DIPHENYLAMINE

CAS No: 122-39-4

EINECS No: 204-539-4

SUMMARY RISK ASSESSMENT REPORT

Final report, 2008

Germany

FINAL APPROVED VERSION

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PREFACE

This report provides a summary, with conclusions, of the risk assessment report of the substance diphenylamine that has been prepared by Germany in the context of Council Regulation (EEC) No. 793/93 on the evaluation and control of existing substances.

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) that can be obtained from the European Chemicals Bureau[1]. The Final RAR should be used for citation purposes rather than this present Summary Report.

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

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TABLES

1 GENERAL SUBSTANCE INFORMATION

1.1 IDENTIFICATION OF THE SUBSTANCE

CAS Number: 122-39-4

EINECS Number: 204-539-4

IUPAC Name: Diphenylamine

Synonyms: Benzenamine, N-phenyl-

Diphenylamin

Anilinobenzene

Benzene, (phenylamino)-

N,N-diphenylamine

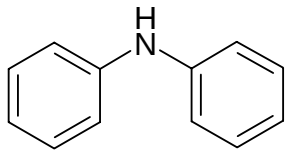
N-Phenylaniline

N-Phenylbenzenamine

Molecular weight: 169 g/mol

Molecular formula: $C_{12}\ H_{11}\ N$

Structural formula:



1.2 PURITY/IMPURITIES, ADDITIVES

Purity: > 99.2 %

Impurities: ≤ 0.03% Aniline
≤ 0.02 % 4-Aminodiphenyl

1.3 PHYSICO-CHEMICAL PROPERTIES

Diphenylamine is a colourless solid (at room temperature and normal pressure) with a floral odour. Data on the physical and chemical properties are given in Table 1.1.

Table 1.1 Summary of physico-chemical properties

Melting point	53 °C [1)]
Boiling point	302 °C
Relative density	1.159
Vapour pressure	0.033 Pa at 20 °C [2)]
Surface tension	72.3 mN/m at 20 °C (saturated solution) [3)]
Water solubility	40 mg/l at 25 °C
Partition coefficient	LogPow 3.4 [4)]
Flash point	not determined
Auto flammability	no self-ignition up to the melting point (53 °C)
Flammability	not flammable [5)]
Explosive properties	no explosive properties [6)]
Oxidizing properties	no oxidizing properties [6)]

1.4 CLASSIFICATION

- (Classification according to Annex I)

Classification and labelling according to the 22nd ATP of Directive 67/548/EEC

T	Toxic
R 23/24/25	Toxic by inhalation, in contact with skin and if swallowed
R 33	Danger of cumulative effects
N	Dangerous to the environment
R 50/53	Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment

- (Proposal of the rapporteur)

Environment

According to the data presented below and the criteria of Directive 93/21/EEC, the Annex I entry is confirmed with respect to the Environment:

N	Dangerous to the environment
R 50/53	Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment

Human Health

Xn, Xi	Harmful
R 22	Harmful if swallowed
R 41	Risk of serious damage to eyes

Remarks

Studies confirming the existing classification with T, R23/24/25 and R33 are not available.

Data on eye irritating properties of the substance are conflicting and poorly documented, but it may be assumed that diphenylamine may pose a risk of serious damage to eyes. There exist two guideline-compliant studies which both report severe eye irritation caused by diphenylamine. In one of these studies irreversibility of effects after 21 days is stated. Hence, appropriate labelling with R41 "Risk of serious damage to eyes" is proposed.

2 GENERAL INFORMATION ON EXPOSURE

Production

In the EU 15 four companies informed on HPV scale production or import of Diphenylamine during the 1990s but they have announced to have stopped the activity. For 1998 a total EU production capacity of 18 000 t/a and a production volume of 12 000 t/a was predicted. Imports were expected to be 1 500 t/a and exports outside the EU 3 500 t/a.

Based on Srour (1994) and the tonnage indicated in IUCLID for years 1992-1993, a total EU market volume of approx. 10 000 t/a (~ 9 000 t/a production + ~ 1 000 t/a imports) is assumed for the risk assessment. Spin database (2003) indicates a total use volume of ca. 50 t/a in years 2000-2001 and 17 t/a for 2005 for the Nordic countries (FIN, S, NO, DK).

The production and import volume which was reported by the Industry participating in the risk assessment during 1998-2003 was in the range of 5000 t/a.

Industry has indicated that a plant in Slovak Republic is producing Diphenylamine. The production volume is in the range from 10000-20000 t/a. In 2003 no export of Diphenylamine from the Slovak Republic to the EU was reported.

Uses

According to Industry, most of Diphenylamine is used as a chemical intermediate and only a minor amount as additive in final products.

Main used of Diphenylamine as intermediate:

-Antioxidants: Diphenylamine can be alkylated nucleophilic with acetone or alkenes to antioxidants widely used in the rubber industry and for lubricants.

-Antiozonants: Diphenylamine nitrosation followed by reductive alkylation with ketones gives antiozonants from the p-phenylendiamine-type used in the rubber industry

-Phenothiazine: Chemical reaction of Diphenylamine with sulphur gives phenothiazine used as stabiliser for plastics.

-Dyestuffs: After chemical reaction several dyestuffs can be prepared.

3 ENVIRONMENT

3.1 ENVIRONMENTAL EXPOSURE

Environmental releases

Releases of Diphenylamine to the environment are expected to occur mainly in chemical industry during production, formulation of heating oil, lubricant additive and plant protection product and processing (use as intermediate). In addition, professional use of Diphenylamine in lubricant oils and as storage aid (plant protection product) cause releases. Diphenylamine is also released from private use of heating oil and unintentionally from consumption of fruits, which are treated with storage aid containing Diphenylamine.

According to the physical-chemical properties of PTBBA, the substance will mainly be released to water and air, whereas releases into soil via sludge application are negligible.

According to industry, the polymerisation process of resins where PTBBA is used as chain stop agent is not causing environmental releases. According to a customer, any resulting waste water or waste from the process and cleaning operations is incinerated

Environmental fate

Based on the molecular structure hydrolysis of Diphenylamine is not expected under environmental conditions.

The quantum yield of the direct photodegradation of Diphenylamine in water showed to be 0.093 with polychromatic light. From this value a half-life of 1.9 h in summer and 33.1 h in winter are calculated (50 degree of latitude, clear sky, clean water near the surface, values integrated over the whole day. Assuming a daily sunlight period of 12 h an overall mean half-life of 1.46 d results.

In most natural water bodies, the rate of photoreaction is affected by dissolved and suspended matter. Using the standard parameters of the regional model (water depth, suspended matter concentration), the reduction in the light intensity may be as large as 98 %. Assuming an even distribution of the substance in the water phase according to the Mackay-type fugacity models only a small part of Diphenylamine in the upper layer of the surface water is available for photolysis in water.

The atmospheric degradation by OH radicals of 1.87 for a k_{OH} of $2 * 10^{-10}$ $cm^3*molec^{-1}*s^{-1}$ (half-life of 1.93 h) is calculated using the QSAR-model package PropertEst version 1.3 including AOPWIN version 1.87.

From the spectroscopic data available for Diphenylamine, direct photolysis in atmosphere is not to be expected.

Using non adapted inocula, mineralisation of Diphenylamine was achieved only up to approx. 25 %. According to Technical Guidance Document, the substance has to be regarded as not readily biodegradable. Furthermore, currently Diphenylamine cannot be considered as inherently biodegradable in spite of the fact that extensive primary degradation of Diphenylamine especially by communities of adapted micro-organisms has been

demonstrated several times. The result of the Mod. MITI (II) Test (Murin et al., 1997) resulted in a degradation of only 38 % but may have been influenced by toxic effects as the substance concentration in this test was 30 mg/l. A test on inhibition of respiration according to OECD 209 showed an EC_{50} of 18.7 mg/l.

The Henry's law constant of 0.139 Pa * m^3/mol calculated from the physico-chemical properties indicates that Diphenylamine is moderately volatile from water.

In the Technical Guidance Document an equation for the calculation of K_{OC} of anilines using $logK_{OW}$ is provided. On this basis, a KOC of 907.8 l/kg was estimated. This K_{OC} indicates a moderate sorption potential.

Diphenylamine shows a moderate to high bioconcentration factor. BCF_{fish}-values up to 253 are reported

Environmental concentrations

The calculation of exposure for the local scenarios developed on the basis of major uses and production was conducted with EUSES using generic values and models presented in the Technical Guidance Document for the only known (closed in 2001) production site and the only known processing site, specific scenarios have been calculated using the data provided.

PEC – aquatic compartment (incl. sediment)

A **$Clocal_{water}$ of 89.8 µg/l** and a **$PEC_{stp,micro-organisms}$ of 3.59 mg/l** for the only known (closed in 2001) European production site has been estimated.

On the basis of information from Industry, it is assumed that there are no production sites with additional processing capacities. A generic $Clocal_{water}$ for production of Diphenylamine was calculated (EUSES use pattern 2). Based on the information from former and present producers and the information presented in Chapter 2.1, it is assumed, that a typical plant has a production volume of 5000 t/a. In the following, the major parameters for the calculation are given:

Emission factor (Table A 1.2; waste water):	0.003
Emission factor (Table A 1.2; surface water):	0
No. of days (Table B 1.6):	300
Fraction directed to surface water from stp:	0.896

The emission scenario document for IC 3 gives a wwtp effluent of 10 000 m^3/d and a dilution factor of 1:40, a **$Clocal_{water}$ of 0.112 mg/l** and **$PEC_{stp,micro-organisms}$ of 4.48 mg/l** result (for calculation details, see Appendix A; production was included in the use pattern 2).

At present, one processing site only using Diphenylamine as intermediate is known (see also chapter 2.1). The processing site has delivered measured data on emissions to water, on which basis a specific local scenario has been developed. A **$Clocal_{water}$ of 62.1 µg/l** and a **$PEC_{stp,micro-organisms}$ of 2.49 mg/l** have been estimated.

Due to the sorption potential of Diphenylamine, an assessment of the compartment sediment seems to be necessary. The concentrations in sediments of each local scenario were calculated applying the equilibrium partitioning method of the Technical Guidance Document (eq. 50).

For the calculation, the regional PEC_{water} of 0.79 µg/l was added to the $Clocal_{water}$ –values given in chapter 3.1.2. to first obtain the local PEC_{water} –values for input into the equation 50. The $K_{susp-water}$ of 23.4 m^3/m^3 was applied. The results are listed in the following.

Production (site specific): $PEC_{sediment}$ = 1.84 mg/kg wwt

Production: $PEC_{sediment}$ = 2.31 mg/kg wwt

Formulation of lubricant: $PEC_{sediment}$ = 0.32 mg/kg wwt

Formulation of storage aid: $PEC_{sediment}$ = 1.24 mg/kg wwt

Processing (intermediate, site specific) $PEC_{sediment}$ = 1.28 mg/kg wwt

Processing (intermediate use): $PEC_{sediment}$ = 4.29 mg/kg wwt

Professional use of lubricant (processing): $PEC_{sediment}$ = 8.99 mg/kg wwt

PECs – Terrestrial compartment

Atmospheric deposition to soil according to site specific local releases are of an order of magnitude of 10^{-5} to 10^{-4} mg/m^2*d. The deposition around the sites is of minor importance for local Diphenylamine concentrations in soil. Application of sludge onto soils around the largest sites does not occur, but sludge is either deposited into an industrial landfill or incinerated. However, many of the industrial sites considered in this risk assessment at generic level (e.g., lubricant processing) may be connected to municipal sewage treatment plants. No information on how sludge is handled was received from industry. Therefore, soil concentrations around all generic sites except production and intermediate processing (which are assumed to have their own biological treatment plants) are calculated taking into account both the application of sludge and deposition. For the generic and site specific production and intermediate processing sites deposition is assumed to be the only input path.

Production (site specific) C_{soil} = $1.7 * 10^{-3}$ mg/kg wwt

$C_{agr,soil}$ = $1.7 * 10^{-3}$ mg/kg wwt

$C_{grassland}$ = $2.8 * 10^{-3}$ mg/kg wwt

Production: C_{soil} = $3.8 * 10^{-4}$ mg/kg wwt

$C_{agr,soil}$ = $3.8 * 10^{-4}$ mg/kg wwt

$C_{grassland}$ = $6.4 * 10^{-4}$ mg/kg wwt

Formulation of lubricant: C_{soil} = 0.53 mg/kg wwt

$C_{agr,soil}$ = 0.53 mg/kg wwt

$C_{grassland}$ = 0.18 mg/kg wwt

Formulation of storage aid: C_{soil} = 2.13 mg/kg wwt

$C_{agr,soil}$ = 2.12 mg/kg wwt

$C_{grassland}$ = 0.72 mg/kg wwt

Processing (intermediate; site specific): C_{soil} = $2.5 * 10^{-4}$ mg/kg wwt

$C_{agr,soil}$ = $2.6 * 10^{-4}$ mg/kg wwt

$C_{grassland}$ = $4.3 * 10^{-4}$ mg/kg wwt

Processing (intermediate use): C_{soil} = $7.0 * 10^{-4}$ mg/kg wwt

$C_{agr,soil}$ = $7.1 * 10^{-4}$ mg/kg wwt

$C_{grassland}$ = $1.19 * 10^{-3}$ mg/kg wwt

Professional use of lubricant (processing): C_{soil} = 15.6 mg/kg wwt

$C_{agr,soil}$ = 15.5 mg/kg wwt

$C_{grassland}$ = 5.3 mg/kg wwt

Concentration in groundwater equals according to the Technical Guidance Document the concentration in soil porewater. PEC for groundwater under agricultural soil is calculated with EUSES (Eq. 67 of TGD) for further use in chapter 4.1. The $K_{soil\text{-}water}$ of 27.4 was applied for the calculation. Contribution of the ambient regional background concentration, which is only affected by deposition, is negligible (although included in calculation). The results are as follows.

Production (site specific): $PEC_{agr.soil,porew}$ = $1.05 * 10^{-4}$ mg/l

Production: $PEC_{agr.soil,porew}$ = $2.4 * 10^{-5}$ mg/l

Formulation of lubricant: $PEC_{agr.soil,porew}$ = 0.033 mg/l

Formulation of storage aid: $PEC_{agr.soil,porew}$ = 0.131 mg/l

Processing (intermediate; site specific) $PEC_{agr.soil,porew}$ = $1.6 * 10^{-5}$ mg/l

Processing (intermediate use): $PEC_{agr.soil,porew}$ = $4.5 * 10^{-5}$ mg/l

Professional use of lubricant (processing): $PEC_{agr.soil,porew}$ = 0.961 mg/l

PEC - Atmosphere

Concentrations in air were predicted according to Technical Guidance Document using EUSES for those scenarios where direct emissions to air are assumed to occur as default. Table 3.5 lists the resulting annual average concentrations in air and annual deposition fluxes.

Since the regional PEC_{air} = $2*10^{-8}$ mg/m^3, the Clocal –values are approximately equal to PECs.

Regional and continental predicted environmental concentrations

The predicted environmental concentrations as calculated by EUSES with the emissions given above are presented in Table 3.1.

Table 3.1: Regional and continental predicted environmental concentrations.

	Concentration		**Concentration**	**Unit**
$PECcont_{water}$	$1.3 * 10^{-4}$	$PECregional_{water}$	$7.85 * 10^{-4}$	mg/l
$PECcont_{sediment}$	$3.46 * 10^{-3}$	$PECregional_{sediment}$	0.0198	mg/kg wwt
$PECcont_{air}$	$3.29 * 10^{-9}$	$PECregional_{air}$	$1.94 * 10^{-8}$	mg/m3
$PECcont_{agrsoil}$	$9.92 * 10^{-4}$	$PECregional_{agrsoil}$	0.0116	mg/kg wwt
$PECcont_{agrsoilporew}$	$6.15 * 10^{-5}$	$PECregional_{agrsoilporew}$	$7.21 * 10^{-4}$	mg/l
$PECcont_{natsoil}$	$1.76 * 10^{-6}$	$PECregional_{natsoil}$	$1.04 * 10^{-5}$	mg/kg wwt

Secondary poisoning

Diphenylamine is moderately bioconcentrating in fish (BCF_{fish} of 155). On the basis of mammalian toxicity data Diphenylamine is classified as toxic. Therefore, an assessment of secondary poisoning is carried out.

For Diphenylamine, the biomagnification factor BMF is 1 according to the Technical Guidance Document. $PEC_{oral,predator}$ is based on the average PEC_{water}s (given as annual averages) of the regional and local scenario (this equals to the assumption that 50 % of food is acquired from the local recipient and 50 % from the region). Table 3.2 presents the resulting $PEC_{oral,predator}$ -values for the generic local scenarios.

Table 3.2. Results for $PEC_{oral,predator}$ for aquatic food chain.

Scenario	**$PEC_{oral,predator}$(mg/kg)**
Production (site specific)	5.78
Production	7.24
Formulation of lubricant	1.07
Formulation of storage aid	3.92
Processing (intermediate; site specific)	4.01
Processing (intermediate use)	13.4

Professional use of lubricant (processing)	4.28

Exposure of birds or mammals via terrestrial food-chain soil → earthworm → worm-eating birds or mammals is derived according to the TGD Eqs. 80-82. $BCF_{earthworm}$ of 31 has been estimated. It is assumed that the predator acquires 50 % of its pray from a local environment (local PECagr,soil applied) and 50 % from the region (regional PECagr,soil applied).

Table 3.3. Results for $PEC_{oral,predator}$ for terrestrial food chain.

Scenario	**$PEC_{oral,predator}$(mg/kg)**
Production (site specific)	0.012
Production	0.010
Formulation of lubricant	0.488
Formulation of storage aid	1.908
Processing (intermediate; site specific)	0.011
Processing (intermediate use)	0.011
Professional use of lubricant (processing)	13.929

3.2 EFFECTS ASSESSMENT

Aquatic compartment (incl. sediment)

Results from acute toxicity tests with species from 3 trophic levels are available. The most sensitive fish from standard tests is Oryzias latipes (EC_{50} = 2.2 mg/l). The lowest EC_{50} for Daphnia magna is 0.31 mg/l and for algae 1.5 mg/l (Scenedesmus subspicatus).

Reliable long-term NOECs are available for invertebrates (Daphnia magna) and several algae species.

For fish and other vertebrates only prolonged tests results are available which are not regarded as long-term tests and which are difficult to evaluate (transient change in behaviour).

Thus, the assessment factor is set at 50 for the aquatic compartment as data from valid long-term tests on 2 trophic levels are available. The lowest no effect concentration is determined for Scenedesmus subspicatus with a 72h-EC_{10}/ NOEC of 0.06 mg/l.

The $PNEC_{aqua}$ is calculated as follows:

$PNEC_{aqua}$ = 60 µg/l : 50 = 1.2 µg/l

The lowest effect data for organisms important to WWTPs is given for activated sludge (EC50 = 18.7 mg/l).

According to Technical Guidance Document an assessment factor of 100 is applied.

$PNEC_{wwtp}$ = 18.7 mg/l / 100 = **0.187 mg/l**

No information on toxic effects in sediment dwelling animals or benthic macroflora is available. However, in view of the high toxicity of Diphenylamine to a broad spectrum of taxa covering all trophic levels, the slow microbial degradation, the (calculated) suspension-water partitioning coefficient, and the maximum concentrations estimated from $Clocal_{water}$ values, a provisional $PNEC_{sediment}$ is derived.

$PNEC_{sediment}$ = **0.0246 mg/kg** (wet weight)

Terrestrial compartment

The only tested organism has been Eisenia fetida with a 14 d LC_{50} of 62.8 mg/kg wet weight.

With an assessment factor of 1 000 according to Technical Guidance Document, the resulting PNEC comes to

$PNEC_{soil}$ = 62.8 mg/kg / 1 000 **= 62.8 µg/kg wwt.**

According to the Technical Guidance Document, the risk assessment has to be performed additionally on the basis of the equilibrium partition method if only one test result with soil dwelling organisms is available. Subsequently, the lowest $PNEC_{soil}$ calculated is chosen for $PEC/PNEC_{soil}$ ratios in risk characterisation.

Application of the equation (72) of the Technical Guidance Document results

$$PNEC_{soil} = \frac{K_{soil\text{-}water} \times PNEC_{water} \times 1\,000}{RHOsoil}$$

$$\mathbf{PNEC_{soil}} = \frac{27.4 \times 0.0012 \text{ mg/l} \times 1\,000}{1\,700 \text{ kg/m}^3} = \mathbf{19.3\ \mu g/kg\ wwt.}$$

From these calculations follows that the latter value for PNECsoil is to be considered in risk characterisation.

Atmosphere

No ecotoxicological data are available for this environmental compartment.

3.3 RISK CHARACTERISATION

Aquatic compartment (incl. sediment)

Risk ratios derived are given in Table 3.5. The $PNEC_{stp,micro\text{-}organisms}$ is 187 µg/l.

Table 3.4: Risk ratios for waste water treatment plant

Scenario	**$PEC_{stp,micro\text{-}organisms}$ (µg/l)**	**PEC:PNEC**
Production (site specific)	$3.59 * 10^3$	19*
Production	$2.2 * 10^3$	12*
Formulation of lubricant	149	0.8
Formulation of storage aid	598	3
Processing (intermediate; site specific)	$2.49 * 10^3$	13
Processing (intermediate use)	$42 * 10^3$	225
Professional use of lubricant (processing)	$4.38 * 10^3$	23

* Production closed in the EU 15

$PNEC_{aqua}$ of 1.2 µg/l has been estimated. The risk ratios for the **regional environment** are as follows. Surface water: $PECreg_{water}$: $PNEC_{aqua}$ = 0.8 µg/l : 1.2 µg/l = **0.5** . For sediment, both the $PECreg_{sediment}$ and the $PNEC_{sediment}$ were derived using equilibrium partitioning approach from corresponding values for surface water and thus the same risk ratio as for surface water results. Table 3.5 shows the risk ratios for the local scenarios.

Table 3.5: Aquatic risk characterisation for the local scenarios

Scenario	**$PEClocal_{water}$ (µg/l)**	**$PEClocal_{water}$:$PNEC_{aqua}$**
Production (site specific)	90.6	26 *
Production	113	94 *
Formulation of storage aid	59.7	50
Formulation of lubricant	14.9	13
Processing (intermediate; site specific)	62.9	52
Processing (intermediate use)	209	174
Professional use of lubricant (processing)	437	365

* Production closed in the EU 15

Since both PEClocal- and PNEC-values for sediment are derived from aquatic values using the equilibrium partitioning method, the risk ratios for sediment in local scenarios are equal to risk ratios for water.

Terrestrial compartment

PNECsoil of 19.3 mg/kg wwt has been estimated. With the $PECregional_{agr,soil}$ of 11.6 µg/kg wwt , a PEC:PNEC of 0.6 results. Table 3.6 presents the risk characterisation ratios for the local scenarios.

Table 3.6: Risk characterisation for agricultural soil.

Scenario	**PEC:PNEC**
Production (site specific)	$1 * 10^{-4}$ (* (**
Production	$3 * 10^{-5}$ (* (**

Formulation of lubricant	27
Formulation of storage aid	110
Processing (intermediate; site specific)	$2 * 10^{-5}$ (*
Processing (intermediate use)	$6 * 10^{-5}$ (*
Professional use of lubricant (processing)	803

(* PECgrassland has been used for deriving the PEC:PNEC –ratio. It is the highest of the PECs for soil when no sludge application occurs.

(** Production closed in the EU 15

Secondary poisoning

$PNEC_{oral}$ of 4.47 mg/kg has been derived. Table 3.7 shows the RCRs for the secondary poisoning route for the aquatic food chain and Table 3.7 for earthworm-based food chain.

Table 3.7: Risk assessment – secondary poisoning for the aquatic food chain.

Scenario	**$PEC_{oral,predator}$ (mg/kg)**	**PEC/PNEC-ratio**
Production (site specific)	5.78	1.3 *
Production	7.24	1.6 *
Formulation of lubricant	1.07	0.2
Formulation of storage aid	3.92	0.9
Processing (intermediate; site specific)	4.01	0.9
Processing (intermediate use)	13.4	3
Professional use of lubricant (processing)	4.28	0.96

* Production closed in the EU 15

Table 3.8: Risk assessment – secondary poisoning for the terrestrial food chain.

Scenario	**$PEC_{oral,predator}$ (mg/kg)**	**PEC/PNEC-ratio**
Production (site specific)	0.012	0.003 *
Production	0.011	0.002 *
Formulation of lubricant	0.488	0.1
Formulation of storage aid	1.908	0.4
Processing (intermediate; site specific)	0.011	0.002
Processing (intermediate use)	0.011	0.002
Professional use of lubricant (processing)	13.929	3.12

* Production closed in the EU 15

4 HUMAN HEALTH

4.1 HUMAN HEALTH (TOXICITY0

4.1.1 Exposure assessment

Occupational exposure

Diphenylamine is an important intermediate for the production of antioxidants, antiozonants, phenothiazine, dyes and other products (approximately 97.5% of the total EU quantity). The EU market volume is about 10 000 t/a.

Diphenylamine is also used as the active substance in storage aid in the post harvest treatment. It is registered at present as a component of plant protection products in Ireland, U.K., France, Spain, Portugal, Italy and Greece. There are no preparations containing diphenylamine permitted for application as storage aid for food produced in Germany. Two companies have notified diphenylamine under the Council Directive concerning placing plant protection products on the market 91/414/EEC ("PPP-Directive"), so assessment in this framework may not be necessary.

According to industry, a small amount of diphenylamine is used in lubricant oils in a concentration of 1 %. There is contradicting information regarding to whether diphenylamine is merely an impurity in alkylated diphenylamine antioxidants for lubricant oils, or whether it is as itself used as a primary constituent. The Nordic Product Register SPIN and the Finnish Product Register show that altogether 3.3 t/a are presently registered for lubricants. The products in the Finnish Product Register contain < 1 % diphenylamine.

Detailed information on the production volumes and the use is given in chapter 2.

The following national occupational limits (8h TWA, Ariel, 2007) are given. The limits in Belgium, France, Greece, Ireland, Italy, Portugal, Spain, Switzerland, United Kingdom and USA amounts to 10 mg/m^3, in Austria, Denmark, Iceland, Finland and Norway amounts to 5 mg/m^3, in Sweden to 4 mg/m^3 and in The Netherlands amounts to 0.7 mg/m^3.

The exposure assessment is based on measured data and literature data, expert judgement and estimations according to the EASE model (Estimation and Assessment of Substance Exposure). The exposure levels should be regarded as reasonable worst case estimates representing the highly exposed workers.

Relevant occupational exposure scenarios are to be expected in the following areas:

- Production of diphenylamine and further processing
- Use of lubricants

Diphenylamine is a colourless solid (vapour pressure 0.03 Pa at room temperature).

For the large-scale chemical industry, it is assumed that the production and further processing of diphenylamine is mainly performed in closed systems. Exposure occurs if the closed system is breached. Diphenylamine is produced in two forms for selling: as flakes and as a

liquid. Measurement values regarding the production of diphenylamine as liquid and as flakes were provided. Since the industry provided only limited information to the measurement values, model estimates were performed additionally. Dermal contact with the liquid substance is limited because the substance is handled at temperatures above 60°C. For handling diphenylamine-flakes, the use of suitable gloves is considered leading to reduced dermal exposure.

Based on information available from industry, it is assumed, that 50 t/a diphenylamine are used in lubricant oils in a concentration of 1 %. Industry has not provided any specific information on the uses of lubricant oils. According to the Nordic and The Finnish Product Register, the substance is used in the classes 'Sale, maintenance and repair of motor vehicles and motorcycles; Retail sale of automotive fuel' and 'Manufacture of machinery and equipment'. The term "lubricant" applies to products based predominantly on mineral oils or on synthetic oils, which are intended as lubricants, power and heat transmission media, engine and process oils, and metal working fluids. Metal working fluids are applied by continuous jet, spray, mist or by hand dispenser. Inhalable aerosols can be generated during machine operations. For activities without the formation of aerosols the inhalation exposure to diphenylamine is considered to be negligible (vapour pressure: 0.03 Pa). Skin contact occurs during preparation or draining of the fluids, handling workpieces, from splashes during machining, changing and setting of tools and during maintenance and cleaning activities.

Summary of exposure data

All values are seen to represent the reasonable worst case situation.

Table 4.1: Summary of exposure data

Exposure scenario	Duration and frequency of activities relevant for exposure	Inhalation exposure Shift average [mg/m3]	Dermal exposure Shift average [mg/p/day]
1. Production of diphenylamine and further processing	shift length, daily	1.0 (EASE, workplace measurements)	21 [1)] (suitable gloves)
2. Use of lubricants, metal working fluids (with 1% diphenylamine)	shift length, daily	0.02 (analogous data)	126 (EASE, without gloves)

[1)] Dermal contacts with the liquid substance are avoided, because of the temperature of 60 °C. For suitable gloves a protection efficiency of 90 % is taken into consideration.

Consumer exposure

There are no measured data on exposure to humans available. It can be assumed that the exposure of consumers to diphenylamine is primarily due to oral exposure from eating fruits and other vegetable foods which are treated with diphenylamine. This exposure can lead up to an intake of 0.0122 mg/kg bw/d for a female adult (age 55 - 64, average body weight approximately 68 kg). Children (age 2-5 years, body weight 16.5 kg) would be exposed to an amount of 0.0677 mg/kg bw/d.

Dermal exposure of consumers is possible by the use of lubricants. An external dermal exposure of 0.7 mg/kg bw/d is estimated assuming a body weight of 60 kg.

Dermal exposure of consumers may occur during the use of lubricants which contain small amounts of unreacted diphenylamine. Two such products with concentrations of <0.1 % and 0.23 % diphenylamine, respectively, are notified in the BfR data base (BfR, 2005). The amount of diphenylamine on skin per day due to use of lubricants can reach a value up to ~ 42 mg, thus resulting in an external dermal exposure of 0.7 mg/kg bw/d assuming a body weight of 60 kg. The use of artist paint containing trace amounts of diphenylamine (<0.01 %) is considered to be negligible for the risk assessment.

Oral exposure of consumers may occur through the consumption of foods preserved with diphenylamine containing fungicides. The European Union has set maximum residue limits (MRLs) for diphenylamine in its specific legislation (Commission Directive 2000/57/EWG). The MRLs are 5 mg/kg for apples, 10 mg/kg for pears, and 0.05 mg/kg for all other commodities. Using these values and the available figures for average food consumption, the maximum oral intake of diphenylamine can be calculated as 0.0677 mg/kg bw/d for children, age 2-5, average body weight 16.5 kg, and as ≈ 0.0122 mg/kg bw/d for adult women, age 55-64, average body weight approximately 68 kg, who are the adult subpopulation with the highest fruit consumption.

Considering the low vapour pressure of the substance (0.033 Pa at 20 °C), inhalation exposure can be neglected.

Humans exposed via the environment

Releases of DPA into the environment following production, formulation and processing were calculated in chapter 3. As stated there is only limited information for the current situation available.
The indirect exposure of humans via environment, i.e. through food, drinking water and air is considered to be low. The regional total daily intake is 0.5 µg kg^{-1} d^{-1}.

Combined exposure

4.1.2 Effects assessment

Toxicokinetics, metabolism and distribution

Orally administered diphenylamine is well absorbed from the gastrointestinal tract in man and in several animal species including rat, rabbit, dog and cow. Up to 3 % of the parent compound and approximately 80-90 % of the dose is excreted as 12 different metabolites, which include 4-hydroxydiphenylamine, 4,4'- 2 hydroxydiphenylamine and sulfate and glucuronide conjugates of these hydroxylated metabolites. In addition, indophenol has been identified as metabolite. N-hydroxylated metabolites responsible for methaemoglobinemia in aromatic amines could not be detemined. From these results it can be assumed that diphenylamine is readily metabolized and excreted and that accumulation seems to be unlikely. There are no data on dermal route of administration or exposure by inhalation. An absorption rate of 100% for the oral route is proposed to be taken for risk characterisation purposes, whereas dermal and inhalation absorption is assumed to be 100% (defaults). The assumption of a default dermal absorption value of 100% is supported by the physicochemical properties of DPA (molecular weight: 169 g/mol; log Pow 3.4; water solubility: 40 mg/l). Due to the potential for absorption and the lack of experimental data, a default absorption value of 100% is also assumed for inhalative uptake.

Acute toxicity

Human data on the acute toxicity of diphenylamine are not available. An oral LD50 value of approximately 600 mg/kg bw/d was detected for male Syrian hamsters. Oral LD50 values exceeding 800 mg/kg bw/d were determined for rats and male Mongolian gerbils. Dermal LD50 values of >2000 mg/kg bw/d are reported for rabbits and of >5000 mg/kg bw/d for rats. Data on acute inhalation toxicity are not available. Based on this information, diphenylamine is to be classified as harmful and labelled with R 22, harmful if swallowed; it is not to be labelled because of acute dermal toxicity. For the assessment of acute inhalation toxicity an animal study according to current EU or OECD guidelines is lacking.

Irritation and corrosivity

Human data on the local irritant or corrosive properties of diphenylamine are not available. The substance caused no or only very slight skin irritation in tests with rabbits. Data of eye irritating properties of the substance are conflicting and poorly documented, but it can be assumed that diphenylamine may pose a risk of serious damage to eyes. There exist two studies (one with documented guideline-compliance), which both report severe eye irritation caused by diphenylamine. In one of these studies irreversibility of effects after 21 days is stated. Hence, appropriate labelling with R41 "Risk of serious damage to eyes" is proposed. All studies on dermal effects demonstrated only a weak skin irritation potential. Hence, diphenylamine is not a corrosive substance.

Sensitisation

Diphenylamine did not produce dermal sensitization in guinea pigs. There is one case of one woman where a contact allergy could be demonstrated. Other studies with 11 or 1012 patients did not demonstrate a skin sensitization that could be attributed to diphenylamine. Cross sensitization to p-phenylenediamine has not been demonstrated in the woman who reacted positive to diphenylamine. In a maximization test carried out on 30 volunteers no sensitization reactions were produced. These data demonstrate that in humans the substance has a weak or no skin sensitising potential. Though the occurrence of cross reactions to p-phenylenediamine is rare, it should not be dismissed. However, based on the overall negative data on people exposed as consumers or as workers the risk phrase 43 - May cause sensitization by skin contact - is not warranted. In addition, in human volunteers the substance produced no contact allergy. Diphenylamine is not suspected to be a potent respiratory sensitiser.

Repeated dose toxicity

From subchronic studies of animals fed with a diet containing diphenylamine the most sensitive indication for toxicity seems to be haematological effects such as a slight anemia and formation of Heinz bodies. Heinz bodies are considered to be indicative for methaemoglobin formation. At higher doses diphenylamine cause kidney changes generally subscribed as polycystic kidney disease, accompanied with different stages of papillary necrosis and nephritis in different species. The only guideline conform 28 day test with oral gavage application revealed some minor weight changes on liver, spleen, and kidney as well as a slight degenerative change on renal tubulus cells in some animals. A clear NOAEL for rats could be demonstrated at 111 mg/kg bw/d for systemic effects under these experimental conditions.

In a JMPR report on diphenylamine more recent guideline conform repeated dose toxicity studies on mice and rats have been described. All of them underline haematotoxicity as the main toxic effect by diphenylamine. However, these studies are not available as original literature.

The primary target organs after long-term dietary exposure of animals to diphenylamine are the hematological system and the kidneys, spleen, and liver. Comparing the LOAELs from the different studies it becomes obvious that adverse effects in rats and dogs occurred at the same doses of about 25 mg/kg bw/d. Mice seem to be less sensitive according to the results from the new short- and long-term studies.

Taking together the data from all animal studies with repeated oral application, the value of 7.5 mg/kg bw/d was proposed as NOAEL for adverse effects after chronic exposure from a two-year carcinogenicity study in rats. This NOAEL is based on haematological and histological effects at dietary levels equal or greater than 25 mg/kg bw/d in female rats (LOAEL). This study was the basis for establishing the actual acceptable daily intake (ADI) of 0-0.08 mg/kg bw/d by the JMPR (1998), too.

The short report (abstract) of a study on formation of Heinz bodies in mice after a feeding period of 12 weeks at 7.5 mg/kg bw/d diphenylamine will not be taken forward for risk characterisation purposes on repeated dose toxicity.

A dermal study in rabbits lasting 21 days revealed dark-red foci in the stomachs of rabbits of each sex at the doses of 500 and 1000 mg/kg bw/d. A NOAEL of 100 mg/kg bw/d can be

derived from this study. After dermal application of diphenylamine to rats over a period of 90 days the NOAEL for systemic toxicity is 500 mg/kg bw/d based on an increase in the relative kidney weight of males at 1000 mg/kg bw/d. All treated animals exhibited dermal hyperplasia at the application side. Thus, the LOAEL for local effects from this study is 500 mg/kg bw/d, whereas no NOAEL could be derived. It is proposed to base risk characterisation for dermal exposure (systemic effects) on the NOAEL of 500 mg/kg bw/d from the 90-day study on rats.

Mutagenicity

Diphenylamine was negative in two Salmonella gene mutation tests. Further studies indicate that diphenylamine is not or only marginally genotoxic to mammalian cells in vitro. Negative results from an in vivo micronucleus test indicate that no mutagenic effects are expressed in vivo. In conclusion the whole amount of data indicates that diphenylamine may not be mutagenic in humans.

Carcinogenicity

In a report on diphenylamine based on recent guideline conform long-term investigations on mice and rats no evidence for increased tumor incidences was found. In a one year study in beagle dogs with bolus application neoplastic alterations could be not found, too. A number of older investigations using several strains of rats and mice and even dogs do not report any diphenylamine related neoplastic alterations. Survival rate and toxicity did not interfere with the interpretation concerning the endpoint tumor development. Since in these studies none neoplastic toxic effects have been clearly detected as being related to diphenylamine treatment, it could be suggested that signs of neoplastic proliferative activity would have become evident under these experimental conditions. In addition the majority of short term in vivo and in vitro tests equally do not show evidence for transforming activity of diphenylamine. The overall results support the assumption that there was no indication on carcinogenic effects to diphenylamine.

Toxicity for reproduction

There are no human data available on reproductive toxicity of diphenylamine. Data from investigations in laboratory animals are limited to studies with the oral route of administration. From the available data obtained from studies with rats it appears that impairment of reproductive capability and capacity is unlikely to occur from treatment with diphenylamine at dosages up to 131 mg/kg bw/d that do not interfere with food intake and body weight gain of the parental animals. From the available data obtained from two developmental studies in two species (rats and rabbits) any specific embryo-/fetotoxic or teratogenic potential is not indicated even at maternally toxic dosages. In a two generation study, no teratogenic effects were observed up to maternal oral doses of 448 mg/kg bw/ d. A NOAEL/developmental toxicity of 46 mg/kg bw/d was deduced based on a growth retardation in the F2 generation during late lactation at doses of 131 and 448 mg/kg bw/d. Maternal toxicity was observed at these doses with respect to reduced body weight, decrease in food consumption and pathological findings in spleen, kidney and liver. With respect to any nephrotoxic properties of diphenylamine developmental studies performed with rats did not reveal the induction of any renal lesions in the offspring. From the available animal data a NOAEL/fertility of 131 mg/kg bw/d, a NOAEL/developmental toxicity of 46 mg/kg bw/d and a LOAEL/developmental toxicity of 131 mg/kg bw/d is recommended for use for risk characterisation purposes.

4.1.3 Risk characterisation

Workers

Introduction to occupational risk assessment

This occupational risk assessment is based upon the toxicological profile of diphenylamine as described in chapter 4.1.2 and the results of the occupational exposure assessment (chapter 4.1.1). The threshold levels identified in the hazard assessment are taken forward to this occupational risk assessment.

For the majority of toxicological endpoints diphenylamine data originate from oral studies. Since workers are predominantly exposed either by inhalation or by skin contact, route to route transformation is an essential step in the occupational risk assessment.

Based on experimental and human data, an oral absorption percentage of 100% is taken forward to risk characterisation. There are no specific data on dermal absorption or by inhalation. Based on physical-chemical properties of diphenylamine the default for both pathways is 100% (see hazard assessment). However, comparing the adjusted experimental NOAELs it is evident that toxic potency of diphenylamine is considerably smaller for the dermal route of administration compared to the oral route. Using the broader concept of bioavailability (instead of absorption) a dermal bioavailability of about 5% (4.2%) is used, whereas for oral bioavailability a value of 100% is taken.

In the following table the occupational exposure scenarios are summarised and the route specific and total internal body burdens are identified. Risk assessment for combined exposure requires the calculation of a total internal body burden; to this end the derived route-specific percentages of bioavailability are used (100% for inhalation exposure and 4.2% for dermal exposure).

Table 4.2: Occupational exposure levels and internal body burden (diphenylamine)

Exposure scenario	Inhalation	Dermal contact		Internal body burden		
				Inhalation(1)	Dermal(2)	Combined
	mg/m^3	mg/p/d	mg/kg/d	mg/kg/d		
1. Production of diphenylamine and further processing	1.0	21	0.3	0.14	0.013	0.15
2. Use of lubricants, metal working fluids (with 1% diphenylamine)	0.02	126	1.8	0.003	0.076	0.08

(1) based on the assumption of 100% bioavailability by inhalation; breathing volume of 10 m^3 per shift and a body weight of 70 kg

(2) based on the assumption of 4.2% dermal bioavailability and a body weight of 70 kg

Calculation of MOS values

MOS values are calculated as quotient of a relevant NOAEL from experimental animal testing or human studies and actual workplace exposure levels. Scientifically based adjustment factors are used for the stepwise extrapolation of animal data to the worker population (e.g. adaptation of scenarios, route-to-route extrapolation, inter- and intraspecies extrapolation and duration adjustment). The multiplicative combination of these different factors yields the reference MOS value as a decision mark for concern. Reference MOS values may be different for each toxicological endpoint.

In a parallel procedure, which gives identical but more direct results, the adjusted toxicological starting point is directly divided by the reference MOS. As a result, an exposure level (in mg/m³ or mg/kg/d) is identified, which may serve as a direct trigger for decisions when compared with the occupational exposure levels. In the context of this risk assessment report this trigger value is called "critical exposure level". Concern will be expressed for scenarios with occupational exposure levels higher than the relevant "critical exposure level".

Acute Toxicity

Local effects see irritation, no further information available

systemic effects

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

Human data on the acute toxicity of diphenylamine are not available. Animal data show an oral LD50 value of approximately 600 mg/kg for male Syrian hamsters and oral LD50 values exceeding 2,000 mg/kg for rats and male Mongolian gerbils.

For rats, a dermal LD50 of greater than 5,000 mg/kg is reported. A dermal LD50 of greater than 2,000 mg/kg is described in a study with rabbits. No clinical signs were noted in the rabbit study. Acute dermal toxicity is less pronounced than acute oral toxicity.

Data on acute inhalation toxicity are not available.

Sublethal toxicity which occurs at lower doses is considered as a more rational starting point for acute toxicity than mortality data. For this risk assessment a developmental toxicity study with rats is taken. Maternal toxicity was evidenced by enlarged spleens at 100 mg/kg/day. The corresponding NOAEL was 50 mg/kg/day. For pregnant rabbits, the corresponding NOAEL was 100 mg/kg/day. The rat data indicate that haematotoxicity could be considered as an acute, primary effect of diphenylamine.

In order to avoid redundant MOS calculations, specific reference is made to the corresponding calculations for repeated dose toxicity. The NOAEL used for acute toxicity (spleen enlargement) is about 7-times higher (50 mg/kg/day / 7.5 mg/kg/day) than the experimental NOAEL for repeated dose toxicity. Because of identical adjustment factors the numerical relationship for the adequate starting points is the same as for the experimental NOAELs. Because of identical route-specific reference MOS values the same numerical relationship

(factor 7) is true for the corresponding critical exposure levels (acute toxicity versus repeated dose toxicity).

For acute toxicity (spleen enlargement) the MOS approach clearly indicates no concern for both exposure scenarios.

Irritation/Corrosivity

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

Dermal and eye irritation

Human data on local irritant or corrosive properties of diphenylamine are not available. According to the results of two skin irritation tests, diphenylamine caused no or only very slight dermal irritation in rabbits. There is no concern for dermal irritation at the workplace.

Data on eye irritating properties of the substance are conflicting and poorly documented, but it may be assumed that diphenylamine may pose a risk of serious damage to eyes. There exist two guideline-compliant studies which both report severe eye irritation caused by diphenylamine. In one of these studies irreversibility of effects after 21 days is stated.

Conclusion ii is proposed on the grounds that control measures exist which can minimise exposure and risk of severe irritation to the eyes, thereby reducing concern. However, these controls must be implemented and complied with to reduce the risk of severe irritation to the eyes.

Inhalative irritation

No data are available concerning respiratory tract irritation of diphenylamine. Dermal irritation data do not indicate that the substance may cause serious effects at the site of initial contact. A risk relevant damage of the airways by acute irritation properties is therefore not anticipated. There is no reason for concern.

Sensitisation

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

Skin sensitisation

Based on experimental data (dermal sensitisation study in guinea pigs) and human evidence (see chapter 4.1.2) diphenylamine is not considered to be a skin sensitiser. There is no reason for concern.

Respiratory sensitisation

No information on the sensitising potential of the substance at the respiratory tract is available. However, diphenylamine is not suspected to be a potent respiratory sensitiser in humans according to the fact that during all the years of use no notice of specific case reports has been given. There is no concern with respect of respiratory sensitisation at the workplace.

Repeated dose toxicity

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

Local effects

Dermal irritation in rabbits (acute exposure) is only very slight. In a dermal 90-day rat study treated animals exhibited dermal hyperplasia at the application side. The LOAEL for this local effect is 500 mg/kg/day. As local effects depend on the surface area concentration of a substance, and not on the internal body burden, for a recalculation from "mg/kg/day" into "mg/cm^2" default values are used (rat body weight 0.25 kg and assuming that 10% (40 cm^2) of a total body surface area of 400 cm^2 was exposed). This gives a value of 3.1 mg/cm^2 diphenylamine (500 mg/kg/day x 0.25 kg x 1/40 cm^2). For both dermal exposure scenarios (exposure levels in the range of 0.1 – 0.15 mg/cm^2) the margin of safety for these chronic local effects (dermal hyperplasia) is considered to be sufficiently high in order to reach a conclusion of no concern.

Systemic effects

Diphenylamine has been extensively tested for repeated dose toxicity in experimental animals (rats, mice and dogs) via the oral route of administration. Haematotoxicity proved to be the main toxic effect of diphenylamine. The primary target organs are the haematological system and the kidney, spleen and liver.

Taking together all data from animal studies with repeated oral application, the value of 7.5 mg/kg/day as NOAEL for adverse effects after chronic exposure from a two-year carcinogenicity study with rats is derived. This NOAEL is based on haematological and histological effects at dietary levels equal or greater than 25 mg/kg/day in female rats (LOAEL).

The calculation of the internal starting point accounts for an oral absorption percentage of 100% and a worker-specific adjustment factor of 7/5 (experimental frequency of exposure is 7

days/week, workers are exposed 5 days/week). Thus, the oral NOAEL of 7.5 mg/kg/day is converted to an internal starting point of 10.5 mg/kg/day (7.5 x 1 x 7/5).

Systemic effects by inhalation

The internal starting point of 10.5 mg/kg/day is converted into an inhalation NAEC (rat, in mg/m³). Absorption (and bioavailability) by inhalation is assumed to be 100%. The internal starting point is divided by 0.384 m³/kg/day (default respiratory volume for the rat for 8 hours) and multiplied by a factor of 6.7/10 (ratio of worker respiratory volumes under standard conditions and under conditions of light activity). Correspondingly, the inhalation starting point is calculated to be 18.3 mg/m³ (10.5 x 1 x 1/0.384 x 6.7/10).

The reference MOS for inhalation is calculated to be 12.5 (2.5 for interspecies differences x 5 for intraspecies differences). The corresponding "critical exposure level" for inhalation exposure is 1.5 mg/m³ (18.3/12.5).

Systemic effects by dermal exposure

The internal starting point of 10.5 mg/kg/day is converted to an adequate dermal starting point of 250 mg/kg/day (10.5 mg/kg/day / 0.042 to account for 4.2% dermal bioavailability). The reference MOS for dermal contact is calculated to be 50 with 4 x 2.5 as default value for interspecies differences of rats and 5 for intraspecies differences. The corresponding "critical exposure level" for dermal exposure is 5 mg/kg/day (250/50).

Alternatively dermal risk assessment can be performed by directly using the dermal NOAEL of 500 mg/kg/day from a 90-day study with rats. The experimental NOAEL of 500 mg/kg/day is directly used as dermal starting point. The corresponding reference MOS calculates 100 (4 x 2.5 for interspecies differences multiplied with 5 for intraspecies differences and 2 for duration adjustment). These considerations result in a dermal "critical exposure level" of 5 mg/kg/day (500/100).

Both calculations (those based on internal or external doses for the dermal route of exposure) yield an identical result of 5 mg/kg/day for the "critical exposure level".

Systemic effects by combined exposure

The internal starting point is 10.5 mg/kg/d. The reference MOS is identical to the dermal reference MOS of 50. The corresponding internal "critical exposure level" results in 0.2 mg/kg/day.

With respect to repeated dose toxicity (systemic effects) there is no concern for both exposure scenarios and for all routes of exposure.

Mutagenicity

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

DPA was negative in two Salmonella gene mutation tests. Further studies indicate that DPA is not or only marginally genotoxic to mammalian cells in vitro. Negative results from an in vivo micronucleus test indicate that no mutagenic effects are expressed in vivo. In conclusion the data indicate that diphenylamine may not be mutagenic in humans.

Carcinogenicity

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

Based on the interpretation of the overall results from various long-term bioassays, diphenylamine is not considered to be a carcinogen in experimental animals (see chapter 4.1.2). Correspondingly, there is no concern for workers as to this toxicological endpoint.

Reproductive dose toxicity

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

Fertility impairment

There are no human data available on reproductive toxicity of diphenylamine. Based on available rat data (see chapter 4.1.2) it appears that impairment of reproductive capability and capacity (i.e. decreased litter size) only occurs at dosages that interfere with food intake and body weight gain of the parental animals. From repeated dose toxicity studies there are no indications for adverse effects to gonads. From the available animal data a NOAEL for fertility impairment of 131 mg/kg/day is recommended for risk characterisation purposes.

In order to avoid redundant MOS calculations, reference is made to the calculations for repeated dose toxicity. The NOAEL for fertility impairment is about 18-times higher (131/7.5) than the experimental NOAEL for repeated dose toxicity. Because of identical adjustment factors for the adequate starting points and the reference MOS the relationship is the same as for the experimental NOAELs and the corresponding "critical exposure levels". The 18-times higher "critical exposure level" compared to that one of repeated dose toxicity results in no concern.

Developmental toxicity

Available data from developmental toxicity studies in two species (rats and rabbits) do not indicate any specific embryo-/fetotoxic or teratogenic potential even at maternally toxic dosages. In a two-generation study (EPA 1998) no teratogenic effects were observed up to maternal oral doses of 448 mg/kg/day. A NOAEL for developmental toxicity of 46 mg/kg/day is based on growth retardation in the F2 generation during late lactation at doses of 131 and 448 mg/kg/day. Maternal toxicity was observed at this doses with respect to reduced body weight, decrease in food consumption and pathological findings in spleen, kidney and liver.

Again, in order to avoid redundant MOS calculations, reference is made to the calculations for repeated dose toxicity. The NOAEL for developmental toxicity (growth retardation) is about 6-times higher (46/7.5) than the experimental NOAEL for repeated dose toxicity. Because of identical adjustment factors the relationship for the adequate starting points is the same as for the experimental NOAELs. Because of identical route-specific reference MOS's the same relationship (factor 6) is true for the corresponding "critical exposure levels" (developmental versus repeated dose toxicity).

Experimental testing of diphenylamine did not result in embryotoxic, fetotoxic or teratogenic effects. Based on these data, diphenylamine is not classified as a reprotoxic substance. However, at maternally toxic doses growth retardation of the offspring is observed. For this adverse effect, the outlined MOS approach did not result in concern.

Summary of occupational risk assessment (diphenylamine)

Risk characterisation for workers is complicated by the situation that data on oral absorption (100%) and the default value for dermal absorption (100%) cannot by itself explain the route-specific potency differences for diphenylamine toxicity. Comparison of oral and dermal experimental results for repeated dose toxicity of diphenylamine indicates a relatively low toxic potency for the dermal route of exposure. Based on the comparison of the adjusted NAELs for oral and dermal repeated dose toxicity a 100% oral bioavailability and a dermal bioavailability of about 5% is taken forward to risk characterisation. Without specific data to the contrary, the default value of 100% absorption by inhalation is interpreted in the sense of 100% bioavailability.

The lowest critical exposure levels for inhalation and dermal contact result from the endpoint repeated dose toxicity with values of 1.5 mg/m³ for inhalation and 5 mg/kg/day for dermal exposure. Compared to the exposure values of 1.0 mg/m³ (scenario 1: Production of diphenylamine and further processing) and 0.02 mg/m³ (scenario 2: Use of lubricant, metal working fluids) for inhalation and 1.8 mg/kg/day (scenario 1) and 0.3 mg/kg/day (scenario 2) for dermal contact there results no concern in the risk assessment for workers for this endpoint and accordingly also no concern for the other ones.

Consumers

Oral exposure of consumers to diphenylamine is primarily due to the consumption of fruits and vegetables which are treated with diphenylamine containing fungicides. This exposure is covered by the legislation on plant protection products. Therefore, no risk characterisation for this intake is performed in this section.

Dermal exposure of consumers is possible by the use of lubricants. An external dermal exposure of 0.7 mg/kg bw/d is estimated assuming a body weight of 60 kg.

Acute toxicity

Consumers are not expected to be exposed to diphenylamine in the range of hazardous doses which can be derived from acute oral or dermal toxicity studies in animals. Information about inhalation toxicity is not available. However, considering the low vapoure pressure of the substance inhalation exposure can be neglected. **Conclusion (ii).**

Irritation / Corrosivity

Human data on the local irritant or corrosive properties of diphenylamine are not available. In tests with rabbits, the substance caused no or only very slight skin irritation. Data on eye irritating properties of the substance are conflicting and poorly documented, but it can be assumed that diphenylamine may pose a risk of serious damage to eyes. Taking into account the intended use of lubricants and the low amount of the substance contained, it can be concluded that there is no concern for eye irritation. **Conclusion (ii).**

Sensitisation

Diphenylamine did not produce dermal sensitisation in guinea pigs. One case is reported of a woman experiencing a contact allergy. Other studies with patients did not reveal any skin sensitisation that could be attributed to diphenylamine. It can be concluded that

diphenylamine does not induce skin sensitisation in humans.There is no indication that diphenylamine may act as a respiratory sensitiser. **Conclusion (ii).**

Repeated dose toxicity

The risk characterisation for dermal exposure (systemic effects) is based on the NOAEL of 500 mg/kg bw/d derived from a 90-day study on rats. The adverse effect observed at higher doses (2000 mg/kg bw/d) was an increase in the relative kidney weight of males. In the same study, a LOAEL of 500 mg/kg bw/d was found for local effects. All treated animals exhibited dermal hyperplasia at the application side. Thus no NOAEL (local) could be derived.
For local effects after dermal exposure, the margin of safety between the exposure level of 0.7 mg/kg bw/d and the dermal LOAEL (local) of 500 mg/kg bw/d is judged to be sufficient taking into consideration the worst-case scenario assumption that both palms have contact with the lubricant and short times of exposure. **Conclusion (ii).**
For systemic effects after dermal exposure, the margin of safety between the exposure level of 0.7 mg/kg bw/d and the dermal NOAEL (systemic) of 500 mg/kg bw/d is judged to be sufficient. **Conclusion (ii).**

Mutagenicity

Diphenylamine was negative in two Salmonella gene mutation tests. Further studies indicate that diphenylamine is not or only marginally genotoxic to mammalian cells in vitro. An in vivo micronucleus test was also negative. In conclusion, the data indicate that diphenylamine is not mutagenic in humans. **Conclusion (ii)**.

Carcinogenicity

In a report on recent, guideline conform long-term investigations with diphenylamine on mice and rats no evidence for increased tumour incidence was found. In a one year study in beagle dogs with bolus application no neoplastic alterations were found. A number of older investigations using several strains of rats and mice and dogs do not report any substance related neoplastic alterations. In addition the majority of short term in vivo and in vitro tests show no evidence for transforming activity of diphenylamine. The overall results support the conclusion that there is no indication of carcinogenic effects of diphenylamine. **Conclusion (ii).**

Reproductive toxicity

There are no human data available for reproductive toxicity of diphenylamine. Data from investigations in laboratory animals are limited to studies with the oral route of administration.
There are no guideline-according studies available regarding effects on fertility. From an unpublished two-generation reproductive toxicity dietary study on Sprague-Dawley rats a NOAEL/fertility of 131 mg/kg bw/d was deduced. External dermal exposure due to lubricants has been estimated to be up to 0.7 mg/kg bw/d. Assuming 100% absorption, this value is compared with the available oral NOAEL. The margin of safety between the exposure level of 0.7 mg/kg bw/d and the oral NOAEL of 131 mg/kg bw/d is judged to be sufficient taking into consideration the worst-case scenario assumption that both palms have contact with the lubricant and short times of exposure. **Conclusion (ii).**
Data from guideline-according developmental toxicity studies are not available. From the data obtained from two developmental studies in rats and rabbits no specific embryo-/fetotoxic or teratogenic potential is indicated even at maternally toxic dosages. In a two generation study no teratogenic effects were observed up to maternal oral doses of 448 mg/kg bw/d. An

NOAEL/developmental toxicity of 46 mg/kg bw/d was derived based on a growth retardation in the F2 generation during late lactation at higher doses. External dermal exposure due to lubricants has been estimated to be up to 0.7 mg/kg bw/d. Assuming 100% absorption, this value is compared with the available oral NOAEL. The margin of safety between the dermal exposure level of 0.7 mg/kg bw/d and the oral NOAEL of 46 mg/kg bw/d is judged to be sufficient taking into account the worst-case scenario assumption that both palms have contact with the lubricant and short times of exposure. **Conclusion (ii).**

Humans exposed via the environment

The local scenario is based on an exposure scenario caused by the application of sewage sludge from a municipal waste water treatment plant which resulted in the highest local diphenylamine concentrations in soil and porewater and is supplemented with the calculated local exposure data (surface water and air) from site B. Model calculations for the local scenario resulted in a total daily dose of 0.0048 mg/kg bw/d. For the regional scenario a total daily dose of 0.00029 mg/kg bw/d was calculated. For the purpose of risk characterisation the highest value of 0.0048 mg/kg bw/d has been used. However, it has to be noted, that the applied model calculations are of preliminary nature and may have to be revised as soon as further knowledge, e.g. on PECregional or the sludge application scenario becomes available.

Repeated dose toxicity

From different short- and long-term studies on mice, dogs and rats with oral administration of diphenylamine a NOAEL of 7.5 mg/kg bw/d was derived (oral two-year carcinogenicity study in rats). The margin of safety between the calculated exposure of 0.0048 mg/kg bw/d and the oral NOAEL of 7.5 mg/kg bw/d is judged to be sufficient. **Conclusion (ii).**

Reproductive toxicity

Regarding effects on fertility, the NOAEL of 131 mg/kg bw/d from an oral study in rats is considered to be the appropriate value for risk characterisation. The margin of safety between the calculated exposure of 0.0048 mg/kg bw/d and the NOAEL of 131 mg/kg bw/d is judged to be sufficient. **Conclusion (ii).**
For developmental toxicity, a NOAEL of 46 mg/kg bw/d was determined based on findings of growth retardation in the F2 generation during late lactation. The margin of safety between the calculated exposure of 0.0048 mg/kg bw/d and the NOAEL of 46 mg/kg bw/d is judged to be sufficient. **Conclusion (ii).**

Combined exposure

4.2 HUMAN HEALTH (PHYSICO-CHEMICAL PROPERTIES)

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

Diphenylamine is not flammable, not explosive or classified as oxidising. Overall, the risks from physico-chemical properties, given the level of control in manufacture and use, are small.

5 RESULTS

5.1 ENVIRONMENT

Table 5.1 gives an overview of the uses and local scenarios for which risk was assessed.

Table 5.1: Overview of the scenarios and conclusions of the assessment.

		Conclusions			
Uses/Scenarios	**Tonnage**	**WWTP**	**Aquatic compartment** (water and sediment)	**Soil**	**Secondary poisoning** (aquatic/terr.)
Production (generic site)	5000 t/a	(i)	(i)	(ii)	(i) / (ii)
Production (site specific)	Confidential	(i)	(i)	(ii)	(i) / (ii)
Use as intermediate	9750 t/a)				
Processing (generic)	4000 t/a	(i)	(i)	(ii)	(i) / (ii)
Processing (site specific)	Confidential	(i)	(i)	(ii)	(ii)/ (ii)
Use in lubricants	50 t/a				
Formulation		(ii)	(i)	(i)	(ii) / (ii)
Professional use		(i)	(i)	(i)	(ii) / (i)
Use in storage aid (plant protection product)	200 t/a				
Formulation		(i)	(i)	(i)	(ii) / (ii)
Processing	No local scenario; releases are taken into account in the reg. and cont. concentrations				
Releases from the private use of fruits	No local scenario; releases are taken into account in the reg. and cont. concentrations				
Use in explosives	~ 0.1 %	Not assessed			
Use as stabilizer, colouring agent	traces	Not assessed			

5.1.1 Waste water treatment plant

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

This applies for all other scenarios except for formulation of lubricant. Up to date information on the tonnage for each use and size of the industrial sites is necessary to refine the

assessment. Further conclusions for the only known production and processing sites are included in the Appendices B1 and B2. Size of waste water treatment plants for production and processing of intermediates as well as site specific emission data or measured data from effluents are needed (see also conclusions for aquatic environment below). In addition, PNECmicro-organisms may be lowered by further testing (now AF of 100 has been applied). However, it is first necessary to obtain better data on the exposure before any testing is conducted.

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

This conclusion applies for the formulation of lubricant.

5.1.2 Aquatic environment (including sediment)

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

The conclusion applies for compartment water to all industrial categories for which local environmental concentrations could be predicted. While the equilibrium partitioning approach was used to derive both the PEC and the PNEC for sediment, same conclusions are drawn for sediment as for water compartment. Up-to-date information on the tonnage of all uses is needed. For the rest of the European use volume of the 10 000 t/a not covered by the only known producer and importer, confirmation is needed whether it is completely imported or produced in additional European sites. It is very probable, that other processing sites than the only known one are located in Europe. Information on their size, waste water treatment and effluent dilution rate is necessary. Information on the size and waste water treatment of lubricant formulation sites is necessary as well. In addition, more information on the end-uses of lubricants containing Diphenylamine is needed in order to be able to allocate the tonnage in lubricant use to several generic use scenarios. There is no information available whether there are any formulation sites of storage aid located in Europe or not. Confirmation for this issue is needed. If any formulation sites are located in Europe, site specific data on their size, emissions and waste water treatment is needed. Hardly any new measured data is available from aquatic environment. Measured data from water and sediment are needed in order to be able to compare the model results with the reality.
After better emission data has been received, the risk ratios could be further reduced by approximately a factor of two in case Diphenylamine would be confirmed to be inherently biodegradable. The available biodegradation data indicates that this might be the case, but no such studies are available, which would allow to assume inherent biodegradation in this version. Therefore, a simulation test could be considered. In addition, a chronic fish-study would reduce the risk ratio in local scenarios at the most by a factor of 5 (AF for derivation of PNECaqua would be reduced from 50 to 10). A chronic fish test belongs to the base set of the Commission Directive 414/91/EEC for evaluation of plant protection products, and the full base set requirements will be delivered to the rapporteur Ireland by May 2004.

The conclusion applies also for sediment because same risk ratios were derived as for water compartment due to the application of equilibrium partitioning method for PEC and PNEC in sediment.

As a conclusion, at this phase, generation of further import, production, use and emission information is preferred instead of conducting any tests.

5.1.3 Terrestrial compartment

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

This conclusion applies for formulation of lubricant and storage aid and professional use of storage aid. Information on the size and waste water treatment of lubricant formulation sites is necessary. In addition, more information on the end-uses of lubricants containing Diphenylamine is needed in order to be able to allocate the tonnage in lubricant use to several generic use scenarios. There is no information available whether there are any formulation sites of storage aid located in Europe or not. Confirmation for this issue is needed. If any formulation sites are located in Europe, site specific data on their size, emissions and waste water treatment is needed.

A secondary alternative is to conduct a biodegradation simulation test (see the conclusions above for the aquatic compartment), the results of which may lower the estimate for PECsoil. In addition, either new terrestrial chronic ecotoxicity data or an improvement of PNECaqua is needed.

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

This conclusion applies for production and processing.

5.1.4 Non-compartment specific effects relevant to the food chain

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

This conclusion applies for the aquatic food chain for the known production site, generic production scenario and generic scenario for intermediate use. Further conclusions on the only known production site are included in the Appendix B1. For the rest of the European use volume of the 10 000 t/a not covered by the only known producer and importer, a confirmation is needed whether it is completely imported or produced in additional European sites. It is very probable, that more than one processing sites are located in Europe. Information on their size, waste water treatment and effluent dilution rate is necessary.
For the terrestrial food chain, this conclusion applies for professional use of lubricant. More information on the end-uses of lubricants containing Diphenylamine is needed in order to be able to allocate the tonnage in lubricant use to several generic use scenarios. Refinement of regional PEC for agricultural soil may reduce the ratio. Due to EUSES –model, sludge from all industrial categories is included in the regional scenario. This technical problem may be circumvented.
After better emission data has been received, the risk ratios could be further reduced by approximately a factor of two in case Diphenylamine would be confirmed to be inherently biodegradable. The available biodegradation data indicates that this might be the case, but no

such studies are available, which would allow to assume inherent biodegradation in this version. Therefore, a simulation test could be considered.

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

Regarding the aquatic food chain, this conclusion applies for formulation of lubricants and storage aid, the known intermediate processing site and professional use of lubricants.

Regarding the terrestrial food chain, this conclusion is drawn for production, intermediate processing, processing of storage aid, formulation of storage aid and formulation of lubricants.

5.2 HUMAN HEALTH

5.2.1 Human health (toxicity)

Workers

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

Consumers

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

This conclusion applies to all exposure scenarios and all toxicological endpoints.

Humans exposed via the environment

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

This conclusion applies to all exposure scenarios and all toxicological endpoints.

5.2.2 Human health (risks from physico-chemical properties)

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