenance worker and from five chemical operators (521). Other exposure data are reported in a compilation of data by King (1996). All exposure data are presented in **Table 4.1**.

Table 4.1 Exposure data during the production of dibutyl phthalate

Substance [a]	Industries and tasks	Number of samples	Exposure levels (mg/m^3) full shift [b]	Reference
DBP	Supervision, handling filter cake, esterification, mechanic	20	up to 0.5	Producer A (1996)
DBP	Filling station	5	up to 5	
DBP	Sampling	4	up to 5.2	
DBP	Emptying and decocting of distant receiver	8	up to 1.1	
DBP	Production		<0.5 [c]	Producer A (1996)
DBP	Production, including drumming	114	0-0.3 [d]; mean 0.04	Producer B (1992)
DBP	Production		mean 0.7	Producer B (1995); in: OSPA (1995)
DEHP	Maintenance workers Chemical operators	50	0.02-4.1	Liss et al. (1985)
Various DEHP	Production Production	14 1	0.2-2.3 < 0.1	King (1996) Producer 1
DEHP	Production	4	<0.016-4.3	King (1996) Producer 2
DEHP	Tanker filling	2	0.013-0.09	
DEHP	Drumming	1	0.14	
Various	Production	24	<0.01-0.31	King (1996) Producer 3 - facility 1
DINP/ DIDP/DIHP	Tanker filling	18	< 0.06	
Various	Production		<2.0	King (1996) Producer 3 - facility 2
DEHP	Production	28[c]	0.03-1.56	King (1996) Producer 4
C_8-C_{13}	Production	10	<0.25	King (1996) - HSE data
C_9-C_{11}	Production	11	<0.25	
DIOP	Production	86	<5.0	King (1996) - Industry data
DIDP	Production	32	<5.0	
DEHP	Production	77	<5.0	

[a] Information regarding the substances is given in Appendix A
[b] Time-weighted average over 8 hours; including data for which duration of measurement is not given
[c] 5 minutes samples <1.0
[d] Time measured unknown

The industry data from King (1996) for DEHP are presented in somewhat more detail. Eighty seven percent of levels were below 0.5 mg/m^3, 95% below 2 mg/m^3 and all results below 5 mg/m^3.

The data from Liss et al. (1985) in **Table 4.1** are only the results with detected levels. There were 44 results below the limit of detection.

Inhalation exposure is also assessed by EASE and EPA transfer model (TGD and Appendix B). It is assumed that exposure occurs because of "breathing" of the system (with process temperatures up to 150°C) and during drumming.

Based on EASE, the estimates of exposure levels of DBP are the following:

- "breathing" of the system; non dispersive use and Local Exhaust Ventilation (LEV): 0.5-3 ppm (ca. 6-35 mg/m^3);
- drumming; non dispersive use with direct handling and dilution ventilation: negligible exposure; this is due to the low volatility of DBP at room temperature.
- cleaning/maintenance: wide dispersive use with direct handling leads to a negligible exposure; this is due to the low volatility of DBP at room temperature.

Concentrations calculated by the EPA transfer model (Appendix B) (typical and worst-case room average concentrations) are given in **Table 4.2**.

Table 4.2 Typical and worst-case average concentrations for drumming of DBP at room temperature: EPA transfer model

Type of container	Concentrations (mg/m^3)	
	Typical	Worst case
Rail car	0.00	0.00
Tank truck	0.00	0.00
Drums (200 l)	0.00	0.02

Dermal exposure data

Dermal exposure can occur during the drumming of DBP, during connecting a transfer line in order to pump dibutyl phthalate into the tanks and during cleaning or maintenance. The dermal exposure estimates made by EASE are given below.

Drumming concerns non-dispersive use with direct handling and intermittent contact. This results in an exposure of 0.1-1 mg/cm^2/day. During drumming the palm of both hands may be exposed; this corresponds with an exposed area of 420 cm^2 (approximately half of two hands), which results in a dermal exposure of 42-420 mg/day.

Connecting a transfer line concerns non-dispersive use with direct handling and intermittent contact. This leads to an exposure of 0.1-1 mg/cm^2. It is assumed that the fingers of both hands will be exposed. This corresponds with an exposed area of 400 cm^2 (somewhat less than the half of two hands), which results in an exposure of 40-400 mg/day.

Cleaning concerns non-dispersive use with direct handling and incidental contact, this leads to an exposure of 0-0.1 mg/cm^2/day. It is assumed that both hands can be exposed, which corresponds with an exposed area of 840 cm^2 (derived from EPA dermal model). This results in a dermal exposure of 0-84 mg/day.

Conclusions for Scenario 1

Inhalation exposure conclusions

A reasonable worst-case exposure level to be used for risk characterisation is chosen as 5 mg/m^3, being approximately equal to the maximum levels measured and comparable to the lower limit of the results by EASE for "breathing". The typical concentration will be less than 2 mg/m^3.

Exposure during the production of dibutyl phthalate may be full shift; short-term exposure may be higher. It is assumed that this may be twice as high as the reasonable worst-case exposure: up to 10 mg/m^3. The measured data mentioned in this report are not all presented with sufficient detail to judge their relevance. In some cases the sample duration and the circumstances in which the measurements were taken or the number of measurements was not given. However, the total number of measurements is large and most activities that are suspected to lead to relatively high exposure levels (drumming, maintenance, sampling) are included several times.

According to the modelling the highest exposure occurs during the "breathing" of the system (assessed by EASE). This is due to the higher temperatures and related higher vapour pressures during processing.

For this assessment, the results of EASE are expected to be relatively high, since the results given by EASE are considered to be applicable for all substances with vapour pressures between 1 and 1,500 Pa. Dibutyl phthalate has a vapour pressure of only 200 Pa at the given temperature, which is towards the lower part of the volatility range for which EASE gives these results.

The measured concentrations for DBP and analogues are considerably lower than the concentrations assessed by EASE. The highest concentrations are comparable with the lower limit of the concentration assessed by EASE.

Dermal exposure conclusions

The assessments made by EASE are used for the dermal exposure assessment. The "reasonable worst-case" dermal exposure level (potential exposure) during the production of DBP is estimated to be 420 mg/day.

4.1.1.2.3 Scenario 2: Production of products containing dibutyl phthalate

Dibutyl phthalate is mostly used in PVA adhesives and PVC. In PVA adhesives, the amount of dibutyl phthalate is up to 15%. In PVC the total amount of plasticizer is about 20-40%. In rubber the total amount of plasticizer is about 10-20%. About 6% of the plasticizers used in PVC are DBP (Peijnenburg et al., 1991). The overall amount of dibutyl phthalate in products is assumed to be up to 15%.

Exposure is possible during the pumping of DBP into solvent tanks and during the mixing step of the process. The equipment used for mixing the compounds may be broken down into two categories: open mill mixing and internal mixing.

For reasons of speed, output and economy, the internal mixing operations are the ones most widely used. In 1981 it was reported that open mill mixing might still be used (Evans, 1981). Open mill mixing was reported for the rubber industry in The Netherlands by Swuste et al. (1993), while Dirven et al. (1993) reported half open mixing in the polymer industry. It appears that (half-) open mixing has not altogether been abandoned.

The open mill mixing process (two roll mill) produces an even and smooth band of polymer around the front roll. The fillers and oils are added alternately, followed by any small additions, and finally the vulcanising materials. During the whole operation, cutting and blending by hand rolling may be carried out. As the powders drop into the mill tray, they are swept to the front by the operator and added back into the mill. The mill tray is usually slightly sloping to help the operator. A very useful aid is to fit a vibratory mechanism, so that the powder is continuously returned to the operator, thus saving physical efforts. The process can be highly mechanized. The so-called Papenheimer is a semi-open mixer.

The banbury mixer (internal mixer) is the most frequently used mixing equipment and is used throughout the rubber and plastic industry. It is a batch-type internal mixing device and consists essentially of a completely enclosed mixing chamber, two rotors, a hopper to receive the materials to be mixed, a ram, and a door or sliding gate to discharge the mixed material. The most common production size is 170 kg. It can vary from 50-600 kg. A normal sequence would be: load rubber/PVC powder, add part of the filler, remaining filler, and plasticizers and softeners. Generally, a two-stage mix is used. The softeners are mixed in the first step which produces the master batch. In the second stage, the master batch is returned to the banbury where the curing agents and accelerators, along with other materials, are added.

After mixing the batch is compounded further. This involves one or more forming steps.

Before the forming can occur, the compound has to be fed from the mixer into the forming step. The transition can occur in different ways.

1. After the mixing operation the compound is fed directly to the next operation. During this transition step the compound will probably not be cooled off completely. It is assumed that the temperature is about 70^{o}C.
2. The compound is mixed and slabbed off and stored prior to the next operation. This transition step probably takes place at room temperature.

There are different forming processes. These correspond for the rubber and plastics industry. Below some examples of forming processes are given.

Extruding

Extruders are machines which force rubbers through a nozzle to give a profiled strip of material. They fall into two types: those in which the pressure is produced by a ram, and those in which the pressure is produced by a screw. The latter is the type of machine most generally used in industry and is known as an extruder, forcing machine, or tuber, whereas the ram extruder is a more specialised machine for short runs. The input and the output of the rubber are open processes. The process in which the rubber is going through the nozzle is a closed system. The process occurs at about 180-190^{o}C; this depends on the product to be formed. During this process dibutyl phthalate can escape from the rubber (Blow and Hepburn, 1981; SPIN, 1989).

Calender

A calender comprises a number of rolls or bowls held in a framework. The rolls rotate to produce sheeting and, by adjusting the distance apart of the rolls, different gauges of sheeting become possible. This is an open process, which takes place at about 180-190^{o}C. Exposure can occur as a result of evaporation from the heated rubber or plastic (Blow and Hepburn, 1981; SPIN, 1989).

Moulding

Moulding is the operation of shaping and vulcanising the plastic or rubber compound, by means of heat and pressure, in a mould of appropriate form. Fundamentally, all processes of moulding are similar, the ways of introducing the material into the mould distinguishes one technique from another. The basic processes are compression, transfer, and injection. These processes are performed in a closed system (Blow and Hepburn, 1981; SPIN, 1989).

The highest exposure will probably occur during the calender step, because this concerns an open process. The temperature of the forming process is 190^{o}C.

For this assessment, the welding of polymers and recycling of polymers is considered to be part of this scenario.

Sources of exposure related to further compounding are: opening of the mixer (usually equipped with LEV), the exit of the extruder (LEV), emission from the nozzle on retraction at injection moulding (usually in rooms with dilution ventilation), the exit of (the second) extruder (dilution ventilation) and the calender mill (dilution ventilation). Cooling in a water bath directly behind the second extruder and the calender mill will also stop emission of fumes (King, 1996). The types of processes mentioned above are also used in the recycling of polymers (BG Chemie, 1994b).

This scenario includes some manual handling. Manual handling of pure dibutyl phthalate can occur when small amounts of dibutyl phthalate are added to the mixers in the paint and polymer industry and during adding of dibutyl phthalate to solvent tanks. When batches in the paint-, lacquers- and varnishes industry are drummed, products containing a percentage of DBP may be manually handled. None of these procedures is done full shift. Drumming is assumed to occur at room temperature (20^{o}C) and adding of DBP into the mixer is assumed to occur at about 60^{o}C (temperature above the mixer, where the dibutyl phthalate is added; the process is performed at high temperatures, so the temperature above the mixture is higher than room temperature). It is hardly possible to add liquids when the temperature is higher.

Sampling of the mixture is, because of the temperature of the mixture, usually performed without manual contact. This results in a dermal exposure during sampling which is negligible.

Inhalation exposure data

Inhalation exposure can occur due to emissions at several processes mentioned above.

Pumping of dibutyl phthalate into the mixers probably takes place at room temperature. Inhalation exposure can occur via displacement emission.

The temperature during mixing operations varies from 150-210^{o}C (Gächter and Müller, 1984; Kirk and Othmer, 1983; Morton, 1987)). Exposure can occur by evaporation of dibutyl phthalate from the mixer. In general it concerns a half open process.

Exposure data of some phthalates are available for the production and processing (including recycling/waste processing. The values are given in **Table 4.3**. In addition to these exposure data some exposure models are used to determine the exposure during the forming step of the process.

Table 4.3 Exposure levels for phthalates in the production or recycling/waste processing of polymers

Substance [a]	Tasks	Number of samples	Exposure levels (mg/m^3) full shift [b]	Reference
Various (including DEHP)	Calendar operators	12	1.0-2.8 [c]	Nielsen et al. (1985) temperature during calendering up to 180°C
	Calendar operators/machine attendants	16	0.1-0.8 [c]	
	Machine attendants	8	0.1-0.2 [c]	
	Repair men	8	0.1-0.3 [c]	
	Mixing workers;	8	0.01-0.02 [c]	
	PVC others	44	0.1-0.3 [c]	
Various (including DEHP)	Calendar operators		0.5-3	Hagmar et al. (1990) In: King (1996)
	Mixing department and machine attendants		0.1-0.5	
	Others		0.1	
DEHP	Extrusion	4	0.05±0.03	TNO (1996) temperature 150-195°C;
DEHP	Extrusion	5	0.3±0.2	temperature 130-200°C; 6.5-15 % plasticizer
DEHP	Calendering	7	0.5±0.5	temperature 180°C
DEHP	Hot embossing	5	0.05±0.02	temperature 150-200°C; 2.4 % plasticizer
DEHP	Welding	4	0.3±0.05	temperature 200°C at lamp
DEHP	Injection moulding	2	0.02±0.01	temperature 180-190°C
DEHP	Compounding	5	0.02±0.01	temperature 120°C; 20 % plasticizer
DEHP	Thermoforming	2	0.02±0.02	temperature 120-130°C
DEHP	High frequency welding	na	<0.02	temperature unknown
DEHP+ DIAP	Pigment dispersion	8	<0.25	King (1996)
DEHP	Filter recovery	11	45%<0.25 100%<0.5	King (1996), HSE data
DEHP	Manufacture of floor tiles	8	100%<0.5	King (1996), HSE data
DEHP	Manufacture of flexible floor covering	12	100%<0.5	King (1996); HSE data
BBP	Manufacture of flexible floor covering	12	100%<0.5	
BBP	Manufacture of rubber gloves	18	100%<0.25	King (1996); HSE data
D79P	Manufacture of rubber gloves	18	100%<1	
DEHP	Manufacture of PVC	7	100%<0.25	King (1996); HSE data
DIDP	Manufacture of PVC	7	100%<0.25	
DIOP	Manufacture of PVC	8	100%<5	King (1996); HSE data
DIOP	Manufacture of shoes (PVC binding)	9	34%<1 44%<2 67%<5 89<10	King (1996); HSE data
Mixed (total)	Manufacture of PVC	143	56%<1 74%<2 93%<5 100%<10	King (1996); Industry data

Table 4.3 continued overleaf

Table 4.3 continued Exposure levels for phthalates in the production or recycling/waste processing of polymers

Substance[a]	Tasks	Number of samples	Exposure levels (mg/m^3) full shift [b]	Reference
Mixed (total)	Manufacture of cables	25	40%<5 80%<2 92%<5 100%<10	King (1996); Industry data
DBP	Manufacture of cables (thermodegradation of PVC)	2	0.19-0.75	Posniak, in King (1996)
DEHP	Manufacture of cables (thermodegradation of PVC)	2	0.28-0.54	
DEHP	PVC boot manufacture; Mixing	16	mean: 0.26 [c] (0.10-1.21)	Dirven et al. (1993) temperature at mixing: 160°C; half open mixing
DEHP	PVC boot manufacture; Extruding	11	mean: 0.12 [c] (0.05-0.28)	temperature at extrusion: 170°C
DEHP	Cable manufacture: Mixing	8	mean: 0.18 [c] (0.01-0.81)	temperature: 200°C; closed process
DEHP	Cable manufacture; Extruding	13	mean: 0.24 [c] (0.01-1.27)	temperature: 200°C
DEHP	Recycling/waste processing	1	1,23[c]	BG Chemie (1994a) several waste processing machines
BBP	Recycling/waste processing	1	0,06[c]	
DEHP	Calendering	2 personal 1 stationary	1,64-1,95 [c] 1,46 [c]	BG Chemie (1994b)
BBP	Calendering	2 personal 1 stationary	0,29-0,33 [c] 0,24 [c]	
DEHP	Calendering	4 personal 2 stationary	0,30-1,08 [c] 0,58-2,09 [c]	BG Chemie (1994b)
DBP	Polymer industry	22	90% < 0.007 95% < 0.008	BGAA (1996)
DBP	Polymer industry; machine welding , and Manual welding of roofing materials	13	median = 0.01 90% < 0.03	BGAA (1996)

a) Information regarding the substances is given in Appendix A
b) Duration of measurements representative for full-shift exposure
c) Duration of measurements 2 hours

A relatively large number of exposure data from several sources are available, mostly on DEHP. Not all sources give very detailed information regarding processes, activities of workers and control measures. The highest exposure levels are reported by King (1996). These are non-published data from the HSE and from Industry (mostly from the UK).

For comparison, possible exposure levels are also estimated using EASE and the EPA transfer model.

Based on EASE the estimates of exposure levels of DBP are the following:

- transition of DBP into mixer at room temperature; non-dispersive use and LEV leads to a negligible exposure; this is caused by the low volatility of dibutyl phthalate at room temperature;
- adding of DBP to mixers at 60°C; exposure is estimated to be negligible because of the low vapour pressure of DBP at 60°C (< 1Pa).
- internal mixer: closed system, breached (= non dispersive use) and LEV: 0.5-3 ppm (ca. 6 to 35 mg/m^3), this procedure may be performed full shift;
- open mill mixing; non-dispersive use with direct handling and dilution ventilation: 10 to 50 ppm (110 to 580 mg/m^3) or non-dispersive use and LEV: 0.5-3 ppm (6 to 35 mg/m^3); it is assumed that the scenario is relevant for 2 hours a day; the eight hour time-weighted average value then becomes 27.5-145 mg/m^3 or 1.5-8.8 mg/m^3;
- drumming (of paints, inks, and similar products); non-dispersive use with direct handling and dilution ventilation: negligible; this is caused by the low volatility of dibutyl phthalate at room temperature.
- forming steps; non-dispersive use and LEV: 0.5-3 ppm (ca. 6 to 35 mg/m^3); this activity can be performed full shift.

Concentrations calculated by the EPA transfer model (typical and worst-case room average concentrations) are the same as for scenario 1 (**Table 4.2**).

Dermal exposure data

Dermal exposure may occur during pumping of dibutyl phthalate into mixers, during drumming of products and during other manual activities. During most parts of the processes dermal exposure is not to be expected, because of the closed systems used and the high temperatures involved. Potential dermal exposure is assessed by EASE.

Based on EASE the estimates of the potential dermal exposure level of DBP are the following:

- pumping: non-dispersive use with direct handling and incidental contact: 0-0.1 mg/cm^2/day; all fingers may be exposed, the exposed area is estimated as about 400 cm^2, leading to an exposure of 0-40 mg/day;
- drumming: non-dispersive use with direct handling and intermittent contact: 0.1-1 mg/cm^2/day; the fingers of both hands or the palm of both hands are exposed, depending on whether it concerns drums or cans; exposed area is 420 cm^2 (palm of both hands, during drumming in drums) or 400 cm^2 (fingers of both hands, during drumming in cans), which results in an upper bound exposure of 42-420 mg/day to the pure substance; since the compound contains up to 15% DBP, the dermal exposure becomes 6-63 mg/day.
- manual adding of DBP to mixers: non-dispersive use with direct handling and intermittent contact; 0.1-1 mg/cm^2/day; assuming that one hand can be totally exposed (immersion of one hand during the adding of DBP, this corresponds with an area of 420 cm^2 and results in an upper bound exposure of 42-420 mg/day;
- cleaning of (parts of) tanks or equipment in paint, ink and cleaning agent industries: non-dispersive use with direct handling and incidental contact, which results in an exposure of

0-0.1 mg/cm^2/day; it is assumed that both hands and a part of the forearms will be exposed (exposed area becomes 1,300 cm^2), resulting in an exposure of 0-130 mg/day to the pure substance; since the liquid in the tank contains only up to 15% DBP, the exposure becomes 0-19.5 mg/day.

Measurements of potential or actual dermal exposure of DBP or other phthalates in the polymer, paint, ink or cleaning agent industries are not available. However, in a facility producing fibre reinforced plastic pipes and tubes, actual dermal exposure to the hardener 4,4'-methylenedianiline (MDA) has been studied. Actual exposure was measured by means of either cotton gloves (a new pair after each break) worn underneath protective gloves, or by hand washing after work (61 full-shift measurements and 1 half-shift measurement; all consisting of consecutive samples). The process is a partly automated winding process that involves some manual activities. MDA is added to a tank of the winding machine using buckets that are filled from the holding tank using a tap that is operated by means of a foot switch. Air is driven from the resin by means of (manual) brushing or rolling. Excessive amounts of resin are removed by means of a kind of spatula, or using a bucket. In the latter case, protective gloves are not always worn. Some specific activities appear to be difficult to do with protective gloves on. One such activity is measuring the diameter of the tube, leading to a high probability of skin contact. All contact moments without protective gloves are of (very) short duration. The MDA formulation used is 68% MDA. The resin contains 16% of this formulation, leading to a total percentage of MDA in the resin of 11%. Actual levels were between non-detected (worker had a very low potential for contact with MDA on that day) and 4,046 μg/day.

The wearing of protective gloves has clearly led workers to use work practices that they would not have used without gloves. Some workers were observed to take of the protective gloves by sticking them into the resin and then retracting the hands. Potential exposure data gathered (by weighing protective gloves before and after use) are therefore not considered to be useful for risk assessment purposes (Hoogendoorn et al., 1995).

Conclusions for Scenario 2

Several sources mention inhalation exposure to phthalates in polymer processing. The total number of measurements is rather large, but the information is not always very detailed.

Only very limited field data of dermal exposure levels in a possibly relevant type of facility are available. The relevance of this type of polymer application to the applications of polymers that (may) contain DBP is not fully established.

Inhalation exposure conclusions

Considering all data and the model results, the reasonable worst-case inhalation exposure level is estimated as 5 mg/m^3 (around the 90-percentile of data given by King (1996) from a number of sources). The typical values will be below 2 mg/m^3. Short-term exposure may be higher. It is assumed that short-term exposure is twice as high as the assessed reasonable worst-case values, i.e. up to 10 mg/m^3.

The measured levels are mostly 8-hour time weighted averages and include activities for which separate assessment using the EASE model have been made. Since many activities are not full-shift, and the activity pattern may be very variable, data on full-shift exposure are more useful for risk characterisation than estimations based on part-shift exposure estimates. The data presented by King (1996) (with relatively little detail and mostly for other phthalates) show the

highest inhalation exposure levels. Even the highest values presented by King (1996) are substantially lower than the higher end of the ranges estimated by EASE. The highest measured levels compare reasonably well with the lower ends of the ranges of EASE for non-dispersive use with LEV. Some published sources present data of situations that include half-open sources. These values are not higher than other values reported.

The results given by EASE are expected to be relatively high compared to the actual exposure during the mixing. The mixture contains only 15% DBP, so the "partial vapour pressure" of the substance in the mixture will influence evaporation, while in the assessment by EASE the vapour pressure for the pure substance is used. At 210^{o}C, the vapour pressure of DBP is approximately 960 Pa, therefore the partial vapour pressure of DBP in an ideal mixture containing 15% of DBP will by approximately 144 Pa, which is towards the lower part of the volatility range for which EASE gives these results.

Dermal exposure conclusions

The assessments made by EASE will be used for estimating potential exposure levels in this scenario. The activity leading to the highest potential exposure is manually adding of pure DBP to mixtures (in situations where small amounts of DBP are used. This could for instance be done in a similar fashion as the adding of MDA in the study in the reinforced plastic pipes manufacture: tapping from a tank into a bucket. The estimate of "reasonable worst-case" potential dermal exposure level in this situation is up to 420 mg/day. Typical potential exposures will be much less (because of smaller areas exposed). The study of MDA exposure indicates that in some of the kinds of facilities in this scenario a reduction of the actual exposure by protective gloves may typically be around 90%. This value does not necessarily hold for other kinds of facilities and is not a reasonable worst-case value, so it cannot be used for risk characterisation.

4.1.1.2.4 Scenario 3: Use of products containing dibutyl phthalate

Use of products containing DBP can be distinguished in aerosol forming and non-aerosol forming activities. Aerosol forming activities are for example spray painting and printing. Some use of materials may involve elevated temperatures (e.g. coating using a bath). During these activities both inhalation and dermal exposure can occur. Non-aerosol forming activities are for example painting or transferring a liquid in the paint and printing industry. During non-aerosol forming activities only dermal exposure will occur, not inhalation exposure, because of the low vapour pressure of DBP at room temperature. DBP is used as an additive in ink and paint and may be used. Gilis et al. (1983) stated that an average of 3% of ink is additive. Examples of additives are plasticizers, photo-initiators, defoaming agents and anti-oxidants. DBP is used as a plasticizer in ink and paint. Considering that dibutyl phthalate is always used in combination with other plasticizers, it is assumed that ink contains up to 2% dibutyl phthalate. Some paints may contain up to 5% of DBP (ECPI, 1996).

Inhalation exposure data

Measurements of DBP in the coating of surfaces in the polymer, leather and electrotechnical industries are presented by BGAA (1996). The measurements have been performed during spray coating, use of adhesives, curtain coating and dip coating (using baths). Measurement duration was 1 hour and presented exposure levels are recalculated to 8-hour time weighted averages. Some of the samples were taken using personal sampling, while others were taken using static sampling. The highest exposure values were recorded during dip coating in heated PVC

emulsions (temperature not presented). The median of the 21 measured levels was 0.009 mg/m^3, the 90-percentile was 0.57 mg/m^3 and the 95%-percentile was 1.01 mg/m^3.

In Finland, short-term measurements have been done, 3 in the plywood industry and 5 in a laboratory. Arithmetic means (and standard deviation) were 0.006 (0.002) and 0.014 (0.008) mg/m^3 respectively for measurement durations up to 1 hour (FIOH, 1995).

King (1996) presented some data reported by industry on exposure to DEHP and DINP in spray coating or spread coating in the automobile industry. The number of measurements is not presented. Exposure levels for spray coating were up to 0.11 mg/m^3 and for spread coating all levels were below 0.001 mg/m^3.

Some measurements have been performed in the printing and spray coating industry for low volatility components. These measurements are not made for additives, but since hardly any other measurements are available, these can serve as an indication of the exposure to low volatility additives. Purdham et al. (1993) measured the exposure to total particulates (TP) and PAHs in the printing industry. Measurements were taken in seven commercial printing operations and in two newspaper press plants. A total of 140 personal samples were taken on workers in the press room. The geometric mean of total particulate personal exposure ranged from 0.18 to 1.25 mg/m^3 for the nine different facilities. The geometric mean total PAH exposure at each site varied from none detected to 0.056 mg/m^3. No benzo(a)pyrene or benzo(a)anthracene was detected in any sample. It was not stated in what concentration the PAHs occurred in the printing ink.

Alexandersson et al. (1987) measured the exposure to hexamethylendiisocyanate (HDI) and biuret modified hexamethylendiisocyanate (HDI-BT) in the car painting industry. The study was conducted in 15 garages in which 41 car painters were measured. The paint used, contained approximately 10% HDI-BT in top paint layer and varnish layer, and 3-6% in the primary paint layer. The mean HDI-BT concentration in the air during car painting was 115 µg/m^3 (range 10-385 µg/m^3: 8-hour TWA values). The results of the investigation indicated high short-time peak levels up to 13.500 µg/m^3 HDI-BT. The exposure to HDI was about 1.0 µg/m^3. Rodrigues (1987) referred to O'Brien, who measured the solvent exposure during several spray coating activities; in all cases the exposure was below 1 mg/m^3. The paint used contained about 2% solvents.

The results of the data found for this scenario are summarised in **Table 4.4**.

Table 4.4 Exposure levels for phthalates and other low volatility components in the use of paints and inks

Substance	VP (Pa) (20°C)	Industry and task	Exposure TWA (mg/m³)	Short-term exp. levels (mg/m³)	Reference
DBP	< 0.1	polymer, leather, electrotechnical / coating	0.009 (median), 0.57 (90%), 1.01 (95%)		BGAA (1996)
DBP	< 0.1	laboratory work		0.006 (mean), 0.002 (sd)	FIOH (1995)
DBP	< 0.1	plywood industry		0.014 (mean), 0.008 (sd)	FIOH (1995)
DEHP and DINP		automobile industry, spray coating	up to 0.11		King (1996) - industry data
DEHP and DINP		automobile industry, spread coating	< 0.001		idem
TP	Unknown	printing	0.2-1.3		Purdham et al. (1993)
PAH	Unknown	printing	0-0.056		idem
HDI	1.35	painting/ spray painting	0.1		Alexandersson et al. (1987)
HDI-BT	Unknown	idem	0.01-0.4	13.5	idem
Solvents	ethyl acetate for example 2900	spray painting	<1		Rodrigues (1987)

TP = Total particulate
TWA = Time-weighted average 8 hour exposure
HDI = Hexamethylendiisocyanate
HDI-BT = Biuret modified hexamethylendiisocyanate
DBP = dibutyl phthalate
DEHP = di(2-ethylhexyl) phthalate
DINP = diisononyl phthalate
Mean = Arithmetic mean
Sd = Standard deviation

Inhalation and dermal exposure are also assessed by EASE.

Inhalation exposure can occur during (spray) painting and printing.

Based on EASE the exposure to dibutyl phthalate is estimated as follows (it is assumed that ink and paint contain up to 5% DBP):

- aerosol forming activity:
  EASE does not give a good answer for this option, since the volatility is "very low" and a combination of this volatility (which is not mentioned as a possibility in the TGD) with aerosol formation is not given; for a volatility "low" (vapour pressure between 1 and 1,500 Pa) the tendency to become airborne is given as "moderate" (TGD, EC, 1996); assuming that for a volatility of "very low"; the tendency to become airborne with aerosol formation would be "low", this leads to an exposure level of 100-200 ppm, assuming wide-dispersive use, direct handling and dilution ventilation; assuming that in aerosol formation the percentage of substance in the aerosol is equal to the percentage in the original liquid, and using a percentage of DBP of 5%, this would give a range of 5-10 ppm (56.8-113.6 mg/m^3);

- non-aerosol forming activity:
  painting or transferring a liquid; non-dispersive use and LEV: negligible exposure.
- cleaning; non-dispersive use with direct handling and dilution ventilation: negligible; this low exposure is caused by the low volatility of DBP at room temperature.

Dermal exposure data

Dermal exposure can occur during spray painting, painting and during transfer of liquid in the paint, printing industry. The dermal exposure assessed by EASE during these activities is given below.

Spray painting concerns wide dispersive use, direct handling and extensive contact. This leads to a dermal exposure of 5-15 mg/cm^2/day. During the spray painting both hands and a part of the forearms could be exposed. This corresponds with an exposed area of 1,300 cm^2. This leads to an exposure of 6,500-19,500 mg/day for the pure substance. Since paints contain up to 5% DBP and the paint is considered to be an ideal mixture, the exposure becomes 325-975 mg/day. When the contact level is intermittent the exposure becomes 65-195 mg/day.

Painting concerns non-dispersive use and direct handling with extensive contact. This leads to an exposure of 1-5 mg/cm^2/day. During painting only the fingers will be exposed, this corresponds with an exposed area of 400 cm^2, which leads to an exposure of 400-2,000 mg/day of the pure substance. Since the paint contains up to 5% DBP, the exposure becomes 20-60 mg/day.

In the printing industry dermal exposure occurs during the transfer of a liquid. This concerns non-dispersive use and direct handling with intermittent contact, which leads to an exposure of 0.1-1 mg/cm^2/day. During the transfer of a liquid only the fingers will be exposed, this corresponds with an exposed area of 400 cm^2. The resulting exposure becomes 40 to 400 mg/day of the pure substance. Since the paint contains up to 5% DBP the exposure becomes 2-20 mg/day.

Conclusions for Scenario 3

Inhalation exposure conclusions

The inhalation exposure estimate to be used for the risk assessment is therefore chosen to be a value between the lower limit of the range given by EASE and the reported exposure values in the literature. The exposure level that is chosen by expert judgement is up to 10 mg/m^3 (worst-case scenario). Typical values are assumed to be in the upper part of the range of the measured data (2 mg/m^3). Short-term exposure may be 2 times higher than the worst-case scenario (based on data in the literature). Inhalation exposure during non-aerosol forming activities is negligible.

There are hardly any measured data for phthalates in this type of use scenario. EASE is not very well suited to estimate exposure levels to very low volatility components in aerosol formation. Extrapolation from the results for low volatility components leads to values of up to 200 ppm (pure substances). Dibutyl phthalate has a vapour pressure less than 0.1 Pa (less than 10 times below the limit for ‘low volatility’ in EASE) at room temperature. The conclusion of severe overestimation by EASE is strengthened by measurements reported by BGAA (1996), King (1996), FIOH (1995), Purdham et al. (1993), Alexandersson et al. (1987) and Rodrigues et al. (1987). The values presented by these sources are much lower than the lower limit of the assessment made by EASE. Even the short-term exposure levels are much lower than the assessed exposure by EASE. The following considerations can be given. It is assumed that HDI-BT has a vapour pressure somewhat below the vapour pressure of HDI; this means that the

vapour pressure of HDI-BT is higher than or comparable to the vapour pressure of DBP. The HDI-BT concentration in paint is furthermore higher than the concentration DBP in ink. The HDI-BT concentration is likely to be higher than the exposure to DBP.

Solvents measured by Rodrigues et al. (1987) have a much higher vapour pressure than DBP, which should result in a much higher exposure level.

The reported data on low volatility substances are presented with limited detail and it is not possible to judge from the presented information whether the reported values are representative of typical or reasonable worst-case situations. It is thus considered possible that higher values than the reported ones are possible, though the exposure will probably still be substantially below the estimates by EASE.

Dermal exposure conclusions

Since there are no data about dermal exposure during the different activities in this scenario the assessment made by EASE will be used for the risk assessment. The potential dermal exposure will be up to 975 mg/day.

4.1.1.2.5 Summary of occupational exposure

In **Table 4.5** the values of the different exposure assessment are given.

Table 4.5 Conclusions of the occupational exposure assessment

Scenario	Exposure		Estimated inhalation exposure level (mg/m³)					Estimated skin exposure level (mg/day) [a]	
	Duration (hr/day)	Frequency (day/year)	Full shift (8-hour time weighted average)			Short term			
			Typical	Method [b]	Worst Case	Method [b]	Level	Method [b]	
1. Production	6-8	100-200	2	Meas.	5	Meas.	10	Expert	420
2. Production of products containing DBP	6-8	100-200	2	Meas.	5	Meas.	10	Expert	420
3. Use of products containing DBP - aerosol forming activities - non-aerosol forming activities	 6-8 6-8	 100-200 100-200	 2 negligible	 Expert EASE	 10 negligible	 Expert EASE	 20 negligible	 Expert EASE	 975

a) Based on EASE dermal exposure model;

b) Meas. = mostly based on measured data; Expert = derived from measured data or model results largely using expert judgement; EASE = mostly based on results of the EASE model

4.1.1.3 Consumer exposure

Dibutyl phthalate (DBP) is used in several products, see Section 4.1.1.1, some of which are available to consumers.

To cover the widespread use of DBP, attention was focussed on products containing a relatively large concentration of DBP such as cosmetics, adhesives and regenerated cellulose film (cellophane) wrapped food. With respect to the use of DBP in cosmetics, the cosmetic industry published a review (Anonymous, 1985). In 1981, most (522 out of 590) DBP containing ingredients belonged to the product category nail polish and enamels (concentration range: ≤0.1-25%). The use of DBP in hairspray was also described in this review, albeit in only 6 out of 590 products. However, Colipa recently checked this use in Europe and Colipa's Working Group Hair Preparations concluded that DBP is not used as ingredient in hairspray (NCV, 1999).

Attention was also given to the (un)intentional use of DBP in children's toys, in view of the general public concern on the use of phthalates in PVC toys.

Four exposure scenarios were considered referring to the above-mentioned uses of DBP: I Nail polish, II Adhesive, III Cellophane wrapped food, and IV Toys for children.

The following data (if available) were used for the consumer exposure assessment:

- physical-chemical data of DBP (molecular weight, Log K_{ow}, vapour pressure at room temperature),
- percentage of DBP in nail polish, adhesives, cellophane wrapped food, and toys,
- actual exposure data for DBP,
- results from a mathematical model for consumer exposure (CONSEXPO - version 1.03, van Veen, 1995), in case no measured exposure data were available.

Scenario I: Nail polish

DBP is a constituent in several cosmetics. With respect to its use as an ingredient in nail polish the exposure is by inhalation as well as by dermal contact via air. The maximal concentration of DBP in the majority of nail polishes is 5% (Anonymous, 1985). As no measured exposure data were available for this use of DBP, the consumer exposure was estimated using CONSEXPO with contact scenario "none" and inhalation exposure scenario "evaporation from mixture". For the dermal exposure scenario "exposure from air" was used. Details of the parameters used and the results of the modelling are presented in Appendix C.

The outcome of the modelling has been obtained through a worst-case approach.

Result of the model

Assuming the use of nail polish 2/week for 10 min with 0.25 g/event (van Veen, 1996), an average inhalatory exposure per event of $4.34 \cdot 10^{-6}$ mg/m^3 was calculated. The yearly average inhalatory exposure (cumulative worst-case) was $8.59 \cdot 10^{-9}$ mg/m^3. The dermal exposure was very low ($4.34 \cdot 10^{-12}$ mg/cm^3) and the subsequent uptake (according to the data) negligible. The inhalatory route results in a total internal dose of $2 \cdot 10^{-9}$ mg/kg bw/day.

Scenario II: Adhesive

When DBP is used in adhesives e.g. used for glueing carpets, the main exposure route is by inhalation. The maximal amount of DBP in adhesives is estimated to be 15%. As no measured exposure data were available for this use, the consumer exposure was estimated using CONSEXPO with contact scenario "painting" and inhalation exposure scenario "evaporation from mixture". Details of the parameters used and the results of the modelling are presented in Appendix D.

The outcome of the modelling has been obtained through a worst-case approach.

Result of the model

Assuming the use of the adhesive 1/year for 2 hours (duration of contact per event 4 hours) with 3 kg product per event resulted in an average inhalatory exposure per event of 3.18 mg/m^3. The dermal exposure via air was calculated to be low ($3.18 \cdot 10^{-}6$ mg/cm^3) and is not taken into account. The inhalatory route results in a total internal dose of $3.43 \cdot 10^{-4}$ mg/kg bw/day.

Scenario III: Cellophane wrapped food

The Scientific Committee for Food of DG III has approved DBP for food contact application (temporary TDI of 0.05 mg/kg bw/day) (EEC, 1994). Several published data on levels of DBP in food were found in literature. Some of them are summarised in **Table 4.6**.

Table 4.6 Concentration ranges of DBP identified in food

Food type	Concentration DBP in mg/kg food	Reference
Margarine	10.6	Page and Lacroix (1992)
Vodka (7 samples)	0.05-0.25	Hatanaka et al. (1994)
Confectionery (47 samples)	0.02-14.1	Castle et al. (1989)
Confectionery, meat pies, cake, sandwiches	0.5-53	Castle et al. (1988)
Cheese, salted meat, chips, milk, vegetable soup	0.07-2.80	Cocchieri (1986)
Butter	2-11	Morita et al. (1973)

It was shown that the migrated amount of DBP increased with storage time of the wrapped product, e.g. the levels of DBP increased from 0.2 to 6.7 mg/kg food over a period from 0-180 days storage for a chocolate-coated confectionary product (Castle et al., 1989).

From the data in **Table 4.6** it is rather difficult to calculate the daily intake of DBP from food sources.

The estimates of the maximum daily intakes of several plasticizers through the diet are based on an English diet. The maximum intake of DBP is estimated to be 1.9 mg/day with a calculated average intake of 0.23 mg DBP/day (MAFF, 1987).

In a Dutch review the average daily intake (referring to the total content of phthalic acid and all phthalate esters present) was estimated to be 0.5-1.5 mg/person/day (RIVM, 1991).

For the risk assessment, the MAFF estimate of 1.9 mg/person/day will be used as a worst-case approach.

Scenario IV: Toys for children

Soft PVC toys and child-care articles

In contrast to other phthalates like diisononyl phthalate (DINP) and di(2-ethylhexyl) phthalate (DEHP), DBP is not added intentionally to soft PVC toys and child-care articles. However, DBP can be present in these toys as by-product/impurity (in trace amounts), due to the use of technical phthalate mixtures in the production process. Although by sucking and chewing DBP might leach from the toys, the maximum extractable amount of DBP is too low to present a significant source of exposure to young children. This view was recently expressed by the EU Scientific Committee on Toxicity, Ecotoxicity and the Environment (CSTEE, 1998), which was asked to give its opinion on phthalate migration from soft PVC toys and child-care articles and the risk this could present to the health of young children putting these toys in the mouth.

From all available data on phthalates leachate from soft PVC toys, as provided by EU Member States and found in literature, CSTEE took the maximum reported emission rates as a worst-case situation. For DBP, a maximum emission rate of 259 µg/dm^2/24 h was reported in a Danish investigation from 1997 (Rastogi et al., 1997). For risk assessment, CSTEE converted this value to a daily DBP dose, assuming that an 8-kg infant mouthed 10 cm^2 of a toy for 6 hrs every day. This resulted in a daily DBP dose of 0.81 µg/kg bw/day. According to the results of a human volunteer study (Könemann, 1998), the assumptions done by CSTEE are worst case.

Other toys

DBP is used intentionally in a lollystick marketed as “Alien glow lolly” in Germany for children from 6-8 years of age. The transparent stick of this lolly has a lightstick inside. The lightstick (two glass vials inside a bendable cylinder) can be activated by breaking the vials (one containing 0.5 ml DBP, the other dimethyl phthalate, 2-methylpropanol and hydrogenperoxide) and mixing the chemicals, and can be used as a luminous bracelet or lollystick (personal communication, Hertel, 1998). Exposure of children to ingredients of the lightstick, in particular DBP, is highly unlikely and only possible in the case of cylinder break. Even in that case, children will be more likely exposed to the luminous mixture than to unreacted DBP. Therefore, this use does not have to be taken into account for risk assessment.

There is some information that other lightsticks containing DBP are/have been marketed in the EU (at least in Sweden). However, in Sweden this used is now banned (KEMI, 1997).

There is no information that DBP is used intentionally in toys other than lightsticks.

4.1.1.4 Humans exposed via the environment

DBP may be released to the environment through wastewater effluents and air at the sites where it is produced, formulated and/or processed/used. Those indirect exposure routes were taken into account in Section 3.

From the daily amounts of DBP released to air the EUSES model (OPS module) calculates local atmospheric concentrations. The calculated annual average DBP concentrations in air are presented in **Table 4.7**.

Table 4.7 Local calculated annual average concentrations in air

Life cycle stage or scenarios	Air concentration (μg/m3)
Production A	0.02
Production B	0.02
Production C	0.02
Processing polymers (IIIa)	2.4
Formulation adhesives (IIIb-1)	0.3
Processing adhesives (IIIb-2)	0.02
Formulation printing inks (IIIc-1)	0.05
Processing printing inks (IIIc-2)	0.2
Production glass fibers (IIId)	1

The total human intake via air, drinking water and food (EUSES) for all emission scenarios at local scale is given in **Table 4.8**.

Table 4.8 Total daily intake via air, drinking water and food at local scale

Life cycle stage or scenarios	Total daily intake (mg/kg/d)
Production A	0.0187
Production B	$9.1 \cdot 10^{-4}$
Production C	$7.86 \cdot 10^{-4}$
Processing polymers (IIIa)	0.0925
Formulation adhesives (IIIb-1)	0.0364
Processing adhesives (IIIb-2)	$6.22 \cdot 10^{-3}$
Formulation printing inks (IIIc-1)	$5.39 \cdot 10^{-3}$
Processing printing inks (IIIc-2)	$9.09 \cdot 10^{-3}$
Production glass fibers (IIId)	0.0395

The regional exposure assessment is discussed in Section 3. In **Table 4.9** the total human intake as well as the intake via air are presented.

Table 4.9 Regional scale air concentrations and total human intake

	Regional
Intake (mg/kg/d)	$3.59 \cdot 10^{-4}$
PEC air (μg/m^3)	0.006

Breast milk

DBP has been identified in human breast milk in concentrations ranging from 10 to 51 µg/kg (Gruber et al., 1998; Bruns-Weller and Pfordt, 2000). Whether the DBP in human breast milk originates from direct or from indirect sources is not clear, but given the diffuse use and the diffuse emissions in the environment, the latter is more likely.

The exposure to babies is calculated according to the WHO (1998). For the first three months in life, an infant consumes an average of 120 grams per day of human milk per kilogram of body weight. After three months of age, the volume consumed per unit weight of the infant decreases with increasing age. By multiplying the concentration (given as mg/kg or mg/l) of a particular substance in whole breast milk by a factor of 0.12, the approximate daily intake of the substance in mg/kg bw/day can be estimated. If the concentration is given in mg/kg milk fat and the milk fat content is not reported, it is assumed that the average fat content of the milk is 3.5%.

Based on the concentrations found, the exposure to DBP via breast milk can be calculated as follows:

minimum: 10 µg DBP/kg milk = $100 \cdot 120$ = 1.2 µg DBP/kg bw/day
maximum: 51 µg DBP/kg milk = $51 \cdot 0.120$ = 6 µg DBP/kg bw/day.

The exposure via breast milk for infants thus varies between 1.2 and 6 µg DBP/kg bw/day.

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

4.1.2.1 Toxicokinetics, metabolism, and distribution

4.1.2.1.1 Absorption and excretion

Oral studies in rats and hamsters given ^{14}C-DBP, showed that DBP is readily absorbed from the gastrointestinal tract; 63 - ≥90% of the administered radioactivity was excreted in urine within 48h (Foster et al., 1982; Tanaka et al., 1978; Williams and Blanchfield, 1975). Fecal excretion was low (1.0-8.2%) (Tanaka et al., 1978).

In 13 individuals who had ingested food which had been in contact with plastic packaging material containing DBP, a mean blood level of 0.10 mg DBP/L was found, while the mean blood level of 9 unexposed men was 0.02 mg/L. These figures indicate oral absorption of DBP also by humans (Tomita et al., 1977).

After a dermal application under covered condition (plastic cap) of 43.7 mg/kg bw (157 μmol/kg bw) ^{14}C-DBP in ethanol to the clipped skin (circular area with diameter of 1.3 cm) of male F344 rats (bw 180-220 g) 10-12% of the administered dose per day was excreted in urine for a total of ca. 60% within 7 days. In feces ca.1% of the dose was excreted in 24 hours (totally ca. 12% within 7 days) (Bronaugh et al., 1982; Elsisi et al., 1989).

An *in vitro* study with undiluted DBP indicated slower absorption by human skin (2.40 μg/cm^2/hr) than by rat skin (93.35 μg/cm^2/hr) (Scott et al., 1987).

In a placental transfer study pregnant Sprague-Dawley rats received a single oral dose of 500 or 1,500 mg ^{14}C-labelled DBP/kg bw on day 14 of gestation. Maternal and fetal tissues were collected at intervals from 0.5 to 48 hours. Radioactivity in embryonic tissues accounted for less than 0.12-0.15% of the administered dose. Levels of radioactivity in placenta and embryo were 1/3 or less of those in maternal plasma. No accumulation of radioactivity was observed in maternal or embryonic tissues. It was shown that unchanged DBP and its metabolites MBP and MBP-glucuronide were rapidly transferred to the embryonic tissues, where their levels were constantly lower than those in maternal plasma. MBP accounted for most of the radioactivity recovered in maternal plasma, placenta and embryo. Unchanged DBP was found only in small amounts (Saillenfait et al., 1998).

After a single oral dose of 500 mg ^{14}C-DBP/kg bw in 50% ethanol to male rats bile duct was cannulated. In bile collected for 6 hours after administration 4.5% of the dose was recovered (Kaneshima et al., 1978).

In two bile duct cannulated rats bile was collected for 3 days after a single oral dose of 60 mg ^{14}C-DBP/kg bw. At day one 27.6 and 52.8% of the dose, respectively, was excreted in bile of the two animals and at day two 4.5 and 3.85%, respectively. Totally 32.2 and 56.7% of the dose was excreted in bile within 3 days. MBP and intact DBP (ratio 1:1) were the main products in the bile (Tanaka et al., 1978).

4.1.2.1.2 Distribution

Male Wistar rats which had received a single oral dose of 0.27 or 2.31 g ^{14}C-DBP/kg bw in corn oil did not show significant retention in any organ. Distribution was similar after both dose-levels. The lowest amount of activity was found in the brain (0.03%) and the highest in the kidneys (0.66%) at 4 hours after administration. At 48 hours after administration only trace amounts (<0.01%) were detected in tissues. Up to 24 hours after dosing 0.4% of the administered activity was found in blood at both dose-levels (Williams and Blanchfield, 1975). Rats receiving orally 60 mg ^{14}C-DBP/kg bw in DMSO did also not reveal significant retention in tissues (totally 14 tissues) 24 hours after dosing. No retention was seen in brain, heart, lung, spleen, testicles, prostate or thymus, 0.06% was found in liver, 0.02% in kidneys, 0.3% in muscle, 0.7% in adipose tissue, 1.53% in intestines, 0.01% in stomach and 0.02% in blood (Tanaka et al., 1978).

Twenty-four male Wistar rats (bw ca. 50 g) received ground rat chow mixed with 2% corn oil and 0.1% unlabeled DBP for up to 12 weeks. Twelve control rats were fed ground rat chow mixed with 2% corn oil. Eight treated rats and 4 control rats were killed after 4, 8 and 12 weeks. For the 4-week study the diets of 4 of the treated rats also contained 10 μCi of ^{14}C-DBP/kg of feed; the other 4 treated rats in the 4-week study were fed this radioactive diet only for the last 24 hours. For the 8- and 12-week studies the diets contained 0.7 μCi ^{14}C-DBP/kg of feed for the last 24 hours. At the end of the studies the rats were killed and organs and tissues (spleen, kidneys, adipose tissue, testes, skeletal muscle, heart, lungs, brain) removed and frozen until analyzed. No substantial accumulation in any tissue was seen (Williams and Blanchfield, 1975).

Seven days after a dermal application under covered condition (plastic cap) of 43.7 mg/kg bw (157 μmol/kg bw) ^{14}C-DBP in ethanol to the clipped skin (circular area with diameter of 1.3 cm) of male F344 rats (bw 180-220 g) only 0.5-1.5% of the applied dose was found in tissues; adipose tissue (0.41%), skin (1.4%) and muscle (1.1%) contained most of the DBP remaining in the body; all other tissues combined (brain, lung, liver, spleen, small intestine, kidneys, testes, spinal cord, blood) contained less than 0.5%. Thirty three percent remained at the site of application (Elsisi et al., 1989).

After inhalation of 50 mg/m^3, 6 hours/day, for 3 or 6 months by rats, DBP levels in several tissues were determined (limit of detection 0.03 mg/kg). DBP was found in brain (0.42-0.68 mg/kg after 3 months, 0.54-1.46 mg/kg after 6 months; 3-4 animals per time interval), lungs (≤0.03-0.27 mg/kg after 3 months, 0.57-0.65 mg/kg after 6 months; 2-3 animals per time interval), liver (0.25-0.29 mg/kg after 3 months, 0.10-0.29 mg/kg after 6 months; 3-4 animals per time interval), kidneys (0.05-0.17 mg/kg after 3 months, 0.13-0.32 mg/kg after 6 months; 3-4 animals per time interval) and testes (0.09-0.16 mg/kg after 3 months, ≤0.03-0.31 mg/kg after 6 months; 3-4 animals per time interval). After exposure to 0.5 mg/m^3 DBP was detected in brain at levels of ≤0.03-0.19 mg/kg after 3 months and at levels of 0.37-0.64 mg/kg after 6 months (3 animals per time interval). In lungs no detectable residues (limit of detection 0.03 mg/kg) were found after 3 months (3 animals analysed) and after 6 months in one out of 2 animals 0.14 mg/kg was detected (≤0.03 mg/kg in second animal). After 3 months, residues in liver were below the limit of detection (≤0.03 mg/kg) in two animals and 0.10 mg/kg in one animal; after 6 months, residues in two animals were below the limit of detection. In kidneys residue levels after 3 months of exposure were non-detectable (≤0.03 mg/kg) in two animals and 0.05 mg/kg in one animal; after 6 months of exposure residues in kidneys were non-detectable in two animals (≤0.03 mg/kg) and 0.04 mg/kg in one animal. In testes residues after 3 months were ≤0.03-0.07 mg/kg (3 animals analysed) and after 6 months below the detection limit (≤0.03 mg/kg) in two animals and 0.26 mg/kg in one animal (Kawano et al., 1980b).

No metabolites were measured in this study.

4.1.2.1.3 Biotransformation

After oral administration of DBP to rats mono-n-butyl phthalate (MBP) was detected in urine together with MBP glucuronide, various ω- and ω-1-oxidation products of MBP (more polar ketones and carboxylates) and a small amount of free phthalic acid (Albro and Moore, 1974; Foster et al., 1982; Tanaka et al., 1978; Williams and Blanchfield, 1975) (see metabolism scheme at the end of this paragraph).

Species differences in the excretion of unconjugated and conjugated MBP were seen. Ratio of MBP-glucuronide to unconjugated MBP was 1 in the rat, 1.5 in the guinea-pig and 2.3 in the hamster (Tanaka et al., 1978). Foster et al. (1982) found 37.6 and 52.5% of the dose as MBP-glucuronide in urine of rats and hamsters, respectively and 14.4 and 3.5% as unconjugated MBP after oral administration of 2 g DBP/kg bw.

In *in vitro* studies with liver homogenates (rat, baboon, ferret), kidney homogenates (rat), and intestinal cell preparations (rat, baboon, ferret, man) hydrolysis of DBP to MBP was demonstrated (Lake et al., 1977; Rowland et al., 1977; Tanaka et al., 1978; White et al., 1980). Very rapid hydrolysis of DBP to MBP was demonstrated by rat liver microsomal fraction (73% within 2 hours). A species difference was observed in that phthalate diester hydrolase activity decreased in the order baboon>rat>ferret. Intestinal mucosal cell preparations of rat, baboon and ferret and also human intestinal preparations were all able to hydrolyse DBP to MBP. Rate of hydrolysis of DBP to MBP by rat gastro-intestinal contents was the greatest with small intestine contents and much slower with caecal and stomach contents (Lake et al., 1977; Rowland et al., 1977). In an *in vitro* study using an everted gut sac preparation from rat small intestine only 4.5% of intact DBP crossed the intestinal mucosa; 95.5% of DBP was hydrolysed to MBP by esterases within the mucosal epithelium before it reached the serosal perfusion solution. Inhibition of esterases reduced the amount DBP hydrolysed to MBP. The same amount of MBP was absorbed by the intestine, but the amount of DBP absorbed was reduced significantly (White et al., 1980).

4.1.2.1.4 Conclusion on toxicokinetics, metabolism and distribution

Dibutyl phthalate is rapidly absorbed and excreted after oral administration as was demonstrated in studies in laboratory animals. Up to more than 90% of oral doses given to rats or hamsters was excreted in urine within 24-48h. Fecal excretion is low (1.0-8.2%).

Also in human oral absorption of DBP takes place. After dermal exposure of rats absorption occurred; ca. 60% of the dose was excreted in urine within 7 days. In feces ca. 12% of the dose was found. An *in vitro* study revealed slower absorption of DBP by the human skin (2.40 μg/cm^2/hour) than by the rat skin (93.35 μg/cm^2/hour).

Data on absorption after exposure by inhalation are not available.

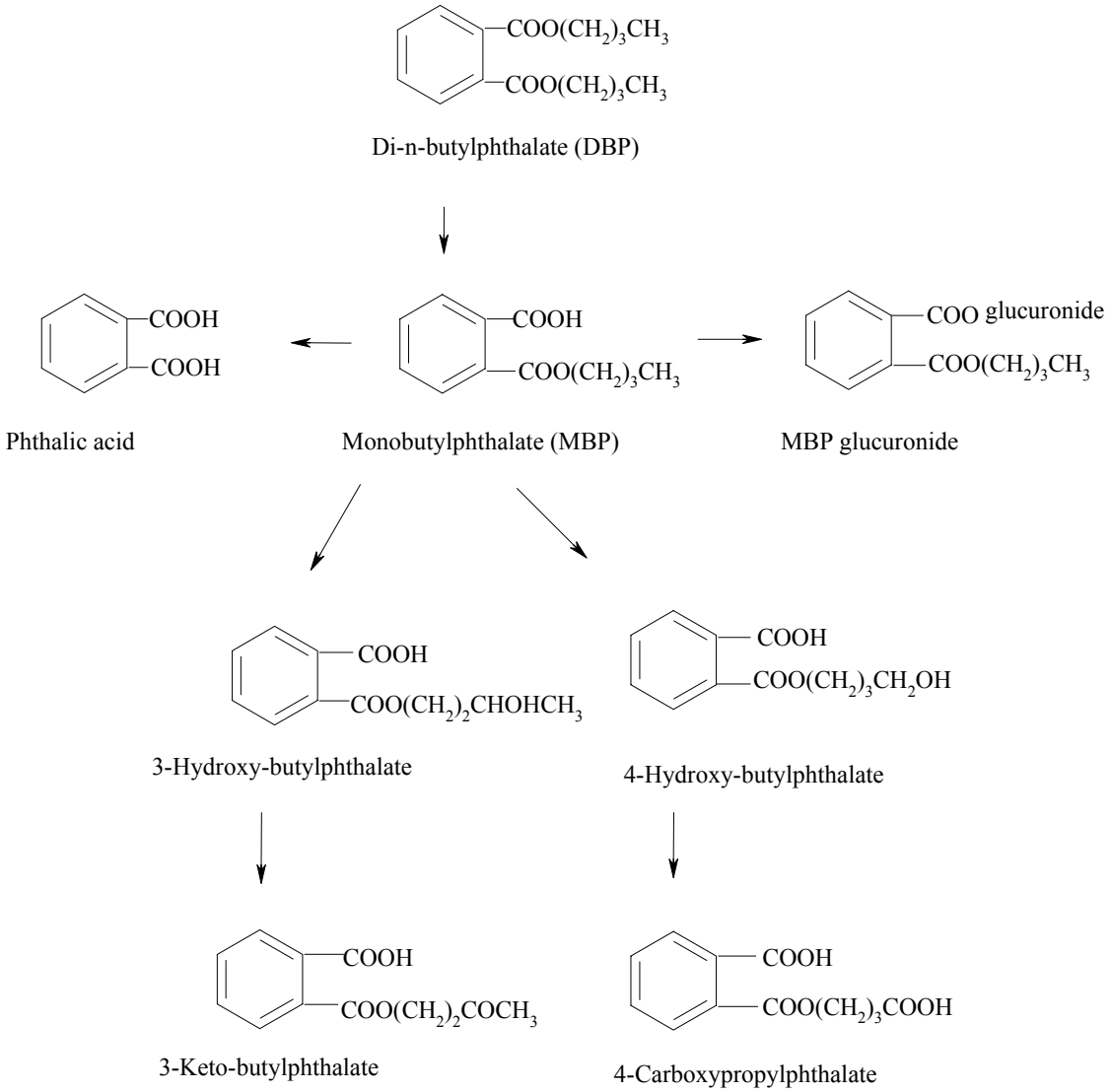
A substantial fraction of DBP is initially excreted in the bile and subsequently enters the enterohepatic circulation. No significant accumulation in tissues was observed in laboratory animals after oral as well as dermal exposure; limited inhalation data revealed an indication for some accumulation in tissues.

The major part of DBP is hydrolysed to MBP and the corresponding alcohol prior to absorption by the small intestines, but hydrolysis can also occur in liver and kidneys. The metabolites that occur in urine are MBP, MBP-glucuronide, various ω- and ω-1-oxidation products of MBP

(more polar ketones, carboxylates) and a small amount of free phthalic acid (see metabolism scheme below). Species differences in the excretion of MBP and its glucuronide were observed; rats excreted a larger proportion unconjugated MBP in urine than hamsters. There are no data on biotransformation after dermal exposure and exposure by inhalation.

Transplacental transfer of DBP and its metabolites was demonstrated in an oral study with ^{14}C-labelled DBP in rats. Levels of radioactivity in placenta and embryo were 1/3 of those in maternal plasma; radioactivity in embryonic tissues accounted for less than 0.12-0.15% of the administered dose. MBP accounted for most of the radioactivity in maternal plasma, placenta and embryo. Unchanged DBP was found only in small amounts. No accumulation of radioactivity was seen in maternal or embryonic tissues.

Metabolic scheme for di-n-butyl phthalate
(Adapted from references Albro and Moore, 1974; Foster et al., 1982; Tanaka et al., 1978)



4.1.2.2 Acute toxicity

4.1.2.2.1 Studies in animals

Several studies have been carried out with different species and by different routes. They are summarised in **Table 4.10**.

Table 4.10 Acute toxicity studies in animals

Acute toxicity	Species	Protocol	Results
A. Oral	mouse	unknown	LD_{50} 5,289 mg/kg bw (RTECS, 1993a)
	mouse	unknown	LD_{50} 4,840 mg/kg bw (BIBRA, 1987)
	rat	other *	LD_{50} 8,000 mg/kg bw (Smith, 1953)
	rat	unknown	LD_{50} 6,300 mg/kg bw (BASF, 1961)
	guinea-pig	unknown	LD_{50} 10,000 mg/kg bw (RTECS, 1993b)
B. Inhalation	mouse	unknown	LC_{50} (2 h) 25 mg/L (Voronin, 1975)
	rat	other *	LC_{50} (4 h) ≥15.68 mg/L (Greenough et al., 1981)
	rat	unknown	LC_{50} (not avail.) 4.25 mg/L (RTECS, 1993c)
C. Dermal	rabbit	unknown	LD_{50} >20,000 mg/kg bw (Clayton and Clayton, 1994; RTECS, 1993d)
D. Other routes			
i.v.	mouse	unknown	LD_{50} 720 mg/kg bw (RTECS, 1993e)
i.m.	rat	other *	LD_{50} >8,000 mg/kg bw (Smith, 1953)
i.p.	mouse	unknown	LD_{50} 3,400 – 4,000 mg/kg bw (BASF, 1961; Calley et al., 1966; Lawrence et al., 1975)
i.p.	rat	unknown	LD_{50} 3,178 mg/kg bw (Singh et al., 1972)
i.p.	rat	unknown	LD_{50} ca.4,200 mg/kg bw (BASF, 1958)
s.c.	mouse	unknown	LD_{50} 20,800 mg/kg bw (RTECS, 1993f)

* See HEDSET

Oral LD_{50} studies in mice and rats resulted in values varying from 4,840 to 5,289 mg/kg bw for the mouse (BIBRA, 1987; RTECS, 1993a) and from 6,300 to 8,000 mg/kg bw for the rat (BASF, 1961; Smith et al., 1953). The oral LD_{50} value for the guinea-pig is 10,000 mg/kg bw (RTECS, 1993b). None of the studies was performed according to a guideline or under GLP conditions.

Acute studies by inhalation revealed a 2-h LC_{50} value for the mouse of 25 mg/L. Pronounced irritation of mucous membranes of the eyes and upper respiratory tract, slowed respiration, ataxia, pareses and paralysis of hind legs were seen (Voronin, 1975). Cats exposed for 5.5 h to 1 mg/L showed irritation of nasal mucous membranes as did mice exposed for 2 h to 0.25 mg/L (no further data available) (BIBRA, 1987; BUA, 1987). Concentrations of 11 mg/L induced salivation, restlessness and languor in cats. Rapid recovery was seen after cessation of exposure (no further data are available) (BUA, 1987).

A group of 5 m and 5 f Sprague-Dawley rats was exposed for 4 hours to an aerosol of 15.68 mg DBP/L of air. Air exposed animals served as controls. Observation period was 14 days. A second delivery of DBP was tested at 12.45 and 16.27 mg/L one month later. Respirable fraction (i.e. diameter <4.7 μm) was 56.9, 64.4 and 59.9% at 15.68, 12.45 and 16.27 mg/L. In the 15.68 mg/L group 2/5 male and 3/5 female animals died, whereas no mortalities were observed in the 12.45 and 16.27 mg/L groups. Due to the unusual death pattern, no LC_{50} value could be determined, but the LC_{50} value was estimated to be ≥15.68 mg/L in this study which was performed under GLP conditions. At 15.68 mg/L apart from a reduction in respiratory rate, behaviour of the rats

showed no differences with control animals. Poor coat condition was seen in all surviving animals during the observation period due to excessive grooming behaviour. Lung/body weight ratios in premature decedents at 15.68 mg/L were elevated, while these ratios were lower than those of controls in males at 12.45 and 16.27 mg/L. Macroscopy of the lungs revealed red/dark foci in several animals scattered among the treatment groups. One m and one f rat exposed to 15.68 mg/L had white foci in all lung lobes. Dark red areas were seen in the lungs of 2 females at 12.45 mg/L and in 1 male and 1 female rat at 16. 27 mg/L (Greenough et al., 1981). A second LC_{50} study in the rat revealed a value of 4.25 mg/L. However the original Russian report of this study is not available, only a summary is provided and the exposure time was not mentioned (RTECS, 1993c). None of the inhalation studies mentioned above was performed according to a guideline.

Dermal studies in rabbits revealed LD_{50} values of >20,000 mg/kg bw, respectively. Only a summary of the study was available and no data about performance according to any guideline or GLP conditions were given (Clayton and Clayton, 1994; RTECS, 1993d).

Acute toxicity studies with other routes of administration (i.v., i.m., i.p., s.c.) (see **Table 4.10**) were also not performed according to a guideline or under GLP conditions.

4.1.2.2.2 Studies in humans

One study concerning accidental ingestion of DBP (10 g) by a 23-yr old man has been reported. Nausea, vomiting and dizziness were noticed and a few hrs later lacrimation, photophobia and pain in the eyes. Finally the cornea was severely damaged (keratitis erosiva). Urinalysis showed microhaematuria, oxalate crystals and pathological leucocyte counts. Recovery occurred within 14 days after treatment with mydriatics and antibiotics (Cagianut, 1954).

4.1.2.2.3 Conclusion on acute toxicity

The oral LD_{50} value for the rat is ≥6,300 mg/kg bw for dibutyl phthalate; the dermal LD_{50} is >20,000 mg/kg bw for the rabbit. With respect to inhalation the 4h LC_{50} for dibutyl phthalate is ≥15.68 mg/L for the rat.

According to the EC criteria, dibutyl phthalate does not need to be classified on the basis of its acute toxicity.

4.1.2.3 Irritation

4.1.2.3.1 Skin irritation

Studies in animals

In a study in rabbits performed with undiluted DBP according to OECD guideline 404, immediately after exposure and 24 hours after the start of the experiment very slight erythema was seen in 2/3 animals. Edema was not seen. 48 hours after the start of the experiment erythema had disappeared. Application area was 2.5·2.5 cm. DBP was not considered to cause skin irritation (BASF, 1990a).

0.5 Ml undiluted Vestinol C (trade name of DBP) was applied to the intact and abraded skin (area 2.5·2.5 cm) of 3 m and 3 f rabbits. Per animal one intact and one abraded area was treated with Vestinol C and one intact and one abraded area with 10% laurylsulphate as positive control (FDA recommended method). Mild reactions were seen at 24 hours; at 72 hours none of the treated sites showed any reaction. Irritation index was reported to be 0.54/8. According to FDA criteria Vestinol C was very mildly irritating. According to EC criteria Vestinol C is not irritating (Greenough et al., 1981).

Studies in humans

No data on humans are available.

4.1.2.3.2 Eye irritation

Studies in animals

In a study in rabbits performed with undiluted DBP according to OECD guideline 405, well-defined conjunctival redness was seen in all animals after 1 and 24 hours, while slight to well-defined redness was seen in all animals after 48 hours. After 72 hours all symptoms had disappeared. Cornea and iris did not show irritation. DBP was considered to be not irritating for the eye in this study (BASF, 1990b).

0.1 Ml undiluted Vestinol C (trade name of DBP) was instilled in the eyes of 3 m and 3 f rabbits (FDA recommended method). The eyes were not rinsed. After 1 hour in 3/6 animals mild and in 3/6 animals very mild redness was seen. Very mild redness was still seen in 2/6 animals after 24 hours. Very mild swelling was seen in 3/6 animals after 1 hour. All eyes had returned to normal after 48 hours. No reactions in cornea or iris were seen. The irritation index was reported to be 0.11/110. DBP was considered to be not irritating for the eye in this study (Greenough et al., 1981).

Studies in humans

No data on humans are available.

4.1.2.3.3 Irritation of respiratory tract

Studies in animals

Cats exposed for 5.5 hours to 1 mg DBP/L showed irritation of nasal mucous membranes as did mice exposed for 2 hours to 0.25 mg/L (no further data available) (BIBRA, 1987; BUA, 1987).

In a 28-day inhalation study in Wistar rats, which were head-nose exposed for 6 hours/day, 5 days/week, for 4 weeks, to DBP (purity 99.8%) as liquid aerosol, at the highest exposure concentration of 509 mg/m^3 red crust formation at the snouts was observed after cessation of daily exposure (recovered within 18 hours) in a maximum of 4/10 animals at a maximum duration from day 13-27. Histopathology showed in all treated groups (1.18, 5.57 or 509 mg/m^3) a dose-dependent increase of hyperplasia of mucous cells at some sites of levels II, III and IV of nasal cavity and a dose-dependent increased incidence of squamoid metaplasia at level I of the

larynx. The epithelium in the respective areas of nasal cavity was regular and infoldings were absent, and signs of inflammation were missing in the whole nasal cavity (Gamer et al., 2000).

Studies in humans

No data on humans are available.

4.1.2.3.4 Conclusion on irritation

Dibutyl phthalate did not show skin or eye irritating properties in rabbits. According to EC criteria dibutyl phthalate does not need to be classified on the basis of the available tests.

Irritation of nasal mucous membranes was seen in mice after exposure by inhalation after 2 h at 0.25 mg/L. Repeated exposure of rats to 509 mg DBP/m^3 (~0.5 mg DBP/L) as aerosol caused red crust formation of snouts. At concentrations ≥1.18 mg/m^3 (≥~0.001 mg/L) local (histopathological) effects in nasal cavity and larynx were seen, but no signs of inflammation. Based on these data DBP does not need to be classified for respiratory irritation.

4.1.2.4 Corrosivity

Not relevant for this substance.

4.1.2.5 Sensitisation

4.1.2.5.1 Studies in animals

Two guinea-pig maximization studies were performed. One of these two tests was performed according to OECD Guideline 406, the other test was performed according to a FDA recommended method under GLP conditions. In both tests no sensitisation reactions were observed (BASF, 1990c; Greenough et al., 1981).

In a repeated patch test in rabbits no sensitisation reactions were seen. The test was neither performed according to a guideline nor under GLP conditions (BASF, 1957).

4.1.2.5.2 Studies in humans

A 44-year-old man noticed eczema under a plastic watch strip on the left wrist. After transferring the watch to the right wrist also eczema occurred. Patch tests with the plastic strip, 20% colophony, 1% p-t-butylphenol, butylphenol formaldehyde resin and 5% DBP were all positive (solvent not given) (Husain, 1975).

A 71-year-woman suffered from recurrent “ear infections” since she wore a hearing aid. She developed dermatitis behind the ears and on the temples, where there was contact with the spectacle frames. Patch tests wit 5% dibutyl phthalate in petrolatum, 5% dimethyl phthalate in petrolatum or 5% diethyl phthalate in petrolatum gave positive results. Patch tests with scrapings from the spectacle frame or the hearing aid gave less positive reactions (Oliwiecki et al., 1991).

Workers in a factory producing shoes from PVC granulate were patch tested with dibutylphthlate. Two groups of 30 workers, with and without dermatitis, respectively, were used. A control group of 30 persons was included in the study. 3/30 Workers with dermatitis and 5/30 without dermatitis reacted positive at patch testing, while none of the controls reacted. Concentration of DBP and solvent used at patch testing was not given (Vidovic and Kansky, 1985).

Two women developed dermatitis of the axillae after using an antiperspirant spray with DBP. Both women reacted positive at patch testing with DBP, but not at patch testing with other constituents of the spray (Calnan, 1975; Sneddon, 1972).

Routine patch testing with a mixture of phthalate esters (2% dimethyl phthalate, 2% diethyl phthalate and 2% dibutyl phthalate in petrolatum) revealed one positive reaction in 1,532 persons tested (Schulsinger and Mollgard, 1980).

Cosmetic products (nail polish with 6 or 9% DBP or deodorant with 4.5% DBP) or 5% DBP in petrolatum were patch tested on 13-159 persons in 11 different studies. The studies included 48-hour closed patch tests, modified maximization tests, (modified) repeated insult patch tests, 21-day cumulative irritancy tests, prophetic patch tests, controlled use studies (lasting 2 days or 4 weeks). In the majority of the studies (9/11) no irritation, (contact) sensitisation or photosensitisation was observed. In 2/11 studies with a 9% nail polish and a 4.5% deodorant, respectively, carried out with 13 and 12 persons, slight irritation was seen. The persons received 21 23-24-hour lasting patches on the same site of the back (only summary available) (Anonymous, 1985).

4.1.2.5.3 Conclusion on sensitisation

Dibutyl phthalate did not show skin sensitising properties in two maximization tests in guinea-pigs. According to EC criteria the substance does not need to be classified on the basis of the available tests.

The results of the available case studies with respect to the possible induction of sensitisation in human by DBP are not appropriate for a definite conclusion due to the limited documentation of the studies and additionally sometimes conflicting results of the studies.

4.1.2.6 Repeated dose toxicity

4.1.2.6.1 Oral studies

Studies in animals

The results of the repeated oral dose studies in animals are summarised in **Table 4.11**.

Table 4.11 Summary of repeated dose toxicity studies in animals

Repetead dose toxicity	Species	Protocol	Results
A. Oral * (general toxicity)	mouse	Other *: 0, 0.25 and 2.5% in diet (~ 0, 500 and 5,000 mg/ kg bw) for 86 or 90 days	LOAEL 500 mg/kg bw (Ota et al., 1973; 1974)
	mouse	Other **: 0, 0.125, 0.25, 0.5, 1.0 or 2.0% in diet for 13 weeks (~ males 163-3689 mg/kg bw; females 238-4,278 mg/kg bw)	0.25% ~ 353 mg/kg bw is NOAEL for males 0.5% ~ 812 mg/kg bw is LOAEL for males 0.125% ~ 238 mg/kg bw is LOAEL for females (NTP, 1995)
	rat	Other *: 0.5 and 5.0 % in diet (~250 and 2,500 mg/kg bw) for 34-36 days	LOAEL 0.5% ~ 250 mg/kg bw (Murakami et al., 1986)
	rat	OECD 408 0, 0.04, 0.2 and 1.0% in diet (~0, 30, 152, 752 mg/kg bw) for 90 days	NOAEL 0.2% ~ 152 mg/kg bw LOAEL 1.0% ~ 752 mg/kg bw - (Schilling et al., 1992)
	rat	Other *: 0, 120 and 1,200 mg/kg bw by in olive oil by gavage for 3 months	LOAEL 120 mg/kg bw (Nikoronow et al., 1973)
	rat	Other **: 0, 0.25, 0.5, 1.0, 2.0 or 4.0% in diet for 13 weeks (~ males176-2,964 mg/kg bw; females 177-2,943 mg/kg bw	NOAEL 0.25% ~ 177 mg/kg bw LOAEL 0.5% ~ 357 mg/kg bw (NTP, 1995)
B. Oral (peroxisome proliferation)	rat	Other *: 0, 0.125% in diet (~0 and 62.5 mg/kg bw) for 1 year	NOAEL 0.125% ~ 62.5 mg/kg bw (Nikoronow et al., 1973)
	rat	Other *:0, 0.01, 0.05, 0.25 and 1.25% in diet (~0, 5, 25, 125 and 625 mg/kg bw) for 1 year	NOAEL 0.25% ~ 125 mg/kg bw LOAEL 1.25% ~ 625 mg/kg bw (Smith, 1953)
	rat	Other **: 0, 20, 60, 200, 600 and 2,000 mg/kg of diet (~0, 1.1, 5.2, 19.9, 60.6 and 212 mg/kg bw) for 2 weeks	NOAEL 200 mg/kg of diet ~ 19.9 mg/kg bw based on increased LAH-11 # and LAH-12 # activities (Jansen et al., 1993)
	rat	Other **: 0, 0.6, 1.2 and 2.5% in diet (~0, 600, 1,200 and 2,100 mg/kg bw for 3 weeks	LOAEL 0.6% ~ ca. 600 mg/kg bw based on increased PcoA ##, LAH-11 # and LAH-12 # activities and increased liver weights (Barber et al., 1987; BIBRA, 1986)
	rat	Other **:0, 0.05, 0.1, 0.5, 1 and 2.5% in feed (~0, 51.5, 104, 515, 1,040, 2,600 mg/kg bw) for 4 weeks	NOAEL 0.1% ~ 104 mg/kg bw for peroxisomal proliferation (based on increased PcoA ## activity) LOAEL for increase of liver weights 0.05% ~ 51.5 mg/kg bw - (BIBRA, 1990)
	rat	Other **: 0, 0.04, 0.2 and 1.0% in diet (~0, 30, 152 and 752 mg/kg bw) for 3 months	NOAEL 0.2% ~ ca. 152 mg/kg bw (based on increased number and/or size of peroxisomes in the liver by histochemistry) - (Kaufmann, 1992)
C. Oral (testicular effects)	rat	Other **: 250, 500 and 1,000 mg/kg bw for 15 days	LOAEL 250 mg/kg bw (Srivastava et al., 1990)

* Tests showed limitations. See next pages and HEDSET
** See HEDSET
\# LAH-11 and LAH-12 =11- and 12-lauric acid hydroxylase, indicators for peroxisomal proliferation
PCoA = cyanide-insensitive palmitoyl-CoA oxidase activity, an indicator for peroxisomal proliferation

General toxicity

In a limited dietary study in mice (ddy, groups of 3 males and 12 females) 0.25 or 2.5% DBP in diet (~ 500 and 5,000 mg/kg bw) was administered for 86 or 90 days. Remarkable vacuolar degeneration and necrosis of single cells in the liver, and cysts and degeneration of epithelial cells in the renal tubules were observed in the high-dose group. In the low-dose group, histological changes were slight in the liver and kidneys but degeneration of parenchyma was observed. (Ota et al., 1973; 1974).

In a well-performed 13-week study in B6C3F1 mice groups of 10 m and 10 f animals received 0, 0.125, 0.25, 0.5, 1.0 or 2.0% DBP in their diet (equal to 0, 163, 353, 812, 1,601 and 3,689 mg/kg bw for males and 0, 238, 486, 971, 2,137 and 4,278 mg/kg bw for females). Growth was statistically significantly decreased at dose-levels ≥0.5% in the diet in males as well as females. Haematology showed a statistically significantly decreased hematocrit value in females at 2.0% in the diet. Relative liver weights were statistically significantly increased at dose-levels ≥0.5% in diet. Absolute and relative kidney weights were increased in females only, at all dose-levels without a dose-relationship, but statistically significant except the absolute kidney weight at 2.0%. Testis zinc concentrations were statistically significantly higher in males at dose-levels ≥0.5%. Serum testosterone concentrations were highly variable but generally higher in the exposed groups; only statistically significant at 0.125%. In males at 1.0 and 2.0% in diet and in females at 2.0% in diet histopathology of the liver revealed hepatocellular cytoplasmic alterations, consistent with glycogen depletion. Small fine, eosinophilic granules, consistent with peroxisome proliferation were seen in cytoplasm of hepatocytes in males and females at 2.0% in the diet. Lipofuscin accumulation in the liver was observed at dose-levels ≥1.0% in the diet. Evaluation of reproductive tissues at 0, 0.125, 0.5 and 2.0% groups showed a statistically significantly decreased left epididymal weight and a statistically significantly increased number of spermatid heads/g of testis at 2.0% in the diet. Epididymal spermatozoal measurements and estrous cycle characterisation did not reveal significant changes. For males the NOAEL in this study is 353 mg/kg bw and the LOAEL 812 mg/kg bw. For females the lowest dose-level of 238 mg/kg bw is a LOAEL; a NOAEL for females could not be determined in this study (NTP, 1995).

In an adequate 3-month dietary toxicity study in Wistar rats which was performed according to OECD guideline 408, 152 mg/kg bw appeared to be the NOAEL. At the next higher dose-level of 752 mg/kg bw changes in hematological (decreased haemoglobin- and haematocrit-values and decreased erythrocyte counts) and clinical chemical parameters (decreased triglyceride levels, increased serum glucose and albumin levels), a statistically significant increase in the activity of cyanide-insensitive palmitoyl-CoA oxidase (PCoA; is an indicator for peroxisomal proliferation), a statistically significant decrease in T3 and statistically significant increases in liver and kidney weights were observed. Histopathology showed decreased or missing lipid deposition in hepatocytes at 752 mg/kg bw. Neurofunctional tests did not show abnormalities at any dose-level. No effect on the testes was observed in this study (Schilling et al., 1992).

In a well-performed 13-week study in F344/N rats groups of 10 m and 10 f animals received 0, 0.25, 0.5, 1.0, 2.0 or 4.0% DBP in their diet (equal to 0, 176, 359, 720, 1,540 and 2,964 mg/kg bw for males and 0, 178, 356, 712, 1,413 and 2,943 mg/kg bw for females). Growth was statistically significantly decreased in males as well as females at dose-levels ≥2.0% in the diet and in addition in males at 1.0%. Feed consumption of males and females at 4.0% in the diet was lower and all animals at this dose-level were emaciated. Hematology revealed in males at dose-levels ≥0.5% in the diet statistically significantly decreased haemoglobin values and erythrocyte counts. Haematocrit values in males were also decreased at dose-levels ≥0.5% in the diet, but statistically significant only at 2.0 and 4.0% in the diet. Statistically significantly increased

numbers of blood platelets were also seen in males at dose-levels ≥0.5% in the diet. Number of nucleated erythrocytes was statistically significantly increased at 4.0% in the diet in both males and females. Clinical chemistry showed statistically significantly decreased cholesterol values in males and females at 2.0 and 4.0% in the diet. Statistically significantly decreased triglyceride levels were seen in males at all dose-levels and in females at dose-levels ≥1.0% in the diet, with a dose-relationship in both males and females. Statistically significant increases in serum alkaline phosphatase (SAP) activity (m at 2.0 and 4.0% and f at doses ≥1.0%) and concentration of bile acids (m at 2.0 and 4.0% and f at doses ≥0.5%) were seen. PCoA activity was increased at dose-levels ≥0.5% in males as well as females with a dose-relationship. Relative liver and kidney weights were statistically significantly increased in males at dose-levels ≥0.5% in the diet and in females at dose-levels ≥1.0% in the diet. Microscopy of the liver showed hepatocellular cytoplasmic alterations, consistent with glycogen depletion, in m and f at doses ≥1.0% in the diet. At 4.0% in the diet small, fine, eosinophilic granules were also observed. Electron microscopy revealed an increased number of peroxisomes in the liver at this dose-level. Lipofuscin accumulation was seen at doses ≥1.0% in the diet. Males at 2.0 and 4.0% in the diet revealed statistically significantly decreased testicular weights. Microscopy of the testes showed a dose-related degeneration of germinal epithelium at doses ≥1.0% in the diet. At 4.0% an almost complete loss of germinal epithelium occurred. Statistically significantly lower testicular Zn and serum testosterone concentrations were seen at 2.0 and 4.0% in the diet; serum Zn concentration was statistically significantly lower at 4.0%. Evaluation of spermatogenesis was performed in males at 0, 0.25, 1.0 and 2.0% in the diet. At 2.0% spermatid heads/testis and per g of testis, epididymal spermatozoal motility, and the number of epididymal spermatozoa per g epididymis were statistically significantly decreased. The NOAEL in this study is 0.25% in the diet equal to 177 mg/kg bw for both males and females (NTP, 1995).

The other studies in rats mentioned in **Table 4.11** under general toxicity and described below, were neither performed according to any guideline nor under GLP conditions and all showed limitations. However these studies may support the NOAELs given above.

A 34-36 days lasting dietary study in groups of 5 male Wistar rats showed decreases in weight gain at both dose-levels of 0.5 and 5% in the diet (equivalent to 250 and 2,500 mg/kg bw). Statistically significant changes in organ weights were seen including the testes, at 5.0%. Several clinical chemical parameters revealed statistically significant changes at 5.0%. Liver showed microscopical changes at both dose-levels. Ultramicroscopical changes in the liver were seen at both dose-levels, more pronounced at 5.0% (among others increasing number of peroxisomes).

The lowest dose-level of 0.5% in the diet (equivalent to 250 mg/kg bw) is a LOAEL in this study (Murakami et al., 1986).

In a 3-month gavage study groups of 10 m and 10 f Wistar rats received 120 or 1,200 mg DBP/kg bw. Behaviour, growth, haematology (haemoglobin value, erythrocyte and leucocyte count) and serum protein fractionation were normal. A statistically significantly increased relative liver weight was seen at both dose-levels; kidney and spleen weights were normal. Macroscopy and microscopy (liver, kidneys, spleen) did not show abnormalities. The lowest dose-level of 120 mg/kg bw is a LOAEL in this study (Nikoronow et al., 1973).

The same group of authors also reported a 12-month dietary study in Wistar rats. Groups of 20 m and 20 f animals received 0 or 0.125% DBP in their diet (equivalent to 62.5 mg/kg bw). Fifteen percent mortality occurred in the treated group compared to 10% in the control group. Body weight gain, food consumption, haematology (haemoglobin value, erythrocyte and leucocyte count), serum protein fractionation, organ weights (liver, kidneys, spleen), macroscopy and

microscopy (liver, kidneys, spleen) did not show abnormalities. 62.5 mg/kg bw is a NOAEL in this study, but the study showed severe limitations (among others only one dose-level tested) (Nikoronow et al., 1973).

In a one-year dietary study with groups of 10 male rats (strain not specified) 50% of the animals died at the highest dose-level of 1.25% in the diet (equivalent to 625 mg/kg bw) during the first week of the study. No specific gross or microscopic pathologic changes were seen. At the other dose-levels (0.25, 0.05 and 0.01% in the diet equivalent to 125, 25 and 5 mg/kg bw) no effect on survival, growth, food consumption, haematology (haemoglobin value, erythrocyte and leucocyte count, differential leucocyte count), macroscopy or microscopy was seen. Organ weights were not determined. 125 mg/kg bw is a NOAEL in this study but the study showed severe limitations (rat strain was not specified; only one sex was used, no biochemistry was carried out, organ weights were not determined) (Smith, 1953).

Peroxisome proliferation

Several phthalate esters are known to induce peroxisomal proliferation in the liver of mice and rats indicated by ultramicroscopical changes in the liver and changes in peroxisomal associated enzyme activities (palmitoyl CoA oxidase (PCoA), 11- and 12-lauric acid hydroxylase (LAH-11, LAH-12). It has been suggested that there is an association between peroxisome proliferation and the occurrence of liver tumours after long-term exposure (ECETOC, 1992, see also under Section 4.1.2.8 Carcinogenicity). Therefore the ability of DBP to induce peroxisomal proliferation is investigated in a number of studies.

The lowest NOAEL for this effect was found in a 2-week dietary study in male Wistar rats given 20, 60, 200, 600 and 2,000 mg DBP/kg of diet (equal to 1.1, 5.2, 19.9, 60.6 and 212.5 mg/kg bw). NOAEL for PCoA activity was 600 mg/kg of diet (60.6 mg/kg bw) and for LAH-11 and LAH-12 activity 200 mg/kg of diet (19.9 mg/kg bw). The overall NOAEL for the induction of peroxisomal associated enzymes is 200 mg/kg of diet (19.9 mg/kg bw) (Jansen et al., 1993).

In a 3-week dietary study in m and f F344 rats doses of 0.6, 1.2 and 2.5% in the diet (ca. 600, 1,200 and 2,100 mg/kg/bw) were given. A NOAEL could not be established because the lowest dose of 0.6% (ca. 600 mg/kg bw) caused increased activities of peroxisome associated enzymes (PCoA, LAH-11 and LAH-12). In addition increased liver weights and decreased serum triglyceride and cholesterol levels were found at this dose-level (Barber et al., 1987; BIBRA, 1986).

In a 4-week dietary study in male F344 rats dose-levels of 0.05, 0.1, 0.5, 1 and 2.5% in the diet (equal to 51.5, 104, 515, 1,040 and 2,600 mg/kg bw) were used. The NOAEL for an increase in PCoA activity was 0.1% in the diet (equal to 104 mg/kg bw). However in this study liver weights were statistically significantly increased at all dose levels with a dose-relationship (BIBRA, 1990).

In a 3-month dietary toxicity study in Wistar rats groups of 3 m and 3 f animals received 400, 2,000 or 10,000 mg DBP/kg of diet (~ ca. 30, 152 and 752 mg/kg bw). At the end of the treatment period peroxisomal proliferation in the liver was determined by a histochemical method, measuring number and/or size of peroxisomes. NOAEL for peroxisomal proliferation appeared to be 2,000 mg/kg of diet (ca. 152 mg/kg bw (Kaufmann, 1992)).

Testicular effects

Rats showed characteristic testicular changes after repeated oral exposure to DBP. In special studies examining these testicular effects in rats the lowest tested dose-level of 250 mg/kg bw induced already changes in testicular enzymes associated with degeneration of spermatogenic

cells and histopathology showed testicular degeneration in 5% of tubules at this dose-level (Srivastava et al., 1990). At doses of 500 mg/kg bw and higher decreases in weight of testes (atrophy) and accessory sex glands, decreased numbers of spermatocytes, degeneration of the seminiferous tubules of the testes, a reduction in testicular zinc levels and serum testosterone levels, increases in testosterone levels in the testes and an increase in urinary zinc excretion were observed (Cater et al., 1977; Gray et al., 1982, 1983; Oishi and Hiraga, 1980b; Srivastava et al., 1990). Also guinea-pigs revealed severe testicular changes after repeated oral administration (7 days) of DBP at a dose of 2,000 mg/kg bw (Gray et al., 1982). Mice and hamsters appeared to be less sensitive for the testicular effects. In mice after oral administration of 2,000 mg DBP/kg bw by gavage for 9 days or 2% DBP in diet (~2,400 mg/kg bw) for 7 days slight testicular effects and no effect, respectively were seen (Gray et al., 1982; Oishi and Hiraga, 1980a). In hamsters 2,000 or 3,000 mg/kg bw given orally for 9 days (Gray et al., 1982) or 500 mg/kg bw given orally for 35 days (Gray et al., 1983) did not cause testicular effects, but 1,000 mg/kg bw given orally for 35 days induced a clear effect (Gray et al., 1983). The species difference in severity of testicular toxicity may be declared by differences in concentrations of free monobutyl phthalate (MBP), a metabolite of DBP, which is known to cause testicular changes in the rat (Foster et al., 1981, 1982; Oishi and Hiraga, 1980c; Tanaka et al., 1978; Zhou et al., 1990).

Studies in humans

No data in humans are available.

Conclusion on oral studies

A NOAEL for general toxicity can be derived from a 3-month oral study in rats performed according to the current standards and is 152 mg/kg bw. The LOAEL in this study is 752 mg/kg bw. Testicular changes were not seen in this study despite the fact that particularly rats are sensitive for these effects. Neurofunctional tests did not show abnormalities.

In studies in rats with special attention to testicular effects the lowest dose-level tested i.e. 250 mg/kg bw, appeared to be an effect level.

Another characteristic effect of phthalate esters is peroxisomal proliferation. In studies focused on this effect the lowest NOAEL for this effect was 19.9 mg DBP/kg bw based on increased activity of peroxisome associated enzymes. However it has to be noted that humans are far less sensitive for this effect than rats or are even insensitive (ECETOC, 1992).

4.1.2.6.2 Dermal studies

Studies in animals

A 90-day dermal study in rabbits (strain not specified) was performed, but not according to current standards. The documentation of the study was inadequate. Number and sex of animals per group and duration of the daily applications were not given. The animals received dermal applications with 0.5, 1.0, 2.0 or 4.0 ml DBP/kg bw to the clipped intact skin. Slight skin irritation and slight dermatitis were reported but no information was given at which dose-levels these effects were seen. At 4.0 ml/kg bw slight renal damage was observed (Lehman, 1955).

Studies in humans

No data on humans are available.

Conclusion on dermal studies

The 90-day dermal study was inadequate for establishing a NOAEL for the dermal route.

4.1.2.6.3 Inhalation studies

Studies in animals

In a 5-day inhalation study groups of 15 male Sprague-Dawley rats were exposed for 6 hours per day to 0, 0.5, 2.5 and 7.0 ppm DBP (ca. 0, 6, 28 and 80 mg/m^3). No effect on body weight, lung or liver weights were seen. Marked changes were seen in microsomal cytochrome P-450 content and cytochrome P-450 related enzymes at the two highest dose-levels in the lung, but not in the liver. Serum alanine aminotransferase (ALAT) and aspartate aminotransferase (ASAT) activity and serum albumin levels were statistically significantly increased at 7.0 ppm. Serum alkaline phosphate (SAP) activity and serum total protein levels were normal (Walseth and Nilson, 1984). (Oral administration affected principally microsomal cytochrome P-450 content and related enzymes in the liver and not in the lung (Walseth and Nilson, 1986), while intraperitoneal injection caused changes in both liver and lung microsomal P-450 content (Walseth et al., 1982).

In a well-performed inhalation experiment according to OECD Guideline No. 412 and (for clinical and neurofunctional examinations and pathology) to OECD No. 407, groups of 5 male and 5 female Wistar rats (mean bw males 281.2 g; mean bw females 195.5 g) were head-nose exposed 6 hours/day, 5 days/week, for 4 weeks, to measured concentrations of 0, 1.18, 5.57, 49.3 or 509 mg DBP (purity 99.8%)/m^3 of air as liquid aerosol [MMAD (=mass median aerodynamic diameter) 1.5-1.9 μm; GSD around 2].

Observations

All animals were checked on state of health twice a day on working days and once a day on weekends or public holidays. Clinical examination of all animals was carried out thrice a day on exposure days and once during post-exposure days. Weekly food consumption, water consumption and body weight were recorded and food efficiency was calculated. On days -1, 7, 14 and 21 open field observations were carried out during 2 minutes on all animals after transfer to a standard arena.

Ophthalmoscopy was performed on all animals before exposure and on animals from control and 509 mg/m^3 group at day 26.

A functional observation battery (starting with passive observations followed by removal from home cage, open field observations and thereafter sensorimotor tests and reflex tests) was carried out on all animals after the exposure period (day 28). Motor activity of all animals was measured on the same day as the functional observations were performed.

At the end of the exposure period haematology, clinical chemistry and urinalysis were carried out on all animals, absolute and relative organ weights (10 organs including brain and reproductive organs) of all animals were determined and macroscopy of all animals was performed. Histopathology was carried out on all gross anomalies and on nasal cavity, larynx,

lungs, liver, lymph nodes (mediastinal) and testes + epididymides/ovaries + oviducts of all animals. In addition, histopathology of ca. 20 other tissues (including brain) of all animals in control and 509 mg/m^3 group was carried out.

Results

No mortality was seen. Clinical observations showed red crust formation at the snouts after cessation of daily exposure to 509 mg/m^3 (recovered within 18 hours) in a maximum of 4 animals and at a maximum duration of the symptom from day 13-27. Ophthalmoscopy did not reveal abnormalities.

The functional observation battery showed statistically significantly increased rearing of males at 49.3 mg/m^3 compared to controls. Since a dose-response relationship is lacking and no other abnormalities were observed during the functional observations, it is considered as incidental. Open field observations, home cage observations, sensorimotor/reflex tests and motor activity measurements did not reveal treatment-related findings.

Occasionally statistically significant decreases in food consumption, water consumption and/or food efficiency occurred in one sex only without any concentration time-response relation. Therefore these changes were considered to be incidental and not treatment-related. Mean body weights of male and female animals did not reveal statistically significant differences from control values.

Haematology, clinical chemistry and urinalysis did not show treatment-related abnormalities. The statistically significant decrease in serum Na in females at 509 mg/m^3 was considered to be of no toxicological significance given the marginal deviation in one sex only.

Statistically significant increases of absolute lung weights were seen in males at 5.57 (+18.4%) and 49.3 mg/m^3 (+11.1%). At 509 mg/m^3 absolute lung weights showed a non-significant increase (+8.1%). Absolute weights of testes showed statistically significant decreases at 1.18 (-11.6%), 5.57 (-10.6%) and 49.3 mg/m^3 (-9.3%). A non-significant decrease (-7.3%) of absolute testes weights was observed at 509 mg/m^3. Relative organ weights did not reveal statistically significant changes. The observed changes in absolute lung and testes weights were regarded as incidental as these changes did not increase with the dose, and given the lack of changes in relative organ weights and the absence of histopathological findings. Macroscopy did not show treatment-related changes. Histopathology revealed in all treated groups a dose-dependent increased incidence of hyperplasia of mucous cells at some sites of levels II (in 0/2/3/5/5 males and 0/3/5/5/5 females at 0, 1.18, 5.57, 49.3, and 509 mg/m³, respectively), III (in 0/0/2/4/5 males and 0/2/4/5/5 females) and IV (in 0/0/1/2/5 males and 0/2/4/4/5 females) of nasal cavity. The severity increased with dose from grade 1 (minimal) to grade 2 (slight). The epithelium in the respective areas of nasal cavity was regular and infoldings were absent, and signs of inflammation were missing in the whole nasal cavity. A dose-dependent increased incidence of squamoid metaplasia (of minimal degree) at level I of the larynx was observed (in 0/1/3/4/5 males and 0/1/3/5/4 females at 0, 1.18, 5.57, 49.3 and 509 mg/m³, respectively). Although the effects in nasal cavity and larynx can be considered as adaptive responses, they are adverse in nature.

Conclusion

No systemic effects, including neurotoxic effects, were observed up to and including the highest exposure concentration of 509 mg/m^3. Therefore, the NOAEC for systemic effects in this study is 509 mg/m³, the highest concentration tested.

For local effects in the upper respiratory tract no NOAEC can be determined in this study since adverse local effects were observed even at the lowest exposure concentration of 1.18 mg/m^3. Therefore 1.18 mg/m^3 is a LOAEC for local effects in the upper respiratory tract in this study (Gamer et al., 2000).

Remark

The exposure concentrations in this study are well-chosen given the (no)effect-concentrations in available oral studies, inhalation studies and an epidemiological study.

In a 93-day inhalation study groups of 15 male rats (strain not specified) (bw 115-130 g) were exposed for 24h per day to 0, 0.098, 0.256 and 0.98 mg/m^3. No clinical signs of toxicity were observed and growth was normal. The authors reported decreased leucocyte counts and an increase of gamma-globulins at 1.0 and 0.25 mg/m^3. However the results for these parameters were given in graphics. These graphics were insufficient to draw clear conclusions on statistical significance of the changes. Furthermore no information was given whether organ weights were determined and macroscopy or microscopy were performed (Men'shikova, 1971).

Groups of 11-14 male Wistar rats (bw 76-99 g) were exposed to 0.5 or 50 mg DBP mist/m^3 for 6 months, 6 days/week, 6h/day (except saturday for 3h). A reduced growth and increased relative brain, kidney, lung and testes weights (only significant for brain and lung weight) were seen at 50 mg/m^3. Absolute organ weights were not given. Haematology showed a decreased number of lymphocytes accompanied by an increased number of neutrophils at both dose levels without any dose-relationship. Changes in biochemical parameters (slightly increased ALAT, ASAT, SAP activities, increased blood glucose, decreased serum cholesterol and increased triglycerides) were seen randomly at the investigated time-points and at both dose-levels without a clear dose-relationship.

The changes in haematological and biochemical parameters were given in graphics. These graphics were insufficient to draw clear conclusions on statistical significance. Macroscopy or microscopy was not performed. The NOAEL in this study is 0.5 mg/m^3 (Kawano, 1980a).

Studies in humans

47 Out of 147 workers employed in the manufacture of artificial leather and exposed chronically to phthalates (predominantly DBP and higher phthalates (dialkyl phthalates (DAP)-789), but also to small amounts of adipates and sebacates and also to tricresylphosphate) experienced polyneuritis predominantly among those with greater length of exposure. 22 Workers were reported to have a functional disturbance of the nervous system. Investigation of the sensory functions revealed an early lowering of the excitability of the vestibular and olfactory receptors and of cutaneous sensitivity. Ambient levels of vapours or aerosols of the plasticizers at the workplace ranged from 1.7-60 mg/m^3. An unexposed control group was not available (Milkov et al., 1973).

A cross sectional study of neurological symptoms was performed on male workers in the production of phthalate esters among which DBP (Gilioli et al., 1978). The study involved 23 workers exposed to phthalates, 6 to phthalic anhydride and 9 to alcohols. Mean concentration of phthalates varied from 1-5 mg/m^3; peak levels were up to 61 mg/m^3. Neurological examination of the phthalate workers revealed polyneuropathy in 12/23 subjects. In 7/23 bilateral painful decreased sensitivity of skin or senses of the hands and feet were noted; 3 showed decreased sense of vibrations. In the alcohol exposed group 2/9 showed sensory neuropathy; in the phthalic anhydride exposed group 1/6 showed hyporeflexia (only summary available).

Conclusion

Three of the four available inhalation studies with durations of 5 days, 93 days and 6 months have a limited design and are not suitable for risk assessment.

In a fourth inhalation study of 28-days duration in rats, performed according to current standards, no systemic effects including neurotoxic effects were observed up to and including the highest exposure concentration of 509 mg DBP/m^3. At all exposure concentrations (1.18, 5.57, 49.3 and 509 mg/m^3) adverse local (histopathological) effects in the upper respiratory tract were observed, but no signs of inflammation. In addition, at the highest exposure concentration of 509 mg/m^3 red crust formation at the snouts was observed after cessation of daily exposure (recovered within 18 hours) in a maximum of 4/10 animals at a maximum duration from day 13-27. It is concluded that 509 mg/m^3, the highest concentration tested, is a NOAEC for systemic effects including neurotoxic effects. The lowest exposure concentration of 1.18 mg/m^3 is a LOAEC for local effects in the upper respiratory tract.

The epidemiological studies on neurological symptoms in occupationally exposed subjects showed several limitations including lack of an appropriate control group, small size of the exposed population, lack of adequate documentation of protocol and results and mixed exposure to other compounds than DBP. Therefore these studies are inadequate for assessment of neurotoxic effects caused by DBP in human in the working environment.

4.1.2.6.4 Conclusion on repeated dose toxicity

An oral NOAEL of 152 mg/kg bw can be derived from a 3-month dietary study in rats performed according to current standards. A NOAEL of 19.9 mg/kg bw for peroxisomal proliferation in rats was found in a special study examining this effect. However it has to be noted that human have a relative low sensitivity for this effect.

The available studies with repeated dermal exposure are not appropriate for establishing a NOAEL.

For repeated inhalation exposure a NOAEC of 509 mg DBP/m^3 (the highest concentration tested) for systemic effects including neurotoxic effects can be established based on a 28-day inhalation study in rats performed according to current standards. For local effects after repeated inhalation exposure a LOAEC of 1.18 mg/m^3 can be derived from the same 28-day inhalation study.

4.1.2.7 Mutagenicity

The available mutagenicity assays are summarised in **Table 4.12**.

Table 4.12 Summary of mutagenicity tests

Genetic toxicity	Species	Protocol	Results
***in vitro* studies:**			
Bacterial test (gene-mutation)	S. typhimurium (4 strains)	other: Ames et al. (1975)	negative - and + S9 of rats and hamsters (Zeiger et al., 1985)
Bacterial test (gene-mutation)	S. typhimurium (4 strains)	other: Ames et al. (1975)	equivocal- S9 in TA100, + S9 negative. In all other strains - and + S9 negative (Agarwal et al., 1985)
Bacterial test (gene mutation)	S. typhimurium (4 strains)	other: Ames et al. (1975)	negative - and + S9. One dose-level. Precipitation occurred (Florin et al., 1979) **
Bacterial test (gene mutation)	S. typhimurium (TA100)	liquid suspension assay	positive - S9 (weak increases (<2x) at cytotoxic doses); + S9 negative (Seed, 1982)*
Bacterial test (gene mutation)	S. typhimurium (TA98, TA100)	modified Ames acc. to Batzinger et al. (1978)	negative - and + S9 up to 1 mg/pl (Kozumbo et al., 1982) **
Bacterial test (gene mutation)	S. typhimurium (TA98, TA100)	unknown	negative + S9. Not tested - S9. One dose-level of 10 mg/pl (Kurata, 1975) **
Bacterial test (gene-mutation)	Escherichia coli (uvrA-)	unknown	negative - S9. Not tested + S9. One dose-level of 10 mg/pl (Kurata, 1975) **
Yeast assay (gene-mutation)	S. cerevisiae (XV 185-14C)	unknown	negative - and + S9. Doses 10, 20 and 100 ul/ml (Shahin and von Borstel, 1977; Zimmermann et al., 1984)
Mouse lymphoma assay (gene-mutation)	L5178Y TK+/-	Clive and Spector, (1975)	negative - S9; positive + S9 (Hazleton, 1986)
Mouse lymphoma assay (gene-mutation)	L5178 TK+/-	Myhr et al. (1985)	positive - S9; not tested + S9 (NTP, 1995)
Cytogenetic assay (chromosomal aberrations)	CHL cells	unknown	negative - S9; not tested + S9 (Ishidate and Odashima, 1977) *
Cytogenetic assay (chrom. aberrations and SCE's)	Chin. hamster ovary cells	unknown	negative for chrom. aberr. - S9. Marginally positive for SCE'S - S9 (<2x increase). Not tested + S9 (Abe and Sasaki, 1977) *
Cytogenetic assay (chromosomal aberrations)	human leucocytes	unknown	negative. No data on metabolic activation. Only summary (Tsuchiya and Hallori, 1977) **
Bacterial test (indirect DNA-repair)	Escherichia coli (pol A-, rec A-)	unknown	negative - S9; not tested + S9. One dose-level of 10 mg/pl (Kurata, 1975) **
Bacterial test (indirect DNA-repair)	Bacillus subtilis (rec A-)	unknown	negative - S9; not tested + S9. One dose-level of 10 mg/pl (Kurata, 1975) **
Cell transformation assay	BALB/3T3 cells	unknown	negative - S9; not tested + S9 (Litton Bionetics, 1985) *

Table 4.12 continued overleaf

Table 4.12 continued Summary of mutagenicity tests

Genetic toxicity	Species	Protocol	Results
***in vivo* studies:**			
SLRL test in Drosophila (gene-mutations)	Drosophila melanogaster	injection (no details)	negative at injection of 0.5 g DBP/kg bw Only summary (Izmerov et al., 1982) **
Micronucleus assay (chromosomal aberrations)	NMRI mice	OECD 474	negative (BASF, 1990d)
Micronucleus assay (chromosomal aberrations)	B6C3F1 mice 0, 0.125, 0.25, 0.5, 1.0, 2.0% in diet for 13 wks.	other see HEDSET	negative (NTP, 1995)

* Tests are not performed adequately but may contribute to the end-evaluation of genetic toxicity of DBP
** Tests cannot be used for end evaluation due to lack of documentation and will not be discussed below

Two bacterial assays in Salmonella typhimurium have been carried out in 4 strains and with several dose-levels according to Ames et al. (1975). In one of these two tests doses of 100-10,000 μg/plate were tested in the absence and the presence of rat and hamster S9 liver-mix and the result was negative (Zeiger et al., 1985). In the second assay doses of 100-2,000 μg/plate were tested. In strain TA100 an increase in the rate of reversions with a maximum (3.5x) at 100 μg/plate was seen without S9 (according to the authors a significant increase). Less than a 2x increase was seen at 200 μg/plate and at higher doses the effect tended to plateau. In TA1535 a very mild increase was seen at the two highest dose-levels without S9. With metabolic activation and in the other strains no mutagenic activity was seen (Agarwal et al., 1985).

A liquid suspension assay was performed in strain TA100 only, without and with S9 at concentrations of 0.045, 0.09 and 0.18 mM/plate (~12.5, 24 en 50 mg/pl). Without S9 a weak increase in mutagenic activity (<2x) was seen at doses of 0.09 and 0.18 mM, which were cytotoxic. With S9 no increased activity was seen (Seed, 1982).

An assay in yeast cells was performed under GLP conditions and showed negative results both without and with metabolic activation (Shahin and von Borstel, 1977; Zimmerman et al., 1984).

In an adequate mouse lymphoma assay doses of 12.5-150 nl DBP/ml were tested. DBP induced gene-mutations in the presence of a metabolic activation system; in the absence of a metabolic activation assay negative results were seen (Hazleton, 1986). In a second mouse lyphoma assay performed only without metabolic activation, doses ≥46 μg/ml induced statistically significant increases in mutant frequencies accompanied by marked decreases in cell survival (NTP, 1995).

In vitro tests for chromosomal aberrations showed negative results. The tests were not performed under GLP conditions and carried out in CHL and CHO cells with doses up to 31 μg/ml and 0.28-287 μg/ml, respectively, without metabolic activation only (Abe and Sasaki, 1977; Ishidate and Odashima, 1977). In the test in CHO cells a slight but statistically significant increase in SCE's (<2x) was seen at all three dose-levels without any dose-relationship (Abe and Sasaki, 1977).

No cell transformation was induced in BALB/3T3 cells but the test was not performed under GLP conditions and without metabolic activation only (Litton Bionetics, 1985).

An adequate micronucleus assay in mice was performed according to OECD guideline 474 and showed negative results (BASF, 1990d). Analysis of peripheral blood samples from mice which

received DBP in their diet (equal to 163-4278 mg/kg bw) for 13 weeks, did not reveal increased incidences of micronuclei (NTP, 1995).

DBP interacted with DNA *in vitro*. However after oral administration of ^{14}C-DBP to mice no binding to hepatic DNA was seen (only summary available) (Okada and Tamesama, 1978).

Conclusion on mutagenicity

In assays detecting gene-mutations in bacteria one assay was negative in all 4 strains tested without and with metabolic activation. In two other assays equivocal and positive results, respectively were seen in strain TA 100 only, without metabolic activation. The positive effects were weak and seen at cytotoxic doses.

A gene-mutation test in yeast cells showed negative results.

In a mouse lymphoma assay performed only without metabolic activation, gene-mutations were induced at highly cytotoxic concentrations. An adequately performed test for gene-mutations in mouse lymphoma cells showed negative effects without metabolic activation; with metabolic activation positive effects were seen. In the same experiment (Hazleton, 1986) diethyl phthalate showed negative results while it is expected that, based on structure-activity relationships, mutagenic activity would increase with decreasing length of the alkyl chain. Also butylbenzyl-, di(2-ethylhexyl)-, diisononyl- and diisodecyl phthalate showed negative results in the same experiment.

No chromosomal aberrations in mammalian cells were seen but the tests were performed without metabolic activation only. In one test also the induction of SCE's was studied and a slight (<2x), but statistically significant increase of SCE's was seen at all three dose-levels, but without any dose-relationship.

A micronucleus study performed according to current standards showed negative results. In mice exposed for 13 weeks to DBP in their diet no induction of micronuclei was observed either.

In conclusion *in vitro* studies gave an indication for a genotoxic effect in one assay, but this effect was not seen with other dialkyl phthalates in the same experiment, a.o. with diethyl phthalate. No genotoxic effects for dibutyl phthalate were observed in *in vivo* studies detecting chromosomal aberrations.

Based on the data available for dibutyl phthalate from a variety of genotoxicity studies as described above and taking into consideration the non-genotoxic properties of other phthalate esters, dibutyl phthalate can be considered as a non-genotoxic substance.

Based on the data above the substance does not need to be classified according to EC criteria.

4.1.2.8 Carcinogenicity

Studies in animals

No adequate long-term carcinogenicity studies in laboratory animals with DBP are available.

Phthalate esters are known to induce peroxisomal proliferation in the liver of mice and rats. In general the longer chain dialkyl phthalates are more potent for the induction of peroxisomal

proliferation than the shorter chain ones and branched chain phthalates seemed more potent than straight (Barber et al., 1987).

Peroxisome proliferation is accompanied by replicative DNA synthesis and liver growth. Many peroxisome proliferators have been shown to induce hepatocellular tumours when administered at high dose-levels for long periods to mice and rats despite being non-genotoxic. The mechanisms of induction of carcinogenicity by peroxisome proliferators may be complex. These mechanisms are considered to have a threshold and include:

- oxidative stress and the induction of indirect DNA damage
- promotion of spontaneous preneoplastic lesion
- sustained growth stimulation

These mechanisms are not mutually exclusive but could cooperate with each other during tumour development.

A variety of independent studies have shown that there are marked species differences in the sensitivity to chemicals that cause peroxisome proliferation. Rats and mice are extremely sensitive, hamsters show a less marked response whilst guinea-pigs, primates and humans are rather insensitive or non-responsive (ECETOC, 1992).

Studies in humans

No data in humans are available.

Conclusion on carcinogenicity

No adequate long-term toxicity and/or carcinogenicity studies in animals as well as humans are available.

4.1.2.9 Toxicity for reproduction

4.1.2.9.1 Studies in animals

Reliable reproduction studies as well as developmental/teratogenicity studies in animals are summarised in **Table 4.13.**

Table 4.13 Summary of reproduction and developmental studies in animals

Species	Protocol	Results
Reproduction (oral studies)		
mouse	continuous breeding protocol (one generation) 0, 0.03, 0.3 and 1.0% in diet (~0, 40, 420 and 1,410 mg/kg bw)	115 d (including 7 d premating and 98 d during cohabitation) NOAEL for embryotoxicity and parental toxicity is 0.3% in diet (~420 mg/kg bw (Lamb et al., 1987; Morissey et al., 1989)
rat	continuous breeding protocol (two generations) 0, 0.1, 0.5 and 1.0% in diet (~ 0, 52, 256 and 509 mg/kg bw for males and 0, 80, 385 and 794 mg/kg bw for females).	119 d (including 7 d premating and 112 d during cohabitation). 0.1% in diet (52 mg/kg bw for males; 80 mg/kg bw for females) is the LOAEL for embryotoxi-city. The NOAEL for maternal toxicity is 0.5% in the diet (385 mg/kg bw) (NTP, 1995; Wine et al., 1997)
rat	other; 0, 120 and 600 mg/kg bw 3 mos exposure followed by a 7d mating period	NOAEL 600 mg/kg bw for maternal toxicity and embryotoxicity (Nikoronow et al., 1973)
rat	other; 0, 5, 50 and 500 mg/kg bw via the diet to male rats only, 60 days before mating up to weaning of F1 pups	NOAEL 500 mg/kg bw with respect to fertility of male rats and embryotoxicity (IRDC, 1984)
rat	other; 0, 5, 50 and 500 mg/kg bw via the diet to female rats only, 14 days prior to mating up to weaning of F1 pups. F1 pups fed 7 weeks post-weaning	NOAEL for maternal toxicity, female fertility and embryotoxicity is 50 mg/kg bw (IRDC, 1984)
rat	other; 0, 250, 500 and 1,000 mg/kg bw exposure of P_0 generation only; two generations were produced	LOAEL 250 mg/kg bw Effects: delayed puberty in males of P_0 generation, urogenital abnormali-ties and decreased fertility of F_1 males and females (Gray et al., 1999)
Developmental toxicity (oral studies)		
mouse	other: 0, 0.005, 0.05 or 0.5% in diet (based upon food intake 0.05 and 0.5% were calculated to be 100 and 400 mg/kg bw) day 1-18 of gestation	NOAEL 0.05% in diet (100 mg/kg bw) for maternal as well as embryotoxicity and teratogenicity (Hamano et al., 1977)
mouse	other: 0, 0.05, 0.1, 0.2, 0.4, 1.0% in diet (~80, 180, 350, 660 and 2,100 mg/kg bw) day 1-18 of gestation	NOAEL for embryotoxicity is 0.2% (~350 mg/kg bw); NOAEL for maternal toxicity and teratogenicity is 0.4% (~660 mg/kg bw) (Shiota et al., 1980)
rat	other; 500, 630, 750, 1,000 mg/kg bw day 7-15 of gestation	NOAEL 500 mg/kg bw for teratogenicity. 500 mg/kg b.w is a LOAEL for maternal and embryo-toxicity (Ema et al., 1993)
rat	other; 0, 0.5, 1.0 or 2.0% in the diet (~331, 555 and 661 mg/kg bw) from day 11-21 of gestation	NOAEL 0.5% in diet (~331 mg/kg bw). Critical effect: undescended testes, decreased anogenital distance in male progeny (Ema et al., 1998)
rat	other; 0, 120 and 600 mg/kg bw day 1-21 of gestation	NOAEL 120 mg/kg bw for embryotoxicity (Nikoronow et al., 1973)
rat	other; 0, 250, 500 and 750 mg/kg bw from day 3 of gestation throughout gestation and lactation. Pups were allowed to mature.	LOAEL 250 mg/kg bw Critical effect: disturbed development of male reproductive tract (Mylchreest et al., 1998)
rat	other; 0, 500, 1,000, 1,500 and 2,000 mg/kg bw on day 14 of gestation	NOAEL 500 mg/kg bw. At doses ≥1,000 mg/kg bw higher incidences of skeletal variations. At doses ≥,1500 mg/kg bw increased no. of resorptions and reduced fetal body wts. (Saillenfait et al., 1998)
rat	other; 0, 100, 250 and 500 mg/kg bw from day 12-21 of gestation.	LOAEL 100 mg/kg bw. Critical effect: delayed (2-days) preputial separation (one litter) (Mylchreest et al., 1999)
rat	other; 0, 250, 500 and 1,000 mg/kg bw exposure of P_0 generation only; two generations were produced	LOAEL 250 mg/kg bw for delayed puberty in males of P_0 generation, urogenital abnormali-ties and decreased fertility of F_1 males and females (Gray et al., 1999)

Reproduction studies

In an oral reproduction study in CD-1 mice according to a continuous breeding protocol and including the production of one generation, doses of 0.03, 0.3 and 1.0% DBP in the diet (ca. 0, 40, 420 and 1,410 mg/kg bw) were administered to groups of 20 m and 20 f animals for a 7-day premating period, after which the animals were grouped as mating pairs and treated during a 98-day mating period. A control group of 40 m and 40 f mice received the basal diet. After the 98-day cohabitation period the pairs were separated and exposed during which period any final litters were delivered and kept for at least 21 days. At the end of the continuous breeding period a 7-day crossover mating trial was performed with Fo animals of control and 1% groups. F_0 parents showed a significantly decreased growth (males only) and significantly increased liver weights (females only) at 1.0% in the diet. At 1.0% in the diet statistically significant decreases in percentage of fertile pairs, no. of litters/pair, no. of live pups/litter and proportion of pups born alive were seen. Lower dose-levels did not cause these effects. Females and not males were affected as was shown in the crossover mating trial. In this trial between control males and 1.0% females statistically significant decreases in percentage of fertile pairs, no. of live pups/litter, proportion of pups born alive and live pup weight were observed. The NOAEL for parental and embryotoxicity is 0.3% in the diet (ca. 420 mg/kg bw) in this study (Lamb et al., 1987; Morissey et al., 1989).

Gray et al. (1999) performed a multigeneration study in LE hooded rats. Both male and female animals (10-12 animals/sex/group) of only the P_0 generation received orally by gavage 0, 250 or 500 mg DBP/kg bw from weaning, through puberty, young adulthood, mating and lactation. Another group of only males received 1,000 mg/kg bw. When the P_0 animals were mated, treated animals were paired with untreated controls. F_1 animals were not treated. After puberty F_1 animals were selected (16/sex/group) for fertility assessment under continuous mating conditions over 11 breeding cycles.

In the P_0 generation delayed puberty (preputial separation) was seen in males at all dose-levels. DBP treatment did not accelerate the age at vaginal opening or induce persistent vaginal cornification, effects indicative of subchronic estrogen exposure. The P_0 generation showed reduced fertility in male and female animals at 500 and 1,000 (males only) mg/kg bw. Infertility in males was related to testicular atrophy and reduced sperm production, while treated females cycled and mated sucessfully, but many treated females (500 mg/kg bw) aborted their litters around midpregnancy. In the F_1 offspring which were exposed only *in utero* and lactational via dams (data only from F_1 animals from dams treated with 0, 250 and 500 mg DBP/kg bw), urogenital malformations/abnormalities including a low incidence of agenesis of the epididymis, hypospadias, ectopic testis, renal agenesis and uterine abnormalities (partial agenesis or lack of implants in one uterine horn) were seen. In addition a few treated animals displayed anophthalmia. Furthermore F_1 males from treated mothers exhibited reduced cauda epididymal sperm numbers. The F_1 offspring showed reduced fecundity (significantly fewer F_2 pups; number pups/litters 179/24, 76/10, and 20/4 for 0, 250 and 500 mg/kg bw, respectively) in similarly treated pairs under continuous breeding conditions. The lowest dose-level of 250 mg/kg bw in this study is a LOAEL.

In an oral reproduction study in Sprague-Dawley rats according to the continuous breeding protocol and including the production of two generations, doses of 0, 0.1, 0.5 and 1.0% in diet (0, 52, 256 and 509 mg/kg bw for males and 0, 80, 385 and 794 mg/kg bw for females) were administered to groups of 20 m and 20 f animals for a 7-day premating period after which the animals were grouped as mating pairs and treated during a 112-day cohabitation period. A control group of 40 m and 40 f rats received the basal diet. After the 112-day cohabitation period

the pairs were separated and exposed during which period any final litters were delivered and kept for at least 21 days. Thereafter treatment of F1 animals was initiated at the same concentration as their parents. At the end of the continuous breeding period also a 7-day crossover mating trial was performed with Fo animals of control and 1% groups. During the continuous breeding phase 1.0% in the diet caused a reduction in growth of Fo females. The total number of live pups/litter was statistically significantly decreased at all dose-levels with a dose-relationship. Live pup wts were significantly decreased at 0.5 and 1.0% in the diet. In the crossover mating trial, designed to determine the affected sex, no effect upon mating, pregnancy or fertility indices were seen. Fo females at 1.0% showed decreased body wts and increased rel. liver and kidney wts. Fo males at 1.0% revealed increased rel. liver-, kidney-, and right cauda epididymis wts. F1 males at 0.5% showed significantly increased kidney weights. Sperm parameters (sperm concentration and motility, % abnormal sperm or testicular spermatid head count), estrous cyclicity, and estrous cycle were not affected. The weight of pups from treated females (1.0% in the diet) was statistically significantly decreased.

During the continuous breeding phase, after the crossover mating trial with the F0 parents and at production of the F2 generation mating, pregnancy and fertility indices for F1 parents were statistically significantly lower at 1.0% in the diet. Live F2 pup wts were statistically significantly lower at all dose-levels (also after adjustment for litter size). Female F1 parents at 1.0% showed statistically significantly lower body wts and absolute organ wts (right ovary, liver, kidneys). In male F1 parents at 1.0% body wt. and rel. wts of all reproductive organs were lower while rel. liver and kidney wts were statistically significantly increased. Epididymal sperm count and testicular spermatid head count were statistically significantly decreased at 1.0%. Epididymides were absent or poorly developed in 12/20 F1 males at 1.0% and in 1/20 F1 males at both lower dosage levels. In 4/20 males at 1.0% and 1/20 at 0.5% in diet testicular atrophy was seen. Testes of 3/20 males at 1.0% were not descended into the scrotal sacs; 4/20 males at this dose-level had poorly developed seminal vesicles and 4/20 had an underdeveloped prepuce or penis. Histopathology showed degeneration of seminiferous tubules in 8/10 F1 males at 1.0% and in 3/10 at 0.5% DBP in the diet. 7/10 F1 males at 1.0% revealed testicular interstitial cell hyperplasia. Histopathology of seminal vesicles revealed in 1/10 F1 males at 1.0% vesiculitis with inspissated secretion. There was no indication of an effect on estrous cyclicity or duration of the estrous cycles in F1 females at all dose-levels.

In this study DBP appeared to be a reproductive toxicant in rats exposed both as adults and during development. The effects on the 2nd generation were greater than on the first generation. The lowest dose-level in this study, 0.1% in the diet (52 mg/kg bw for males; 80 mg/kg bw for females) is a LOAEL for embryotoxicity. The NOAEL for maternal toxicity is 0.5% in the diet (385 mg/kg bw) (NTP, 1995; Wine et al., 1997).

In a fertility study female Wistar rats were exposed for 3 months before mating followed by a 7-day mating period to 0, 120 or 600 mg DBP/kg bw. Pregnant females were killed on day 21 of pregnancy. The study was not performed according to any guideline or under GLP conditions and the information given was limited. No maternal or embryotoxicity was seen in this study. 600 mg/kg bw is a NOAEL for embryotoxicity and maternal toxicity in this limited study (Nikoronow et al., 1973).

In fertility studies in Charles River COBS CD rats, performed under GLP conditions, either male or female rats were exposed beginning 60 and 14 days, respectively, prior to mating, during mating, gestation and lactation. In the study in which females only were exposed, F1 weanlings were selected from all groups and were given either control diets or the same diets as their mothers for a 7-week post-weaning period (IRDC, 1984).

In the male fertility study no effect on survival, appearance, behaviour, body wts, hematology and fertility was observed. Organ wts of treated males showed a statistically significantly increased absolute as well as relative liver and kidney wt. at 500 mg/kg bw. Relative kidney wts were also significantly increased in males at 50 and 5 mg/kg bw but these increases were less pronounced, without a dose-relationship. Histopathology of the kidneys did not reveal abnormalities. In addition well-performed 3-month rat studies revealed only at doses ≥350 mg/kg bw increased kidney wts. Therefore the increased kidney wts at 50 and 5 mg/kg bw seen in this male fertility study are considered as biologically insignificant. Reproductive performance, parturition, neonatal viability, growth of newborn, organ wts. and histopathology in weanlings did not reveal abnormalities. The NOAEL for male fertility and embryotoxicity in this study is 500 mg/kg bw, the highest dose tested (IRDC, 1984).

In the female fertility study no effect on survival, appearance, behaviour, hematology or fertility of treated females was seen. Growth of females was reduced slightly pre-mating, during the entire gestation period and during lactation period at 500 mg/kg bw, statistically significant at week 7, 9 and 11. At 50 mg/kg bw also reductions in weight gain during the entire gestation period were seen, but less pronounced. Organ wts of treated females showed a statistically significantly increased relative kidney wt. at 500 mg/kg bw Histopathology did not reveal abnormalities. Reproductive performance, parturition and neonatal viability did not reveal abnormalities. Pup wt. at birth and growth of pups during entire lactation period was lower at 500 mg/kg bw. Organ wts and histopathology of weanlings did not show abnormalities. During the 7 week post-weaning period also reduced body wts were seen both with and without continuing treatment at all dose-levels, sometimes reaching statistical significance, but without any dose-relationship. Organ wts after 7-week post-weaning period revealed slightly decreased testicular weights in weanlings fed 500 mg/kg bw. After the 7-week post-weaning period histopathology revealed testicular lesions in 6/10 weanlings (2 with mild granuloma unilateral, 1 with severe unilateral degradation, 1 with moderate bilateral degeneration, 2 with a trace of bilateral degeneration) fed 500 mg/kg bw. In the group derived from mothers fed 500 mg/kg bw and given control diet for 7 weeks post-weaning, 2/9 weanlings showed testicular lesions (1 with a trace of unilateral degeneration, 1 with severe unilateral degeneration). The NOAEL in this study is 50 mg/kg bw study based on maternal toxicity and embryotoxicity (IRDC, 1984).

Conclusion on reproduction studies

Male fertility of mice did not appear to be affected up to the highest dose-level of 1.0% in the diet (equivalent to 1410 mg/kg bw) in a one-generation study while female fertility was clearly affected at this dose-level. At 1.0% in the diet also embryotoxic effects were observed. The NOAEL in this study in mice is 0.3% in the diet equivalent to 420 mg/kg bw based on effects on maternal fertility and embryotoxicity.

Concerning the available reproduction studies in rats a NOAEL of 50 mg/kg bw can be established based on embryotoxicity in a one-generation reproduction study with exposure of females only. The same study protocol with exposure of male animals only, gave a NOAEL of 500 mg/kg bw.

However in a two-generation reproduction study in rats with a continuous breeding protocol and with exposure of both male and female animals the lowest dose-level of 0.1 % in the diet (52 mg/kg bw for males and 80 mg/kg bw for females) appeared to be a LOAEL based on embryotoxic effects (NTP, 1995; Wine et al., 1997). It has to be noted that the LOAEL of

52 mg/kg bw[5] (0.1% in the diet) was derived from a more extensive study with improved sensitive endpoints (such as sperm parameters, estrous cycle characterisation and detailed testicular histopathology) (Foster, 1997) compared to the study with the NOAEL of 50 mg/kg bw. According to Foster (1997), the protocol of the continuous breeding study was supposed to identify adequately compounds with endocrine activity.

In conclusion, effects on pup weight and number of live pups per litter were seen in the absence of maternal toxicity at the lowest dose-level of 52 mg/kg bw in a 2-generation reproduction study in rats with a continuous breeding protocol. Other available reproduction studies in rats showed effects on fertility and embryotoxic effects at oral doses ≥ 250 mg/kg bw.

Reproduction or fertility studies with dermal exposure or exposure by inhalation to DBP are not available.

Developmental studies

Developmental studies in mice and rats have been performed. None of these studies was performed according to any guideline and no data on GLP conditions were available.

Lowest dose level administered to mice (ICR-JCL strain) was 0.005% in the diet during day 1-18 of gestation in a study of Hamano et al. (1977). Next higher dose levels were 0.05 and 0.5% in the diet (equal to 100 and 400 mg/kg bw). No. of spontaneous abortions and no. of mice with live offspring was not different from controls in any treated group. At 0.5% in the diet maternal toxicity (increased kidney wts) and embryotoxicity (lower no. of live offspring) were observed. In addition teratogenic effects were induced at 0.5% as was demonstrated by a statistically significantly higher incidence of external anomalies (non-closing eye-lid, encephalocele, cleft palate, spina bifida). Also a higher (but not statistically significantly) incidence of skeletal anomalies, especially of sternum, was seen at this dose-level. The rate of ossification was normal in all treated groups. The NOAEL for maternal, teratogenic and embryotoxic effects in this study is 0.05% in the diet equal to 100 mg/kg bw (Only summary available).

In a study of Shiota et al. (1980) mice (ICL-ICR strain) received 0.05, 0.1, 0.2, 0.4 or 1.0% DBP in their diet (ca. 80, 180, 350, 660 and 2,100 mg/kg bw) during day 1-18 of pregnancy. Maternal growth was statistically significantly reduced at 1.0%. Fetal mortality and no. of resorptions were increased at dose-levels from 0.1% onwards, but statistically significant at 1.0% only and without any dose-relationship. No. of corpora lutea and implantations were normal. Fetal wts were decreased in all treated groups, but statistically significant at 1.0 and 0.4% only. In all treated groups the incidence of skeletal variations was higher (lumbar ribs) and ossification was statistically significantly retarded as shown by the lower number of ossified coccygia. The effect on the fetal weights at the lower three dose-levels and the effect on the incidences of skeletal variations at all dose-levels can be attributed to the relatively low litter size in the control group. Limited evidence for teratogenicity was seen in this study at 1.0%. At this dose-level only 2 male and 1 female fetus survived and 2 out of these 3 survivors showed exencephaly. The dose-level of 0.2% in the diet (ca. 350 mg/kg bw) is a NOAEL with respect to embryotoxicity.

[5] 52 mg/kg bw was chosen as LOAEL in order to be consistent with the EU Scientific Committee on Toxicity, Ecotoxicity and the Environment. When asked to express its opinion on phthalate migration from soft PVC toys and child-care articles, the CSTEE identified the LOAEL of 0.1% in the diet from the 2-generation reproduction study as the most critical LOAEL for DBP and set it at 52 mg/kg bw (CSTEE, 1998). However, as the embryotoxic effects observed are more likely to occur from maternal than from paternal dosing, the LOAEL of 0.1% in the diet would in fact correspond more to 80 mg/kg bw than to 52 mg/kg bw. This can be accounted for when interpreting the MOS.

For maternal toxicity and teratogenicity 0.4% in the diet (ca. 660 mg/kg bw) is a NOAEL. It has to be noted that a low number of litters was evaluated in this study and that the documentation of this study was limited.

In a developmental study in Wistar rats, 500, 630, 750 or 1,000 mg DBP/kg bw was given by gavage during day 7-15 of pregnancy. A dose relatedly increased incidence of animals with reddish-brown staining of facial fur and piloerection was seen. Maternal death (2/11) occurred at 1,000 mg/kg bw. Maternal body weight gain was decreased at all dose-levels with a dose-relationship, statistically significant at doses of 630 mg/kg bw and higher. Food consumption showed a statistically significant decrease during gestation at 750 and 1,000 mg/kg bw. No. of implantations/litter was normal. Complete resorption of implanted embryos was seen in all animals at 1,000 mg/kg bw and in 10/12 at 750 mg/kg bw. At 630 and 500 mg/kg bw 2/12 and 2/11 litters, respectively, were completely resorbed. In control group none of the litters was resorbed. Statistically significantly higher numbers of resorptions and dead fetuses/litter, higher incidences of postimplantation loss/litter and statistically significantly lower numbers of live fetuses/litter were noted at doses of 630 mg/kg bw and above. At 500 mg/kg bw, no. of resorptions and dead fetuses/litter and postimplantation loss were still increased but not statistically significant. Also the number of live fetuses/litter was still lower at 500 mg/kg bw but not statistically significant. Statistically significantly lower fetal wts were seen at 750 and 630 mg/kg bw and also at 500 mg/kg bw the fetal wt. was lower but not statistically significant. The incidences of fetuses with external malformations were higher at 630 and 750 mg/kg bw, statistically significant at 750 mg/kg bw. Cleft palate was predominantly observed. The number of fetuses with skeletal malformations was higher at 630 mg/kg bw, but not statistically significant (predominantly fused sternebrae and cervical vertebral arches). At 750 mg/kg bw too few fetuses were available for skeletal examination. 500 mg/kg bw is a LOAEL in this study for maternal toxicity and embryotoxicity. For teratogenic effects 500 mg/kg bw is a NOAEL (Ema et al., 1993).

In a follow-up study by Ema et al. (1994) pregnant Wistar rats received oral doses (by gavage) of 750, 1,000 or 1,500 mg DBP/kg bw during day 7-9, 10-12 or 13-15 of gestation. Dams were killed on day 20 of pregnancy. Postimpantation loss was 100% at 1,500 mg/kg bw at each dosing period. At 750 and 1,000 mg/kg bw post implantation loss was significantly increased regardless of the dosing period. No teratogenicity was seen at treatment during day 10-12. Treatment on day 7-9 with 750 and 1,000 mg/kg bw caused a significant increase in number of skeletal malformations (deformity of vertebral column in cervical and thoracic regions and of ribs), but neither external nor internal malformations. Treatment on day 13-15 with 750 or 1,000 mg/kg bw caused a significant increase in the incidence of fetuses with external and skeletal malformations such as cleft palate and fusion of the sternebrae. The frequency of malformations showed a dose-relationship.

Ema et al. (1997b) reported complete resorption of 9/10 litters at dosing via food at a level of 2% in the diet (~895 mg DBP/kg bw) to pregnant Wistar rats on day 0-11 of gestation. Furthermore post-implantation loss/female was 98.7%. The dams showed significantly decreased weight gains and food intake.

Ema et al. (1997a) also carried out a serial study to identify the critical periods for skeletal and external malformations in rats. The animals received a single oral dose of 1,500 mg DBP/kg bw in olive oil on one of gestational days 6-16. The dams were killed on day 20 of gestation. No maternal death was seen. Maternal body weight gains in the 2-days immediately after dosing were significantly decreased. Maternal body weight gain over 0-20 days of gestation given DBP on day 6 or on one of days 6-13 was significantly decreased. The net weight gain of the dams

(body weight minus gravid uterine weight) and the food intake were sigificantly decreased when DBP was given on day 16 of pregnancy. Post-implantation losses were significantly increased at dosing of dams on one of gestational days 6-16, except for days 7 and 11. Decreased fetal weights were observed at dosing on gestational days 6, 7, 8, 9, 10 (only females), 11 or 15 but not at dosing of dams on days 12, 13, 14 or 16. Significant increases in the incidences of fetuses with skeletal malformations, of fetuses with skeletal and internal malformations and of fetuses with external and skeletal malformations were observed after dosing on day 8, on day 9 and day 15, respectively. Deformity of cervical vertebrae was seen frequently after dosing on day 8. Deformity of cervical and thoracic vertebrae and ribs and dilatation of the renal pelvis were seen predominantly after dosing on day 9. Cleft palate and fusion of the sternebrae were exclusively seen after dosing on day 15.

In a study of Sallenfait et al. (1998) pregnant Sprague-Dawley rats received a single oral dose of 0, 500, 1,000, 1,500 or 2,000 mg DBP/kg bw on day 14 of gestation. The dams were killed on day 21 of gestation. Maternal body weight gain and gravid uterine were decreased, statistically significant at 1,500 and 2,000 mg/kg bw. Increased incidences of resorptions and reduced fetal fetal body weights were observed at 1,500 and 2,000 mg/kg bw. A decreased number of live fetuses per litter was observed at 2,000 mg/kg bw. At doses ≥1,000 mg/kg bw higher incidences of skeletal variations were found. No post-implantation losses were seen in this study. The lowest dose level of 500 mg/kg bw was a NOAEL in this study.

In a study by Nikoronow et al. (1973) groups of 10 pregnant Wistar rats received for the first 21 days of pregnancy 0, 120 or 600 mg DBP/kg bw in olive oil by gavage. At 600 mg/kg bw number of resorptions was statistically significantly increased and number of fetuses and fetal wt showed statistically significant decreases. Number of dead fetuses and incidences of skeletal malformations were not affected. Placental wt was statistically significantly decreased at both 120 and 600 mg/kg bw. 120 mg/kg bw is a NOAEL for embryotoxicity in this limited study.

In a recent developmental study in rats the effects of DBP on prenatal and early neonatal development of the reproductive tract were examined. Groups of 10 pregnant CD rats (Sprague-Dawley) received by gavage 0, 250, 500 or 750 mg DBP (purity 99.8%)/kg bw in corn oil from gestation day 3 throughout pregnancy and lactation until the offspring were at postnatal day 20 with a 2-day interruption at parturition and on the following day (postnatal day 1-2). Dams were killed at weaning (postnatal day 21). Pups were killed at sexual maturity (postnatal day 100-105).

Observations

Dams were examined daily for clinical signs. Body weights were recorded daily and food consumption weekly. Dams that died or were euthanized intercurrently, were submitted to gross pathological examination, including the uterine contents (gross external examination and number of live and dead fetuses, resorptions, implantation sites). Dams which were killed on postnatal day 21, were weighed. Organ weights (ovary, uterus, liver, kidneys) of the dams were determined and post implantation sites were counted.

On postnatal day 1 live pups were counted and examined for clinical signs of toxicity, and mortality was recorded. Anogenital distance of the pups was measured. Pups were grouped by sex according to anogenital distance, and weighed. During lactation period, pups were weighed weekly in groups (by sex and litter) and examined for external abnormalities. At weaning pups were housed in groups of 3-5 animals according to treatment and sex. Individual pup weights were recorded weekly. Vaginal opening was monitored daily from postnatal day 29 until each animal acquired the developmental landmark or postnatal day 48, whichever came first.

Beginning at the onset of vaginal opening, daily vaginal lavage was conducted for 2 weeks. Males were examined for preputial separation from postnatal day 38 until acquisition. During this period, animals were also inspected for scrotal testes and hypospadias. After killing at sexual maturity (age 100-105 days) post mortem examination was conducted on all male and 3 female offspring/litter. Body and organ weights (liver, kidneys, adrenals, testes, seminal vesicles, epididymides, prostate, uterus, ovaries), position of testes, and gross morphology of internal and external genitalia were noted. Histopathology of the testes was conducted on all rats with gross lesions of the reproductive organs and on up to 2 gross morphologically normal animals per litter per dose group. Sperm motility was determined in the right cauda epididymis (if missing, sperm analysis was not conducted).

Results

Maternal body weight and food consumption were not affected. 3 Females at 750 mg/kg bw and one at 500 mg/kg bw were not pregnant and had no implantation sites. Since pregnancy is typically achieved in approximately 85-90% of mated females, this apparent decrease may be due to the random assignment of successfully mated females among treatment groups but could also be due to preimplantation loss since dosing began on day 3 of gestation, before implantation (on day 5-6 of gestation). Uterine weight was decreased at 500 and 750 mg/kg bw, but without any dose-relationship (significant at 500 mg/kg bw only). At 750 mg/kg bw the number of live pups per litter at birth was decreased significantly. During the second half of the pregnancy body weight gain of the dams at this dose-level was slightly lower which is consistent with the smaller litters. No reduction in implantation sites on postnatal day 21 was observed at this dose-level. No effects on the proportion of pups born alive, their weights, and sex ratio were observed. Pup weight during lactation and pup weight at weaning and beyond were also not affected. Pup survival to weaning was decreased significantly at 750 mg/kg bw but survival from weaning to killing on postnatal day 100-105 was not affected.

In male offspring at birth anogenital distance was decreased at 500 and 750 mg/kg bw and at sexual maturity a dose-dependent increase in the incidence of malformations of internal and external genitalia was observed at all dose-levels. Hypospadias were observed in 3, 21 and 43% of males at 250, 500 and 750 mg/kg bw, respectively. Underdeveloped or absent epididymis, frequently bilaterally, was observed in 9, 50 and 70% of the males at 250, 500 and 750 mg/kg bw, respectively, and was associated with atrophy of seminiferous tubules (50-100% of tubules affected in all treated groups) and abnormal or reduced spermatogenesis. At 500 and 750 mg/kg bw seminal vesicles were not developed or their weight was decreased by 16 and 32%, respectively. Mean weight of the prostate gland was decreased by 27% at 750 mg/kg bw. One animal from each of 500 and 750 mg/kg group had no prostate at postmortem examination. An increased incidence of dilated renal pelvis was observed in male offspring at all dose-levels. Mean kidney weight was significantly decreased at 750 mg/kg bw.

In female offspring DBP treatment had little effect on development of the reproductive system. At 500 mg/kg bw 1/30 rats (1/8 litters) and at 750 mg/kg bw 2/9 rats (1/4 litters) had no vaginal opening. Besides these animals, no significant changes in the age at vaginal opening and first estrus, the length of the estrous cycle, and the frequency of cornified smears in the treated groups were observed. At necropsy the rat without a vaginal opening at 500 mg/kg bw, had no patent vagina, no uterus and no left kidney. In another rat at 500 mg/kg bw right uterine horn was half of the size of the left. In one female at 750 mg/kg bw the length of the left horn was normal, but only the distal segment of the right horn near the ovary was present. A NOAEL cannot be established in this study. The results of this study suggested that DBP does not possess

estrogenic activity but rather shows antiandrogenic activity at these dose-levels (Mylchreest et al., 1998).

In a follow-up study of Mylchreest et al. (1999) DBP was shown to disrupt the androgen-regulated male sexual differentiation during prenatal exposure, without interacting directly with the androgen receptor, as does flutamide, a known antiandrogen. At the highest dose-level of 500 mg/kg bw (in corn oil), given orally by gavage to pregnant rats during day 12-21 of gestation, one dam showed weight loss after day 18 of pregnancy and delivered dead and moribund fetuses. At all dose levels (100, 250 and 500 mg/kg bw) delayed preputial separation in F_1 males (killed at sexual maturity at the age of 100-105 days) was seen. At the lowest dose level of 100 mg DBP/kg bw this delay (of 2 days) was attributable at least in part, to one markedly affected litter. Furthermore malformations of the (F_1) male reproductive tract were observed at 250 and 500 mg/kg bw, i.e. retained thoracic nipples and decreased anogenital distance. In addition, at 500 mg/kg bw hypospadias, cryptorchidism, agenesis of the prostate, epididymis, and vas deferens, degeneration of seminiferous epithelium and interstitial cell hyperplasia (5 animals from 2 litters) of the testis were seen. Interstitial cell adenoma occurred at 500 mg/kg bw in 2 males (in one litter). In F_1 females no abnormal uterine or vaginal development or kidney agenesis were seen. In contrast to flutamide, DBP caused a low incidence of prostate agenesis and hypospadias with no vaginal pouch.

Gray et al. (1999) reported that DBP administered orally (500 mg/kg bw) to LE hooded pregnant rats during day 16-19 of gestation reduced anogenital distance in male progeny (killed at the age of 9 months), induced retained nipples and permanently reduced androgen-dependent tissue weights. When 500 mg DBP/kg bw was given orally on gestation day 14 to lactational day 3 to SD pregnant rats again altered sexual differentiation was seen in male progeny (killed at the age of 6 months) and the effects were more pronounced than in LE hooded rats exposed for 4 days (day 16-19 of gestation).

Gray et al. (1999) also performed a multigeneration study in LE hooded rats. Both male and female animals (10-12 animals/sex/group) of only the P_0 generation received orally by gavage 0, 250 or 500 mg DBP/kg bw from weaning, through puberty, young adulthood, mating and lactation. Another group of only males received 1,000 mg/kg bw. When the P_0 animals were mated, treated animals were paired with untreated controls. F_1 animals were not treated. After puberty F_1 animals were selected (16/sex/group) for fertility assessment under continuous mating conditions over 11 breeding cycles.

The P_0 generation showed reduced fertility in male and female animals at 500 and 1,000 (males only) mg/kg bw. Infertility in males was related to testicular atrophy and reduced sperm production, while treated females cycled and mated successfully, but many treated females (500 mg/kg bw) aborted their litters around midpregnancy. In the F_1 offspring (data only from F_1 animals from dams treated with 0, 250 and 500 mg DBP/kg bw) urogenital malformations/abnormalities including a low incidence of agenesis of the epididymis, hypospadias, ectopic testis, renal agenesis and uterine abnormalities (partial agenesis or lack of implants in one uterine horn) were seen. In addition a few treated animals displayed anophthalmia. Furthermore F_1 males exhibited reduced cauda epididymal sperm numbers. The F_1 offspring showed reduced fecundity (significantly fewer F_2 pups; number pups/litters 179/24, 76/10, and 20/4 for 0, 250 and 500 mg/kg bw, respectively) in similarly treated pairs under continuous breeding conditions. The lowest dose-level of 250 mg/kg bw in this study is a LOAEL.

In a study by Ema et al. (1998) pregnant Wistar rats received a diet with 0, 0.5, 1.0 or 2.0% DBP (~0, 331, 555 or 661 mg/kg bw, respectively) during day 11- 21 of gestation. The dams were

killed on day 21 of pregnancy. Body weight gain and food consumption of dams during treatment period was decreased significantly at 1.0 and 2.0% DBP in the diet with a dose-relationship. No post implantation loss, no changes in number of live fetuses, number of resorptions or number of dead fetuses were seen. At 2.0% weights of male and female fetuses were significantly decreased. An increased incidence of fetuses with cleft palate and fusion of the sternebrae were seen at 2.0% in the diet. At 1.0 and 2.0% in the diet the number of male fetuses with undescended testes (internal malformation) and decreased anogenital distance was increased. Anogenital distance of female fetuses in the treated groups was comparable to control values. The NOAEL in this study is 0.5% DBP in the diet (~331 mg/kg bw).

Conclusion on developmental studies

Developmental studies in rats and mice have been performed. For several studies it is unclear whether they were performed according to a guideline or under GLP conditions. Embryotoxic as well as teratogenic effects were observed. In a study in mice the dose-level of 0.05% in the diet, equivalent to 100 mg/kg bw, was a NOAEL for maternal toxicity, embryotoxicity and teratogenicity. In a second study in mice 0.2% in the diet (ca. 350 mg/kg bw) was a NOAEL for embryotoxicity; in this last study the NOAEL for maternal toxicity and teratogenicity is 0.4% in the diet (ca. 660 mg/kg bw). In this study there is a limited evidence for teratogenicity at 1.0% in the diet (ca. 2100 mg/kg bw) in the presence of maternal toxicity. However this second study showed limitations regarding the number of animals and reporting.

In several recent developmental studies in rats delayed preputial separation and a markedly disturbed development of the male reproductive tract (internal and external) of rat offspring exposed via their mothers during gestation or during gestation and lactation, was observed at oral doses ≥ 250 mg/kg bw. Maternal toxicity was seen at oral doses ≥500 mg/kg bw. In female offspring sporadic cases of reproductive tract malformations were observed at doses ≥ 250 mg/kg bw. Age at vaginal opening and estrus cyclicity were not affected. At the lowest oral dose level of 100 mg DBP/kg bw, studied in developmental studies in rats, still delayed preputial separation in male progeny was seen. The results of these studies indicate that DBP does not possess estrogenic activity but rather shows antiandrogenic activity. A NOAEL could not be derived from the available developmental studies in rats.

Developmental studies with dermal exposure or exposure by inhalation to DBP are not available.

Estrogenic activity

Recently (i.e. the last few years) concern has been raised about the possible estrogenic activity of environmental contaminants among which the phthalate esters. During the last two years several studies on this subject have been published in which many environmental contaminants have been examined for a possible estrogenic activity in a number of *in vitro* assays. The relevance of positive effects detected in these assays to human health has not yet been established.

Dibutyl phthalate was tested for possible estrogen activity *in vitro* in two human breast cancer cell lines, i.e. ZR-75 and MCF-7, by Jobling et al. (1995). DBP showed mitogenic effects on cell growth of ZR-75 cells. The growth response was less than the responses shown by β-estradiol and octylphenol. DBP also stimulated transcriptional activity of the estrogen receptor as seen in an assay with transiently transfected MC-7 cells. In addition DBP increased the transcriptional activity of the receptor in the presence of 10^{-11}M 17β-estradiol.

Harris et al. (1997) found estrogenic activity for DBP in an *in vitro* recombinant yeast screen. The potency of DBP was estimated to be 10^{-7} the potency of 17β-estradiol. In addition Harris et al. (1997) found DBP to be also mitogenic in human breast cancer cells (ZR-75 and MCF-7).

Zacharewski et al. (1998) also investigated *in vitro* the estrogenic activity of DBP using an estrogen receptor competitive ligand-binding assay and mammalian (human breast cancer MCF-7 and HeLa cells) and yeast-based gene expression assays. In addition the effect on uterine weight and vaginal cell cornification *in vivo* using ovariectomized immature and mature (Sprague-Dawley) rats, respectively, was examined. DBP was able to compete with 17β-estradiol for binding to the rat uterine estrogen receptor *in vitro*. However the affinity for the estrogen receptor was weak. In MCF-7 cells DBP revealed weak induction of estrogen receptor-mediated gene expression while in HeLa cells no estrogen receptor-mediated activity was exhibited. In the recombinant Saccharomyces cerevisiae yeast strain PL3 DBP showed weak estrogenic activity.

The *in vivo* studies did not show reproductible, dose-dependent increases of uterine weight or cornification of vaginal epithelial cells by DBP. Gray et al. (1999) also did not find an estrogenic effect of DBP *in vivo* in a 3-day uterotropic and sex behaviour (lordosis) assay in adult ovariectomized rats with subcutaneous doses of 200 or 400 mg DBP/kg bw/day or oral gavage doses of 1,000 mg/kg bw/day administered for 2 days and followed on the third day by subcutaneous administration of 0.5 mg progesterone.

Conclusion on estrogenic activity

In some special *in vitro* assays DBP showed weak estrogenic activity. The estrogenic effects were not confirmed in *in vivo* studies. Therefore the relevance of the effects observed *in vitro* for the *in vivo* estrogenic activity of DBP is questionable.

4.1.2.9.2 Studies in humans

In a cross-sectional investigation 189 women working in processes involving DBP exposure, were examined gynaecologically. DBP concentrations exceeded 0.5 mg/m^3 but quantitative data were not given and also exposure to a variety of other unspecified compounds took place. Data on a control group were not specified. An indication was found for induction of hormonal changes reflected in reduced fertility and changes in the vaginal cycle (only summary available) (Aldyreva et al., 1975).

Conclusion on studies in humans

The epidemiological study on possibly reproductive effects in occupationally exposed women showed several limitations including lack of an appropriate control group, small size of the exposed population, lack of adequate documentation of protocol and results and mixed exposure to other compounds than DBP. Therefore this study is inadequate for assessment of reproductive effects caused by DBP in humans in the working environment.

4.1.2.9.3 Conclusion on toxicity for reproduction

Concerning reproduction, fertility as well as developmental studies a NOAEL of 50 mg/kg bw can be established based on embryotoxicity in a one-generation reproduction study in rats with

exposure of females only. However, a LOAEL of 52 mg/kg bw can be established based on embryotoxic effects in rats in the absence of maternal toxicity in a two-generation reproduction study with a continuous breeding protocol including improved sensitive endpoints (such as sperm parameters, estrous cycle characterisation and detailed testicular histopathology) and with exposure of both male and female animals. The protocol of this study was supposed to adequately identify compounds with endocrine activity. Therefore the LOAEL of 52 mg/kg bw will be used for risk assessment.

Based on the available developmental studies in mice an oral NOAEL of 100 mg/kg bw, can be derived for teratogenicity, embryotoxicity and maternal toxicity. At the next higher dose-level of 400 mg/kg bw embryotoxic and teratogenic effects were seen in the presence of maternal toxicity.

In rats developmental studies with exposure during gestation or during gestation and lactation, revealed delayed preputial separation and reproductive tract malformations in male offspring at oral doses ≥ 250 mg/kg bw. Maternal toxicity was seen at doses ≥ 500 mg/kg bw. At the lowest oral dose-level of 100 mg DBP/kg bw, studied in developmental studies in rats, still delayed preputial separation in male progeny was seen. A NOAEL could not be derived from the developmental studies in rats.

No reproduction, fertility or developmental studies with dermal exposure or exposure by inhalation to DBP are available.

In some special *in vitro* assays DBP showed weak estrogenic activity. However, the estrogenic effects were not confirmed in *in vivo* studies. Therefore the relevance of the estrogenic effects observed *in vitro* for the *in vivo* estrogenic toxicity of DBP is questionable. Moreover results of developmental studies described above were indicative of an antiandrogenic effect of DBP rather than an estrogenic effect. The epidemiological study on possibly reproductive effects in occupationally exposed women is inadequate for assessment of possible reproductive effects caused by DBP in humans in the working environment.

Based on the available reproduction, fertility and developmental studies and according to EC Criteria, dibutyl phthalate is placed in Category III for effects on fertility and in Category II for effects on developmental toxicity and is labelled with R-phrase 62: “Possible risk of impaired fertility” and R-phrase 61: “May cause harm to the unborn child”.

4.1.3 Risk characterisation

4.1.3.1 General aspects

Dibutyl phthalate is rapidly absorbed and excreted after oral administration as it was demonstrated in studies in laboratory animals. Up to more than 90% of oral doses given to rats or hamsters were excreted in urine within 24-48 hours. Fecal excretion is low (1.0-8.2%).

Also in humans, oral absorption of DBP takes place.

After dermal exposure of rats to DBP ca. 60% of the dose was excreted in urine within 7 days. In feces ca. 12% of the dose was found. An *in vitro* study revealed slower absorption of DBP by the human skin (2.40 μg/cm^2/hr) than by the rat skin (93.35 μg/cm^2/hr).

Data on absorption after exposure by inhalation are not available.

A substantial fraction of DBP is initially excreted in the bile and subsequently enters the enterohepatic circulation.

No significant accumulation in tissues was observed in laboratory animals after oral as well as dermal exposure; limited inhalation data revealed an indication for some accumulation in tissues.

The major part of DBP is hydrolysed to MBP and the corresponding alcohol prior to absorption by the small intestines, but hydrolysis can also occur in liver and kidneys. The metabolites that occur in urine are MBP, MBP-glucuronide, various ω- and ω-1-oxidation products of MBP (more polar ketones, carboxylates) and a small amount of free phthalic acid. Species differences in the excretion of MBP and its glucuronide were observed; rats excreted a larger proportion unconjugated MBP in urine than hamsters.

There are no data on biotransformation after dermal exposure and exposure by inhalation.

Transplacental transfer of DBP and its metabolites was demonstrated in an oral study with ^{14}C-labelled DBP in rats. Radioactivity in embryonic tissues contained less than 0.12-0.15% of the administered dose. MBP accounted for most of the radioactivity in maternal plasma, placenta and embryo. Unchanged DBP was found in only small amounts. No accumulation of radioactivity was seen in maternal or embryonic tissues.

None of the acute toxicity studies have been performed according to current standards. Based on the available data DBP is slightly toxic if swallowed (LD_{50} rat is ≥ 6,300 mg/kg bw), slightly to moderately toxic by inhalation (LC_{50} rat ≥15.68 mg/L) and slightly toxic in contact with the skin (LD_{50} dermal rabbit > 20,000 mg/kg bw).

With respect to skin and eye-irritation, studies performed according to current standards were available. DBP appeared to be not irritating for the skin and the eye. In a 28-day inhalation study in rats adverse local effects in the upper respiratory tract were observed but no signs of inflammation. Hence, DBP is not irritating to the respiratory system.

Concerning sensitisation one study in animals performed according to current standards and a study performed under GLP conditions was available. DBP did not reveal skin sensitising properties in these animal studies.

The available case studies in humans are not appropriate for a definite conclusion with respect to the possible induction of sensitisation by DBP.

A 90-day study performed according to current standards with repeated oral administration in rats revealed a NOAEL of 152 mg/kg bw. At 752 mg/kg bw hematological and clinical chemical changes, increased liver and kidney wts and histopathological changes in the liver were seen. However no testicular changes were seen in this study up to and including the highest dose-level of 752 mg/kg bw while in special studies in rats on these effects even the lowest dose-level of 250 mg/kg bw showed an effect (changes in testicular enzymes associated with degeneration of spermatogenic cells). No neurotoxicity was seen in this study. In addition a NOAEL of 19.9 mg/kg bw in rats with respect to peroxisomal proliferation was found in a special study focused on this effect. However, humans have a low sensitivity for this phenomenon.

Studies with repeated dermal exposure were not appropriate for establishing a NOAEL or LOAEL.

For repeated inhalation exposure a NOAEC of 509 mg DBP/m^3 (the highest concentration tested) for systemic effects including neurotoxic effects can be established based on a 28-day inhalation study in rats performed according to current standards. In this 28-day inhalation study in rats the lowest exposure concentration of 1.18 mg/m^3 is a LOAEC for local effects (histopathological changes in upper respiratory tract).

The epidemiological studies on neurological symptoms in occupationally exposed subjects showed several limitations including lack of an appropriate control group, small size of the exposed population, lack of adequate documentation of protocol and results and mixed exposure to other compounds than DBP. Therefore these studies are inadequate for assessment of neurotoxic effects caused by DBP in humans in the working environment.

With respect to mutagenicity *in vitro* studies gave an indication for a genotoxic effect in one assay, but in the same experiment, this effect was not seen with other dialkyl phthalates (a.o. diethyl phthalate). No genotoxic effects for dibutyl phthalate were observed in *in vivo* studies detecting chromosomal aberrations.

Based on the data available for dibutyl phthalate from a variety of genotoxicity studies as described above and taking into consideration the non-genotoxic properties of other phthalate esters, dibutyl phthalate can be considered as a non-genotoxic substance.

No adequate long-term toxicity and/or carcinogenicity studies in animals or humans are available. Phthalate esters are known to induce peroxisomal proliferation in the liver of mice and rats. In general the longer chain dialkyl phthalates are more potent for the induction of peroxisomal proliferation than the shorter chain ones and branched chain phthalates seemed more potent than straight. Many peroxisome proliferators have been shown to induce hepatocellular tumours when administered at high dose-levels for long periods to mice and rats despite being non-genotoxic. The mechanisms of induction of carcinogenicity by peroxisome proliferators may be complex but are considered to have a threshold. A variety of independent studies have shown that there are marked species differences in the sensitivity to chemicals that cause peroxisome proliferation. Rats and mice are extremely sensitive, hamsters show a less marked response whilst guinea-pigs, primates and humans are rather insensitive or non-responsive.

Concerning reproduction, fertility as well as developmental studies a NOAEL of 50 mg/kg bw can be established based on embryotoxicity in a one-generation reproduction study in rats with exposure of females only. However, a LOAEL of 52 mg/kg bw can be established based on embryotoxic effects in rats in the absence of maternal toxicity in a two-generation reproduction study with a continuous breeding protocol including improved sensitive endpoints (such as sperm parameters, estrous cycle characterisation and detailed testicular histopathology) and with

exposure of both male and female animals. The protocol of this study was supposed to adequately identify compounds with endocrine activity.

Based on the available developmental studies in mice an oral NOAEL of 100 mg/kg bw, can be derived for teratogenicity, embryotoxicity and maternal toxicity. At the next higher dose-level of 400 mg/kg bw embryotoxic and teratogenic effects were seen in the presence of maternal toxicity.

In rats developmental studies with exposure during gestation or during gestation and lactation, revealed preputial separation and reproductive tract malformations in male offspring at oral doses ≥250 mg/kg bw. At the lowest oral dose of 100 mg/kg bw, studied in developmental studies in rats, still delayed preputial separation in male progeny was seen. Maternal toxicity was seen at oral doses ≥500 mg/kg bw. From the developmental studies in rats a NOAEL could not be derived.

In some special *in vitro* assays DBP showed weak estrogenic activity. However, the estrogenic effects were not confirmed in *in vivo* studies. Therefore the relevance of the estrogenic effects observed *in vitro* for the *in vivo* estrogenic activity of DBP is questionable

Moreover results of recent developmental studies are indicative of an antiandrogenic effect rather than an estrogenic effect of DBP.

No reproduction, fertility or developmental studies with dermal exposure or exposure by inhalation to DBP are available.

The epidemiological study on possibly reproductive effects in occupationally exposed women is inadequate for assessment of possible reproductive effects caused by DBP in humans in the working environment.

Based on all available studies an overall oral LOAEL of 52 mg/kg bw can be established for dibutyl phthalate. This figure is derived from a two-generation reproduction study in rats with a continuous breeding protocol and based on embryotoxic effects (see footnote 5).

4.1.3.2 Workers

Assuming that oral exposure is prevented by personal hygienic measures, the risk characterisation for workers is limited to the dermal and inhalation routes of exposure.

Acute toxicity

Given the low toxicity observed in the acute oral, inhalation, and dermal studies and the anticipated occupational exposure levels it is concluded that DBP is of no concern for workers with respect to acute effects (**conclusion (ii)**).

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

Irritation

Skin

Given the effects observed in the skin irritation studies with rabbits it is concluded that DBP is of no concern for workers with respect to acute skin irritation (**conclusion (ii)**).

It is reported that slight skin irritation and slight dermatitis were observed in the 90-day dermal toxicity study with rabbits. However, because the documentation of this study was inadequate (e.g., no details on dose levels at which these effects were observed, information on dermal area doses is lacking, no information on onset and duration of effects) this study cannot be used to draw quantitative conclusions on local skin effects after repeated exposure to DBP in occupational settings.

Inhalation

Given the effects observed in the acute and repeated dose inhalation studies (mice, cats, and rats) it is concluded that DBP is of no concern for workers with respect to irritation of the respiratory tract (**conclusion (ii)**).

Eyes

Exposure to the eyes is possible accidentally by splashing. Given the effects observed in the eye irritation studies with rabbits it is concluded that DBP is of no concern for workers with regard to acute eye irritation (**conclusion (ii)**).

Corrosivity

Given the results from the skin and eye irritation studies, it is concluded that DBP is of no concern for workers with regard to corrosivity (**conclusion (ii)**) (see irritation).

Sensitisation

From the dermal sensitization studies in guinea pigs it is concluded that DBP is not sensitizing to the skin. However, given the observations in humans it cannot be excluded that dermal exposure to DBP may lead to sensitisation of workers (see Section 4.1.2.5). From the data available it is not clear whether or not the risk is limited to workers with an atopic constitution. So, it cannot be concluded that DBP sensitising in humans. **Conclusion (ii)** is considered to be applicable.

There are neither data from human experience nor from other sources indicating respiratory sensitisation.

Repeated dose toxicity

Risk characterisation for local effects after repeated exposure to DBP is described in the paragraph on irritation.

Dermal exposure

Dermal NOAELs cannot be concluded from the toxicological database available. Two starting points should be considered for risk assessment with respect to repeated dose dermal toxicity: (a) the NOAEL from the semichronic oral study with rats (152 mg/kg bw/d), performed according to current standards, and (b) the NOAEC from the 28-day inhalation toxicity study (6 hr/d) with rats (509 mg/m^3, equivalent to 146.6 mg/kg bw/day, assuming 300 g bodyweight and a respiratory rate of 240 ml/min). Although slight irritation was reported to occur after repeated dermal exposure route-to-route extrapolation using the oral NOAEL is considered justifiable, given the effect levels in this dermal study (> 0.5 ml/kg, i.e. 520 mg/kg bw/d). It is also assumed that local respiratory effects do not interfere with the applicability of inhalation-to-dermal

extrapolation for a risk characterisation for systemic effects. Therefore, the risk due to dermal exposure to DBP is estimated using either the oral or the respiratory NOAEL as starting points.

For the route-to-route extrapolation correction is made by worst-case assumptions for differences between oral and dermal absorption and between inhalation and dermal absorption. As mentioned in Section 4.1.2.1 over 90% of DBP given orally is absorbed. As for dermal exposure, the log-P_{ow} (4.57) and the molecular weight (278) do not point to a high dermal absorption rate. From *in vitro* studies it is concluded, that DBP is absorbed more slowly by human skin than by rat skin. However, this study does not allow a conclusion with respect to the total amount absorbed. From an *in vivo* study with rats it is seen that approximately 10% is absorbed per day, leading to a total absorption of ca. 72% within 7 days. Results from *in vivo* dermal absorption studies can only be applied for conclusions on percutaneous absorption when the experimental exposure conditions resemble the estimated actual exposure conditions. Details on exposure conditions in this study are lacking. Considering the available data, dermal absorption is assumed to be 10% (worst-case estimate).

Data on absorption after inhalation is lacking. Therefore, 100% respiratory absorption is used as a default value.

Given the estimated dermal occupational exposure levels (see Section 4.1.1.2 and **Table 4.5**) the MOSs for the different exposure scenarios vary between 11 and 25 using the oral NOAEL and between 10 and 20 using the respiratory NOAEL. The MOSs are listed in **Table 4.14**. The MOSs are evaluated by comparison with the minimal MOS (3.6 based on the oral study and 36 based on the inhalation study). In Appendix E the assessment factors used to establish the minimal MOS are given (**Table E.1**). There is concern when the MOS is significantly lower than the minimal MOS. The risk-ratios (minimal MOS divided by the MOS) are given in **Table 4.14**.

Table 4.14 Occupational risk assessment of DBP for repeated dose toxicity (systemic effects) after chronic dermal exposure

Scenario/subscenario	Risk characterisation for dermal exposure				
	Estimated dermal exposure (mg/day) worst case	MOS [a]	Risk-ratio [b]	MOS [c]	Risk-ratio[d]
1: Production	420	25	<1	20	1.8
2: Production of products containing DBP	420	25	<1	20	1.8
3: Use of products containing DBP - aerosol forming activities - non-aerosol forming activities	 975 negligible	11	 <1 <1	10	 3.6 <1

a) Calculation based on the oral NOAEL of 152 mg/kg bw/d assuming a worker body weight of 70 kg.

b) The ratio minimal MOS/MOS, with a minimal MOS of 3.6 (see Appendix E, Table E.1)

c) Calculation based on the respiratory NOAEL of 146.6 mg/kg bw/day (based on a NOAEC of 509 mg/m^3) assuming a worker body weight of 70 kg

d) The ratio minimal MOS/MOS, with a minimal MOS of 36 (see Appendix E, Table E.1)

Note: Application of the assessment factors on the oral NOAEL results in a Health Based Occupational Recommended Value of 2,956 mg/day for systemic effects after chronic dermal exposure. The HBORV based on the inhalation NOAEC results in a Health Based Occupational Recommended Value of 285 mg/day.

Clear conclusions on reliability of either oral-to-dermal or inhalation-to-dermal extrapolation cannot be drawn. Both methods have uncertainties, either due to differences in exposure conditions or to possible toxicokinetic differences (it may be assumed that the dermal route resembles more the respiratory route of exposure than the oral route, given, e.g., the first-pass effect of the liver). Therefore, the highest risk ratios, based on the inhalation toxicity study, are used for the risk characterisation. Given the risk-ratios for dermal exposure as mentioned in **Table 4.14** it is concluded that for occupational exposure Scenario 3 (aerosol forming activities) systemic health effects due to repeated dermal exposure cannot be excluded (**conclusion (iii)**). There are no concerns for systemic effects for the occupational scenarios 1, 2, and 3 (non-aerosol forming activities).

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

There is no information available to determine the risk for local skin effects after repeated dermal exposure.

Inhalation exposure

The NOAEC of 509 mg/m^3 from a 28-day inhalation study with rats is used as starting point for the risk characterisation for systemic effects after repeated inhalation exposure. Given the estimated inhalation occupational exposure levels (Section 4.1.1.2 and **Table 4.5**) the MOS for the different exposure scenarios varies between 51 and 102. The MOSs are listed in **Table 4.15**. The MOSs are evaluated by comparison with the minimal MOS (90). In Appendix E the assessment factors used to establish the minimal MOS are given (**Table E.2**). There is concern when the MOS is significantly lower than the minimal MOS. The risk-ratios (minimal MOS divided by the MOS) are given in **Table 4.15**.

Table 4.15 Occupational risk assessment of DBP for repeated dose inhalation toxicity (systemic effects)

Scenario/subscenario	Risk characterisation for inhalation exposure		
	Estimated inhalation exposure (mg/m^3) worst case	MOS [a]	Risk-ratio [b]
1: Production	5	102	<1
2: Production of products containing DBP	5	102	<1
3: Use of products containing DBP - aerosol forming activities - non-aerosol forming activities	 10 negligible	 51	 1.8 <1

a) Calculation based on the NOAEC of 509 mg/m^3

b) The ratio minimal MOS/MOS, with a minimal MOS of 90 (see Appendix E, table E.2)

Note: Application of the assessment factors on the inhalation NOAEL results in an Health Based Occupational Recommended Value of 5.7 mg/m^3 for systemic effects after chronic inhalation exposure.

Given the risk-ratios for inhalation exposure as presented in **Table 4.15**, it is concluded that there is no concern with respect to systemic effects due to repeated respiratory exposure for all occupational scenarios (**conclusion (ii)**).

The LOAEC of 1.18 mg/m^3 from a 28-day inhalation study with rats is used as starting point for the risk characterisation for local effects after repeated inhalation exposure. Given the estimated inhalation occupational exposure levels (Section 4.1.1.2 and **Table 4.5**) the MOS for the different

exposure scenarios varies between 0.1 and 0.2. The MOSs are listed in **Table 4.16**. The MOSs are evaluated by comparison with the minimal MOS (27). In Appendix E the assessment factors used to establish the minimal MOS are given (**Table E.3**). There is concern when the MOS is significantly lower than the minimal MOS. The risk-ratios (minimal MOS divided by the MOS) are given in **Table 4.16.**

Table 4.16 Occupational risk assessment of DBP for repeated dose inhalation toxicity (local effects)

Scenario/subscenario	Risk characterisation for inhalation exposure		
	Estimated inhalation exposure (mg/m^3) worst case	MOS [a]	Risk-ratio [b]
1: Production	5	0.2	114
2: Production of products containing DBP	5	0.2	114
3: Use of products containing DBP - aerosol forming activities - non-aerosol forming activities	 10 negligible	 0.1	 229 <1

a) Calculation based on the LOAEC of 1.18 mg/m^3

b) The ratio minimal MOS/MOS, with a minimal MOS of 27 (see Appendix E, Table E.3)

Note: Application of the assessment factors on the inhalation NOAEL results in an Health Based Occupational Recommended Value of 0.04 mg/m^3 for local effects after chronic inhalation exposure

Given the risk-ratios for inhalation exposure as presented in **Table 4.16**, it is concluded that there is concern with respect to local effects due to repeated respiratory exposure for all occupational scenarios (**conclusion (iii)**).

Combined exposure

Given the risk-ratios for systemic effects for all scenarios calculated for the different routes, it can be concluded that internal exposure of the worker as result from uptake via both routes in these scenarios will give rise to comparable adverse systemic health effects due to the toxicity after dermal exposure. It can be assumed that inhalation exposure in this scenario will not additionally contribute to that risk. Therefore, **conclusion (ii)** is applicable for all occupational scenarios, except for Scenario 3 (aerosol forming activities) (**conclusion (iii)**).

The risk assessment for combined exposure is not applicable for local effects.

Mutagenicity

From the results of the mutagenicity studies it is concluded that DBP may be considered as a non-genotoxic substance (**conclusion (ii)**).

Carcinogenicity

No adequate carcinogenicity studies of DBP are available. There are no urgent reasons for concern for workers with regard to carcinogenicity (see also Section 4.1.2.8) (**conclusion (ii)**).

Toxicity for reproduction

Dermal exposure

As starting point for the risk characterisation for reproduction toxicity the LOAEL (52 mg/kg bw/day) from the two-generation reproduction toxicity study in rats is used. Given the estimated dermal occupational exposure levels (Section 4.1.1.2 and **Table 4.5**) the MOS for the different exposure scenarios varies between 3.7 and 8.6. The MOSs are listed in **Table 4.1.7**. The MOSs are evaluated by comparison with the minimal MOS (7.2). In Appendix E the assessment factors used to establish the minimal MOS are given (**Table E.4**). There is concern when the MOS is significantly lower than the minimal MOS. The risk-ratios (minimal MOS divided by the MOS) are given in **Table 4.17**.

Table 4.17 Occupational risk assessment of DBP for reproduction toxicity after chronic dermal exposure

Scenario/subscenario	Risk characterisation for dermal exposure		
	Estimated dermal exposure (mg/day) worst case	MOS [a]	Risk-ratio [b]
1: Production	420	8.6	<1
2: Production of products containing DBP	420	8.6	<1
3: Use of products containing DBP - aerosol forming activities - non-aerosol forming activities	 975 negligible	 3.7	 1.9 <1

[a] Calculation based on the LOAEL of 52 mg/kg bw/day assuming a worker body weight of 70 kg
[b] The ratio minimal MOS/MOS, with a minimal MOS of 7.2 (see Appendix E, Table E.4).
Note: Application of the assessment factors on the oral NOAEL results in an Health Based Occupational Recommended Value of 506 mg/day for reproduction effects after chronic inhalation exposure

Given the risk-ratios for dermal exposure as presented in **Table 4.17**, it is concluded that there is no concern with respect to reproduction toxicity due to repeated dermal exposure for any occupational scenario (**conclusion (ii)**).

Inhalation exposure

As starting point for the risk characterisation for reproduction toxicity the LOAEL (52 mg/kg bw/day) from the two-generation reproduction toxicity study in rats is used. Given the estimated inhalation occupational exposure levels (Section 4.1.1.2 and **Table 4.5**) the MOS for the different exposure scenarios varies between 36 and 73. The MOSs are listed in **Table 4.18**. The MOSs are evaluated by comparison with the minimal MOS (80). In Appendix E the assessment factors used to establish the minimal MOS are given (**Table E.5**). There is concern when the MOS is significantly lower than the minimal MOS. The risk-ratios (minimal MOS divided by the MOS) are given in **Table 4.18**.

Table 4.18 Occupational risk assessment of DBP for reproduction toxicity after chronic inhalation exposure

Scenario/subscenario	Risk characterisation for inhalation exposure		
	Estimated inhalation exposure (mg/m^3) worst case	MOS [a]	Risk-ratio [b]
1: Production	5	73	1.1
2: Production of products containing DBP	5	73	1.1
3: Use of products containing DBP - aerosol forming activities - non-aerosol forming activities	 10 negligible	 36	 2.2 <1

[a] Calculation based on calculation based on a respiratory volume of 10 m^3/workday, a worker body weight of 70 kg, and an oral LOAEL of 52 mg/kg bw/day

[b] The ratio minimal MOS/MOS, with a minimal MOS of 80 (see Appendix E, Table E.5)

Note: Application of the assessment factors on the oral NOAEL results in an Health Based Occupational Recommended Value of 4.6 mg/m^3 for reproduction effects after chronic inhalation exposure

Given the risk-ratios for inhalation exposure as presented in **Table 4.18**, it is concluded that there is no concern with respect to reproduction toxicity due to repeated respiratory exposure for any occupational exposure scenario (**conclusion (ii)**).

Occupational limit values

The Health-Based Recommended Occupational Exposure Level (HBROEL) of the Dutch Expert Committee on Occupational Standards (DECOS) amounts to 5 mg/m^3 (DECOS, 1993). This level is based on an oral study in dogs with a NOAEL of 18 mg/kg bw/d). This NOAEL was mentioned in a review, referring to an FDA file (Note: Details on the study and on bibliographic reference were not reported in this review. It is assumed that recent inhalation studies are of greater value than this study with dogs). Route-to-route extrapolation was performed assuming 100% oral and inhalation absorption, a bodyweight for the worker of 70 kg, and a respiratory volume of 10 m^3/day; after application of an uncertainty factor of 5 a limit value of 25.2 mg/m^3 was obtained. Because phthalate esters have a low vapour pressure it was assumed, that the low toxicity would be overruled by another phenomenon, namely the formation of an aerosol. Therefore, the maximum allowable concentrations for dust, 5 mg/m^3 for respirable dust and 10 mg/m^3 for total inhalable dust, were recommended as HBROEL.

The TLV established by the ACGIH also amounts 5 mg/m^3, based on "its low toxicity" (500, documentation revised in 1991). It was noted, that data were not sufficient to establish a no-effect-level for effects on the reproductive system, considered to be the primary target of DBP.

It may be emphasized that the argumentation of DECOS and ACGIH differ from that followed in the underlying report. Other toxicity studies were used as starting point, either due to the date of publication or to confidentiality of data.

Based on the calculated HBORV values in this risk assessment report (i.e. 0.04 mg/m^3 for local effects after chronic inhalation exposure), it is recommended to reconsider the current values taking into account all available toxicological data.

4.1.3.3 Consumers

From the identified uses attention has been paid to the use of DBP in nail polish (scenario I), adhesives (scenario II), regenerated cellulose film (cellophane) wrapped food (scenario III), children's toys (scenario IV).

The inhalation exposures with respect to the use of DBP in nail polish and adhesives has been estimated using the CONSEXPO model (see Section 4.1.1.3).

Scenario I

The use of DBP in nail polish is considered to occur frequently.

For the use of DBP in nail polish an inhalatory exposure estimate (yearly average) of $8.59 \cdot 10^{-9}$ mg/m^3 has been calculated by the CONSEXPO model (see Section 4.1.1.3).

The available studies after repeated exposure to humans are inadequate for the assessment of any effect in humans. The main toxic effects of repeated oral exposure to animals are on reproduction parameters, with an overall LOAEL of 52 mg/kg bw/day for embryotoxicity. In the inhalation studies these effects are not observed. The NOAEC of 509 mg/m³, the highest concentration tested, from a 28-day inhalation study with rats will be used as starting point for the risk characterisation.

The margin of safety between the inhalatory NOAEC of 509 mg/m^3 and the exposure level of $8.59 \cdot 10^{-9}$ mg/m^3 is $6 \cdot 10^{10}$. Taking into account the worst-case character of the exposure assessment, this high safety margin, even when realizing that the NOAEC was from a 28-day study only, is considered to indicate no concern for consumers using nail polish containing DBP (**conclusion (ii)**).

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

Scenario II

For the use of DBP containing adhesives it is assumed that the use will be occasionally and the exposure is acute. The inhalatory exposure was estimated using the CONSEXPO model, with the assumption of 3 kg product/event containing 15% DBP once a year for 2 hours (duration of contact per event 4 hours); the model predicts exposure to peak airborne concentrations of 3.18 mg/m^3 and a total internal dose of $3.43 \cdot 10^{-4}$ mg/kg bw/day (see Section 4.1.1.3).

Toxic effects in humans after acute exposure have not been described, in rats the 4h LC_{50} is ≥15,680 mg/m^3. The MOS (about 5,000) between this value and the estimated human exposure indicates no concern taking into account the rather extensive database available and the worst-case approach of the exposure assessment (**conclusion (ii)**).

Scenario III

With respect to the intake of DBP via food the MAFF estimate of 1.9 mg/person/day (= 0.027 mg/kg bw/day for a 70 kg person) is used. The margin of safety between the overall oral LOAEL of 52 mg/kg bw/day based on embryotoxic effects in a two-generation reproduction study and this exposure is 1,925. Taking into account intra- and interspecies differences and the use of a LOAEL instead of a NOAEL from a reproduction study, this MOS is considered sufficient (**conclusion (ii)**).

Scenario IV

Soft PVC toys and child-care articles

Comparing the worst-case infant exposure of 0.81 µg/kg bw/day with the overall LOAEL of 52 mg/kg bw/day, a MOS of approximately 65,000 can be calculated. This high MOS, even when realizing that a LOAEL instead of a NOAEL was used, is considered sufficient (**conclusion (ii)**). This is in agreement with the conclusion by CSTEE (1998), who also compared the worst-case infant exposure of 0.81 µg/kg bw/day with the critical effect of DBP, i.e. reduced F_2 pup weights observed in an oral two-generation reproductive toxicity study with rats (LOAEL 52 mg/kg bw/day). Taking into account an additional uncertainty factor of 5 because a LOAEL is used, the CSTEE estimated a MOS of approximately 13,000 for DBP, and considered this high MOS for DBP no reason for concern.

4.1.3.4 Humans exposed via the environment

Local scale

Toxicological starting points for the risk characterisation for humans indirectly exposed via the environment are the oral LOAEL of 52 mg/kg bw/d (total daily intake) and the inhalatory NOAEC of 509 mg/m^3 (air; the highest concentration tested). Calculated concentrations in air and total daily intake values were given in **Tables 4.7** and **4.8**, respectively. The corresponding MOS values are given in **Tables 4.19** and **4.20**.

Table 4.19 Local MOS values (air and total daily intake) at production

Scenario	Production A	Production B	Production C
MOS total	2,781	$5.72 \cdot 10^4$	$6.61 \cdot 10^4$
MOS air	$2.12 \cdot 10^7$	$2.12 \cdot 10^7$	$2.55 \cdot 10^7$

Table 4.20 Local MOS values (air and total daily intake) at formulation/processing

Scenario	IIIa	IIIb-1	III-b2	III-c1	III-c2	III-d
MOS Total	562	1,429	8,360	9,647	5,721	1,316
MOS air	$2.16 \cdot 10^5$	$1.5 \cdot 10^6$	$3.35 \cdot 10^7$	$9.55 \cdot 10^6$	$2.1 \cdot 10^6$	$4.76 \cdot 10^5$

From the MOSs at production (**Table 4.19**) and at formulation/processing (**Table 4.20**) it is concluded that there is no concern for humans indirectly exposed via the environment **(conclusion (ii)).**

Regional scale

Toxicological starting points for the risk characterisation for humans indirectly exposed via the environment are the oral LOAEL of 52 mg/kg bw/d (total daily intake) and the inhalatory NOAEC of 509 mg/m^3 (air; the highest concentration tested). Calculated concentrations in air and total daily intake values were given in **Table 4.9**. The corresponding MOS values are $1.45 \cdot 10^5$ and $8.93 \cdot 10^7$, respectively. From these MOS values it is concluded that there is no concern at the regional scale (**conclusion (ii)**).

Breast milk

Comparing the maximum infant exposure via breast milk (6 µg DBP/kg bw/day) with the overall LOAEL of 52 mg/kg bw/day, a MOS of 8,667 can be calculated. This MOS, even when realizing that a LOAEL instead of a NOAEL was used, is considered sufficiently high to conclude that there is no concern for breast-fed babies (**conclusion (ii)**).

4.2 HUMAN HEALTH (PHYSICO-CHEMICAL PROPERTIES)

Flammability, explosive properties and oxidizing properties are not considered to form a hazard. There is no need for further information and/or testing with regard to physico-chemical properties (**conclusion (ii)**).

5 RESULTS

5.1 ENVIRONMENT

Conclusion (i) There is need for further information and/or testing.

This conclusion is reached because:

- there is a need for better information to adequately characterise the risks to plants exposed via the atmosphere (the airborne toxicity to plants).

The information requirement is a long-term plant toxicity test.

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

This conclusion applies to effects on the aquatic compartment (including sediment), soil and secondary poisoning.

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.

This conclusion is reached because of:

- concerns for general systemic toxicity as a consequence of repeated dermal exposure arising from aerosol forming activities.
- concerns for adverse local effects in the respiratory tract as a consequence of repeated inhalation exposure in all occupational exposure scenarios.

It is possible that in some industrial premises adequate worker protection measures are already being applied.

5.2.1.2 Consumers

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

5.2.2 Human health (risks from physico-chemical properties)

Conclusion (ii) There is at present no need for further information or testing or 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 III 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 III 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 III 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 t/a)
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 III 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	Oxidizing (Symbols and indications of danger for dangerous substances and preparations according to Annex III 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 III of Directive 67/548/EEC
SAR	Structure-Activity Relationships
SBR	Standardised birth ratio
SCE	Sister Chromatic Exchange
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 III 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 Organization
WWTP	Waste Water Treatment Plant
Xn	Harmful (Symbols and indications of danger for dangerous substances and preparations according to Annex III of Directive 67/548/EEC)
Xi	Irritant (Symbols and indications of danger for dangerous substances and preparations according to Annex III of Directive 67/548/EEC)

Appendix A Abbreviations and vapour pressure of some phthalates

Abbreviations and vapour pressure of some phthalates (Peynenburg et al., 1991, ref. 524).

Abbreviation	Phthalate	Vapour pressure at 25°C (Pa)
DBP	Dibutyl phthalate	0.0097
DEHP (DOP)	Di(2-ethylhexyl) phthalate	0.00086
DIDP	Diisodecyl phthalate	0.00074
DIAP	not given	not given
BBP	Butylbenzyl phthalate	0.0011
D79P	Dialkyl(C7-C9) phthalate	not given
DIOP	Diisooctyl phthalate	0.00074
DINP	Diisononyl phthalate	$7.2 \cdot 10^{-5}$

Appendix B Estimation of concentrations due to transfer operations – USEPA transfer model[6]

The USEPA transfer model is a model in which the equilibrium concentrations reached in a room during liquid transfer is calculated. These calculations actually consist of two parts. In the first part the generation of vapours by displacement of air from containers during liquid transfer is calculated. The generation rate of the vapour is then used as an input variable in a mass balance ventilation model. For several input parameters typical and worst-case default values have been established from empirical knowledge. If more specific information is lacking, the default values can be used to calculate concentrations. These concentrations are spatially averaged concentrations. To calculate exposure levels from these concentrations the time workers spend in this and other environments and the concentrations in the other environments should be known or estimated. As a worst-case assumption it can be assumed that workers spend a whole shift transferring liquids, since transferral is often the activity with the highest levels of emission.

The formula to calculate the concentrations is given in formula 1.

$$C_m = 1{,}000 \cdot (f \cdot M \cdot V \cdot r \cdot P)/(R \cdot T_l \cdot Q \cdot k) \qquad \text{formula 1}$$

f = saturation factor
M = molar weight (mg/mol)
V = volume of container (m^3)
r = fill rate (h^{-1})
P = vapour pressure of subst.(Pa)
R = universal gas constant (= 8.3144 J/mol.K)
T_l= temperature of the liquid (K)
Q = ventilation rate (m^3/h)
k = mixing factor
C_m= calculated concentration level (mg/m^3)

The following input data are standard for each assessment in this Appendix:

Input:	data	Transfer operations:
M	278.34	a drum
kwc	0.1	b can
knorm	0.5	c tank truck
p	0.0026	d tank car
Twc	293	
Tnorm	293	

The results are presented in the table below

Worst Case

	f	M	V	r	P	Tl	Q	k	Cm
a	1.0	278	0.200	30	0.00	293	850	0.1	0.02
b	1.0	278	0.010	30	0.00	293	850	0.1	0.00
c	1.0	278	19.000	2	0.00	293	1203000	0.1	0.00
d	1.0	278	76.000	1	0.00	293	1203000	0.1	0.00

6 US EPA. Approaches for developing screening quality estimates of occupational exposure used by the US EPA's Office of Toxic Substances and their applicability to the OECD SIDS Program. USEPA Office of Toxic Substances (Washington, DC) 1991. Appendix I. US New Chemical methods to assess inhalation exposure to vapors and gases using mass balance models.

Typical case

	f	M	V	r	P	Tl	Q	k	Cm
a	0.5	278	0.200	20	0.00	293	5100	0.5	0.00
b	0.5	278	0.010	20	0.00	293	5100	0.5	0.00
c	1.0	278	19.000	2	0.00	293	4812000	0.5	0.00
d	0.5	278	76.000	1	0.00	293	4812000	0.5	0.00

Appendix C CONSEXPO report – Nail polish

Generated by CONSEXPO version 1.03

Compound: DBP (CAS: 84-74-2)
Subject: person
Weight: 70.000 kg (uninspected default)

CONTACT

Contact scenario: none
Parameter definition of scenario:
Duration of contact per event: 10.000 min
Duration of actual use per event: 5.000 min
Frequency of contact: 104.000 1/year
Start of contact: 0.00e+00 min

INHALATION

Exposure
Scenario: evaporation from mixture
Person uses product (volume around person=5 m^3).
Mean event concentration (average case): 4.343e-06 mg/m^3
Year average (average case): 8.588e-09 mg/m^3
Mean event concentration (cumulative worst case): 4.343e-06 mg/m^3
Year average (cumulative worst case): 8.588e-09 mg/m^3

Exposure estimates based on the following parameters:
Release area: 20.000 cm^2
Temperature: 25.000 Celsius
Ventilation rate: 15.000 m^3/hr
Room volume: 25.000 m^3
Product amount: 0.250 g
Weight fraction: 5.000 %
Molweight solvent: 100.000 g/mol

Uptake

Model: fraction model
Average case estimate : 5.195e-05 mg/year
: 2.032e-09 mg/(kg.day)
Cumulative worst-case estimate : 5.192e-05 mg/year
: 2.031e-09 mg/(kg.day)

Uptake estimates based on the following parameters:
Absorbed fraction: 0.990 – 1.000 fraction, uniform distribution
Inhalation rate: 11500.000 cm^3/min
Respirable fraction: 1.000 fraction

DERMAL

Exposure
Scenario: exposure from air
Mean event concentration (average case): 4.343e-12 mg/cm^3
Year average (average case): 8.588e-15 mg/cm^3
Mean event concentration (cumulative worst case): 4.343e-12 mg/cm^3
Year average (cumulative worst case): 8.588e-15 mg/cm^3

Exposure estimates based on the following parameters:
See inhalatory exposure

Uptake
Model: diffusion model
Average case estimate : 8.447e-15 mg/year
: 3.304e-19 mg/(kg.day)
Cumulative worst-case estimate : 8.447e-15 mg/year
: 3.304e-19 mg/(kg.day)

Uptake estimates based on the following parameters:
Contact area: 1.000 cm2
Blood volume at contact area: 0.100 cm^3
Blood flow at contact area: 0.129 cm3/min
Partition coefficient product/blood: 100.000 dimless
Skin permeability: 1.87e-06 cm/min

ORAL
No exposure

Appendix D CONSEXPO report – Adhesive

Generated by CONSEXPO version 1.03

Compound: DBP (CAS: 84-74-2)
Subject: person
Weight: 70.000 kg (uninspected default)

CONTACT

Contact scenario: Painting
Parameter definition of scenario:
Duration of contact per event: 4.000 hr
Duration of actual use per event: 2.000 hr
Frequency of contact: 1.000 1/year
Start of contact: 0.00e+00 min

INHALATION

Exposure
Scenario: evaporation from mixture
Person does not use product.
Mean event concentration (average case): 3.176e+00 mg/m3
Year average (average case): 1.449e-03 mg/m3
Mean event concentration (cumulative worst case): 3.176e+00 mg/m3
Year average (cumulative worst case): 1.449e-03 mg/m3

Exposure estimates based on the following parameters:
Release area: 40.000 cm2
Temperature: 25.000 Celsius
Ventilation rate: 15.000 m3/hr
Room volume: 5.000 m3
Product amount: 3.000 kg
Weight fraction: 15.000 %
Molweight solvent: 100.000 g/mol

Uptake

Model: fraction model
Average case estimate : 8.765e+00 mg/year
: 3.428e-04 mg/(kg.day)
Cumulative worst-case estimate : 8.765e+00 mg/year
: 3.428e-04 mg/(kg.day)

Uptake estimates based on the following parameters:
Absorbed fraction: 1.000 fraction
Inhalation rate: 11500.000 cm3/min
Respirable fraction: 1.000 fraction

DERMAL

Exposure
Scenario: exposure from air
Mean event concentration (average case): 3.176e-06 mg/cm3
Year average (average case): 1.449e-09 mg/cm3
Mean event concentration (cumulative worst case): 3.176e-06 mg/cm3
Year average (cumulative worst case): 1.449e-09 mg/cm3

Exposure estimates based on the following parameters:
See inhalatory exposure

Uptake
Uptake unknown

ORAL

No exposure

Appendix E Establishment of the minimal MOSs used for the risk characterisation

Table E.1 Assessment factors applied for the calculation of the minimal MOS for systemic effects after chronic dermal exposure

Aspect	Assessment factors applied to oral NOAEL	Assessment factors applied to inhalation NOAEL
Interspecies differences	4 · 3[a]	4 · 3 [a)]
Intraspecies differences	3	3
Differences between experimental conditions and exposure pattern of the worker	1 [b)]	10 · 1 [b)]
Type of critical effect	1	1
Dose-response curve	1	1
Confidence of the database	1	1
Route-to-route extrapolation	0.1 [c)]	0.1 [d)]
Minimal MOS	3.6	36

a) Extrapolation via caloric demand, together with an uncertainty factor for remaining interspecies differences

b) A factor for extrapolation from subacute to semichronic and from semichronic to chronic exposure is introduced because it is necessary to take into account (a) that in general adverse effect levels for specific effects will decrease with increasing exposure times, (b) that adverse effects may appear a long time after exposure has been discontinued, and (c) other and more serious adverse effects may appear with increasing exposure times. Default values for extrapolation from subacute to semichronic and from semichronic to chronic exposure are both 10. The results from oral toxicity studies can be used to conclude on the effect of duration of exposure. Given the effects and the NOAELs observed in the subacute (LOAEL ~ 250 mg/kg bw/d), semichronic (NOAEL ~ 152 mg/kg bw/d) and the two 1-year studies (NOAELs ~ 62.5 mg/kg bw/d and 125 mg/kg bw/d) it is concluded that the nature and severity of the effects most likely will not increase with longer duration of exposure. Therefore, for extrapolation of semichronic to chronic occupational exposure, an assessment factor of 1 is introduced. However, because of the limitations in the subacute oral toxicity study, a default factor 10 is introduced for extrapolation from subacute to semichronic exposure.

c) For route-to-route extrapolation correction is made by differences between oral and dermal absorption (90% versus 10%).

d) For route-to-route extrapolation a correction for differences in absorption is necessary. A factor 0.1 is introduced because dermal and inhalation absorption are 10 and 100%, respectively

Table E.2 Assessment factors applied for the calculation of the minimal MOS for systemic effects after chronic inhalation exposure based on a 28-day inhalation toxicity study

Aspect	Assessment factors
Interspecies differences	3 [a)]
Intraspecies differences	3
Differences between experimental conditions and exposure pattern of the worker	10 · 1 [b)]
Type of critical effect	1
Dose-response curve	1
Confidence of the database	1
Overall	90

a) Because an inhalation study is used a factor for allometric scaling is not necessary, and a factor 3 is applicable.

b) A factor for extrapolation from subacute to chronic exposure is introduced because it is necessary to take into account (a) that in general adverse effect levels for specific effects will decrease with increasing exposure times, (b) that adverse effects may appear a long time after exposure has been discontinued, and (c) other and more serious adverse effects may appear with increasing exposure times. Default values for extrapolation from subacute to semichronic and from semichronic to chronic exposure are both 10. The results from oral toxicity studies can be used to conclude on the effect of duration of exposure. Given the effects and the NOAELs observed in the subacute (LOAEL ~ 250 mg/kg bw/d), semichronic (NOAEL ~ 152 mg/kg bw/d) and the two 1-year studies (NOAELs ~ 62.5 mg/kg bw/d and 125 mg/kg bw/d) it is concluded that the nature and severity of the effects most likely will not increase with longer duration of exposure. Therefore, for extrapolation from semichronic to chronic occupational exposure an assessment factor of 1 is introduced. However, because of the limitations in the subacute oral toxicity study, a factor 10 is introduced for extrapolation from subacute to semichronic exposure

Table E.3 Assessment factors applied for the calculation of the minimal MOS for local effects after chronic inhalation exposure based on a 28-day inhalation toxicity study

Aspect	Assessment factors
Interspecies differences	3 a)
Intraspecies differences	3
Differences between experimental conditions and exposure pattern of the worker	1 b)
Type of critical effect	1
Dose-response curve	1
Confidence of the database	3 c)
Overall	27

a) Because an inhalation study is used a factor for allometric scaling is not necessary, and a factor 3 is applicable
b) A factor for extrapolation of exposure duration is not considered necessary since it is assumed that exposure duration will only have influence on the severity of the effects and not on the level of toxicity
c) A factor 3 is introduced for the extrapolation of a LOAEC to a NOAEC

Table E.4 Assessment factors applied for the calculation of minimal MOS for reproduction effects after chronic dermal exposure based on a 2-generation toxicity study in rats

Aspect	Assessment factors
Interspecies differences 1)	4 · 3
Intraspecies differences	3
Differences between experimental conditions and exposure pattern of the worker	1
Type of critical effect	1
Dose-response curve 2)	2
Confidence of the database	1
Route-to-route extrapolation 3)	0.1
Minimal MOS	7.2

1) Adjustment via caloric demands together with an uncertainty factor for remaining interspecies differences
2) A factor 2 is considered applicable for extrapolation form LOAEL to NAEL
3) For route-to-route extrapolation a correction for differences in absorption is necessary. The dermal absorption is 10% and the oral absorption 90%, therefore a factor 0.1 is introduced

Table E.5 Assessment factors applied for the calculation of minimal MOS for reproduction effects after chronic inhalation exposure based on a 2-generation toxicity study in rats

Aspect	Assessment factors
Interspecies differences [1)]	4 · 3
Intraspecies differences	3
Differences between experimental conditions and exposure pattern of the worker	1
Type of critical effect	1
Dose-response curve [2)]	2
Confidence of the database	1
Rout-to-route extrapolation [3)]	1.1
Minimal MOS	80

1) Adjustment via caloric demands together with an uncertainty factor for remaining interspecies differences
2) A factor 2 is considered applicable for extrapolation form LOAEL to NAEL
3) For route-to-route extrapolation a correction for differences in absorption is necessary. The inhalation absorption is 100% and the oral absorption 90%, therefore a factor 1.1 is introduced

European Commission

EUR 19840 EN **European Union Risk Assessment Report dibutyl phthalate, Volume 29**

Editors: B.G. Hansen, S.J. Munn, R. Allanou, F. Berthault, J. de Bruijn, M. Luotamo, C. Musset, S. Pakalin, G. Pellegrini, S. Scheer, S. Vegro.

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The report provides the comprehensive risk assessment of the substance dibutyl phthalate. It has been prepared by The Netherlands 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 dibutyl phthalate concludes that there is a need for further information to adequately characterise the risks to plants exposed via the atmosphere.

The human health risk assessment for dibutyl phthalate concludes that there is at present concern for workers, and no concern for consumers and humans exposed via the environment.

The conclusions of this report will lead to risk reduction measures to be proposed by the Commissions committee on risk reduction strategies set up in support of Council Regulation (EEC) N. 793/93.

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