EUROPEAN COMMISSION
DIRECTORATE-GENERAL
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Institute for Health and Consumer Protection
European Chemicals Bureau
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ANILINE

CAS No: 62-53-3

EINECS No: 200-539-3

Summary Risk Assessment Report

2004 **Special Publication I.04.67**

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SUMMARY RISK ASSESSMENT REPORT

Final report, 2004

Germany

The risk assessment of aniline has been prepared by Germany on behalf of the European Union.

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PREFACE

This report provides a summary, with conclusions, of the risk assessment report of the substance aniline 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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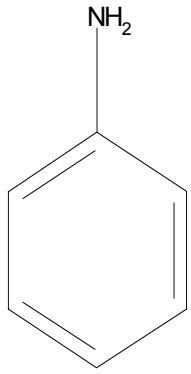
1 GENERAL SUBSTANCE INFORMATION

1.1 IDENTITY OF THE SUBSTANCE

CAS No:	62-53-3
EINECS No::	200-539-3
IUPAC name:	aminobenzene
Synonyms:	aniline, phenylamine
Molecular weight:	74.08 $g \cdot mol^{-1}$
Molecular formula:	C_6H_7N
Structural formula:	



1.2 PURITY/IMPURITIES, ADDITIVES

Purity:	≥ 99.5% w/w	
Impurities:	water	0.1%
	nitrobenzene	< 20 ppm
	phenol	< 50 ppm
	low boiling fraction	50-250 ppm
	high boiling fraction	< 100 ppm
Additives:	none	

1.3 PHYSICO-CHEMICAL PROPERTIES

Table 1.1 Physico-chemical properties

Property	Value
Physical state	at 20°C and 1,013 hPa: colourless oily liquid with a characteristic odour and taste
Melting point	- 6.2°C 1)
Boiling point	184.4°C at 1,013 hPa 1)
Relative density	1.022 at 20°C 1)
Vapour pressure	0.4 hPa at 20°C 1)
Surface tension	70.5 mN/m at 20°C 1)
Water solubility	35 g/l at 20°C 1)
Partition coefficient	log Pow 0.9 at 20°C (experimental) 2)
Flash point	76°C (closed cup)
Flammability	non flammable
Ignition temperature	630°C (DIN 51794)
Explosive properties	not explosive
Oxidising properties	no oxidising properties
Conversion factor	1 ppm = 3.87 mg/m^3

1) There is no information about the applied method
2) Shaking-flask method

1.4 CLASSIFICATION

The classification and labelling of aniline has recently been discussed and MS agreement has been reached, as follows:

Classification	Carc. Cat. 3; R40 Muta. Cat. 3; R68 T; R23/24/25-48/23/24/25 Xi; R41 R43 N; R50
Labelling	T; N R: 23/24/25-40-41-43-48/23/24/25-68-50 S: (1/2-)26-27-36/37/39-45-46-61-63

Carc. Cat. 3; R40	Limited evidence of a carcinogenic effect
Muta. Cat. 3; R68	Possible risk of irreversible effects
T; R23/24/25-48/23/24/25	Toxic by inhalation, in contact with skin and if swallowed Danger of serious damage to health by prolonged exposure through inhalation, in contact with skin and if swallowed
Xi; R41	Risk of serious damage to eyes
R43	May cause sensitisation by skin contact

N; R50	Very toxic to aquatic organisms
S1/2	Keep locked up and out of the reach of children
S26	In case of contact with eyes, rinse immediately with plenty of water and seek medical advice
S27	Take off immediately all contaminated clothing
S36/37/39	Wear suitable protective clothing, gloves and eye/face protection
S45	In case of accident or if you feel unwell, seek medical advice immediately (show the label where possible)
S46	If swallowed, seek medical advice immediately and show this container or label
S61	Avoid release to the environment. Refer to special instructions/Safety data sheets
S63	In case of accident by inhalation: remove casualty to fresh air and keep at rest

Concentration limits

$C \geq 25\%$:	T, N; R23/24/25-40-41-43-48/23/24/25-68-50
$10\% \leq C < 25\%$:	T; R20/21/22-40-41-43-48/23/24/25-68
$1\% \leq C < 10\%$:	T; R20/21/22-40-43-48/23/24/25-68
$0{,}2\% \leq C < 1\%$:	Xn; R48/20/21/22

2 GENERAL INFORMATION ON EXPOSURE

The major starting product in the manufacture of aniline is nitrobenzene. The oldest method for the reduction of nitrobenzene uses iron and acetic acid. As a further product, high-grade synthetic iron oxides are produced which are used as pigments. A modern method is the catalytical reduction of nitrobenzene. After hydrogenation, the reaction mixture is separated to an organic phase containing aniline with dissolved water and an aqueous phase containing 4% aniline. The crude aniline is purified by distillation. Aniline is stripped from the aqueous phase and returned to the raw condensate.

In the European Union, aniline is produced or imported by nine companies. For 1998 a total European use amount of 652,000 t was estimated. Recent figures supplied by the aniline producing and processing companies (confidential) showed that the actual production and use of aniline is higher than the estimated volume. The sum of the uses at known processing sites for which exposure scenarios were calculated in the risk assessment covers 95% of the total European use.

Aniline is exclusively used as an intermediate in chemical industry (MC I, IC 3; UC 33). No direct uses without chemical transformation were identified. The use pattern of aniline in the EU is:

- production of MDA,
- production of rubber chemicals (e.g. mercaptobenzothiazole, diphenylguanidine, diphenylamine, aniline ketone condensates etc.),
- production of dyes,
- production of plant protecting products,
- production of pharmaceuticals,
- production to other products.

MDA is the main product from aniline. For 1998 it was estimated that 76% of the estimated production volume of aniline was processed to MDA. The actual amount of aniline processed to MDA based on data supplied by the aniline producing and processing companies (confidential) has increased to a large extent compared to the values estimated. The second main product from aniline are rubber chemicals. For 1998 it was estimated that 14% of the estimated production volume of aniline was processed to rubber chemicals.

The other products are only of minor importance concerning the production amount.

3 ENVIRONMENT

3.1 ENVIRONMENTAL EXPOSURE

Releases of aniline into the atmosphere and into the hydrosphere occur during production and processing.

There is different information about releases into the environment during production and processing. Release factors calculated for the different production and/or processing sites range from < 0.013 ppm up to 16,000 ppm for the hydrosphere and from 0 ppp to 380 ppm for the atmosphere. No release factor was calculated for sites where more than 2 life-cycle steps take place.

Furthermore, non-intentional environmental releases are considered in the exposure assessment:

- Plant protection agents where aniline is formed as a degradation product:
  Aniline is processed to a series of plant protecting agents. It is known to be formed back by biotransformation from both phenylurea and phenylcarbamate derivatives. The major part is released in agricultural soils. When these agents are released into the hydrosphere, unknown amounts of aniline may be formed as well.
- Microbial reduction of nitrobenzene:
  Aniline is metabolised from nitrobenzene under anaerobic conditions. However, because of the ready biodegradability of aniline, it is assumed that no significant environmental pollution will result from this source.
- Rubber chemicals (degradation product):
  Aniline is not used in the rubber industry, it is formed by reaction of other rubber chemicals which are its subsequent products. As precursor, a series of compounds comes into consideration: sulfenamide or guanidine accelerators (e.g. cyclohexyl-2-benzothiazolsulfenamide, diphenyl-guanidine), and N-phenyl-p-phenylenediamine derivatives (PPDs) which are used as anti-ageing agents. The contribution of each precursor is unknown, as there are no quantitative data about aniline formation rates available.
- Thermal degradation of polyurethanes:
  Aniline was detected in the working place atmosphere in foundries where it is formed by thermal degradation of MDI-based polyurethane bound foundry core materials.
- Coal and oil industry:
  Aniline was detected in the effluents from coal carbonisation plants in a concentration range between 0.48 and 21 mg/l.
- Landfills:
  Aniline was detected in the leachate plume from a mainly rural and municipal waste landfill.

Releases into the terrestrial compartment are expected via deposition from the atmosphere and via degradation of plant protection agents which are its subsequent products.

The environmental behaviour of aniline is determined by the following characteristics:

- estimated atmospheric half-life 3.2 hours,
- low volatilisation because of the low Henry's law constant (0.1 - 0.2 $Pa \cdot m^3 \cdot mol^{-1}$),
- no hydrolysis,
- photolysis in surface waters, but no quantification possible,

- readily biodegradable in sewage treatment plants and surface waters; biodegradation is considered as major degradation pathway in the hydrosphere,
- reaction with humic substances in soils and sediments; it is assumed that 20% of the aniline in soil is rapidly mineralised and 80% are covalently bound to the organic fraction. For this reaction product with humic substances a biodegradation half-life of 350 days for soil and 3,500 days for sediment is assumed,
- low bioaccumulation in fish and sediment dwelling oligochaetes.

In wastewater treatment plants (WWTPs) 87% of the substance is estimated to be removed by biodegradation.

According to a Mackay I model the hydrosphere is the target compartment for aniline (87%) followed by soil (4.8%) and sediment (4.8%).

Predicted Environmental Concentrations (PEC) (sum of local and regional concentration) are calculated for the local aquatic environments of the production and processing sites using all site-specific information available. If no site-specific information was available, the default values from the TGD were used. The resulting PEClocal range between < 0.14 µg/l and 590 µg/l for sites emitting into rivers and between < 0.15 µg/l and 920 µg/l for sites emitting into the sea or estuaries.

For the release of aniline from rubber chemicals a PEClocal of 0.63 µg/l was calculated based on a first rough approach. So far, the databasis for the exposure estimation is extremely poor and the resulting PEC cannot be considered as safe.

PEC estimation for the sediment compartment was performed using the local aquatic $PEC_{water.}$ With a Koc value of 410 l/kg and 10% organic matter in suspended particles, sediment concentrations between < 1.4 µg/kg ww and 8,900 µg/kg ww were calculated for the production and processing sites. The PECs are the sum of the aniline fractions being dissolved in the porewater, physically and covalently bound.

For the release of aniline from rubber chemicals a PEC_{sed} of 6.1 µg/kg ww was derived.

For the exposure calculation for the atmosphere, site-specific data are used as far as they were submitted. For those sites where no release amount was submitted, a factor of 380 ppm was used for a worst-case approach. This factor was the highest release factor calculated from site-specific emission data. For the production and processing sites $PEClocal_{air}$ between 0.00067 and 3,900 µg/m^3 were calculated.

For the release of aniline from rubber chemicals a $PEClocal_{air}$ of 0.92 µg/m^3 was derived based on a first rough approach. So far, the database for the exposure estimation is extremely poor and the resulting PEC cannot be considered as safe.

Aniline reaches soils via deposition from the atmosphere or by degradation of plant protection agents. As mentioned above, aniline can be biodegraded or be bound onto the soil organics, where the reaction product accumulates.

For the production site with the highest emission into the atmophere a $PEClocal_{soil}$ of 5.6 µg/kg dw was estimated due to atmospheric deposition. For the release of aniline from rubber chemicals a $PEClocal_{soil}$ of 1.6 µg/kg dw was calculated.

Aniline is formed as a metabolite during biodegradation of phenylurea and phenylcarbamate derivatives. Exposure scenarios are calculated for the two compounds fenuron and siduron,

because these substances are known to be applied within the EU. For the exposure model the highest application rates are considered. A local PEC_{soil} of 640 µg/kg dw was obtained.

The BCF of 2.6 l/kg indicates that there is no bioaccumulation potential due to the exposure of the organisms via water. A biomagnification via food chain due to the route fish → fish-eating bird is not expected. However, a bioaccumulation of the reaction product with humic acids can be expected. This could lead to a bioaccumulation for the route sediment or soil → sediment or soil dwelling worm → worm-eating mammal or bird. Due to missing experimental data on bioaccumulation with sediment and soil organisms a scenario cannot be calculated for aniline.

No reliable monitoring data are available that can be compared with the estimated environmental concentrations.

For the assessment of regional exposure the emissions during production and processing of aniline, and the emissions by the rubber industry are considered. Not considered are the releases from the agricultural use of the plant protection products and the releases from tyres into soils near roads, because in these cases aniline is either rapidly biodegraded or reacts with soil organics under formation of a subsequent product which cannot be handled in one exposure model. The resulting values are:

Water	0.13 µg/l
Sediment	3.4 µg/kg dw
Atmosphere	$2.2 \cdot 10^{-4}$ µg/m^3
Soil	$36 \cdot 10^{-3}$ µg/kg dw

The results indicate that a regional exposure is only relevant for the hydrosphere. A high atmosphere pollution is only possible in the vicinity of a strong point source, and a relevant soil pollution due to atmospheric deposition can be excluded on the regional scale.

3.2 EFFECTS ASSESSMENT

Aquatic compartment (incl. sediment)

For aniline many ecotoxicity tests are reported but most of them give only a rough estimation of the ecotoxic effect values as in most cases nominal concentrations are given. It has to be expected that the real concentrations are lower because of photolysis. This is a problem especially with the algae tests, as it was shown that algae enhance the photo-transformation rate of aniline to a great extent.

Short- and long-term tests are available with fish, invertebrates and algae. The most sensitive aquatic species to aniline in both short- and long-term tests is *Daphnia magna*. From the NOEC from three 21-day reproduction tests in the range of 4 to 24 µg/l an arithmetic mean value of 15 µg/l was calculated. In a fish early-life-stage test with *Pimephales promelas* a 32-day NOEC of 0.39 mg/l was derived. For the green alga *Selenastrum capricornutum* a 72-hour EC50 of 19 mg/l and a 72-hour NOEC of 2 mg/l was determined. With an assessment factor of 10 a Predicted No Effect Concentration (PNEC) of 1.5 µg/l was derived from the mean NOEC for *Daphnia magna*.

Prolonged sediment toxicity test using spiked sediment has been carried out with the midge *Chironomus riparius* and the aquatic oligochaete *Lumbriculs variegatus*. The most sensitive benthic species was *Lumbriculus variegatus*. For the endpoint survival an EC10 of 34.5 mg/kg dw

(nominal) was obtained. No NOEC or EC10 value could be determined for the endpoints reproduction and growth as clear effects were seen from the lowest concentration level on (31.25 mg/kg dw nominal). The actual measured concentrations appear to be lower than the nominal concentrations with a mean recovery of 37.5%. The EC10 for survival corrected by this mean recovery is 15.3 mg/kg dry weight. From this value a $PNEC_{sediment}$ of 153 µg/kg dw (equivalent to 58.8 µg/kg ww) was derived using an assessment factor of 100. This factor is justified as from the most sensitive species, *Lumbriculus variegatus*, no NOEC for reproduction or growth could be estimated. The derivation of a PNEC for microorganisms is based on results from tests on nitrification inhibition, as this was the most sensitive endpoint both in tests with *Nitrosomonas* spec. and industrial sludge. With an assessment factor of 10 a PNEC of < 0.1 mg/l was derived for municipal sewage treatment plants and of 2 mg/l for industrial sewage treatment plants, as the test with industrial sludge is more realistic for this kind of treatment plants than the test with *Nitrosomonas* spec.

Terrestrial compartment

Concerning the terrestrial compartment, effect values are available for plants only. The toxicity of aniline to *Lactuca sativa* in natural soil was determined. From a 14-day EC50 for growth inhibition of 33 mg/kg soil (dw) and an assessment factor of 1,000, a $PNEC_{soil}$ of 33 µg/kg dw was estimated. Considering the fate of aniline in soils (partial degradation, rapid formation of covalent bonds with soil organics) the practicability of this test for the risk assessment appears to be questionable.

Atmosphere

From a fumigation study with aniline using pine seedlings it was concluded that aniline may cause effects on plants even at very short exposure periods of a few hours. No $PNEC_{plant}$ could be derived from this test. To enable an assessment of the effects of aniline on plants exposed via the atmosphere, a plant fumigation test was performed. Three species of higher plants (*Avena sativa*, *Brassica pekinensis* and *Abies grandis*) were exposed in laboratory exposure chambers for 14 days to 3 aniline concentrations (0.1 mg/m³, 0.3 mg/m³ and 1 mg/m³) and a control. The lowest NOEC of 0.3 mg/m³ was found for *Brassica pekinensis* for the endpoints plant length, wet and dry weight as well as macroscopic changes. With an assessment factor of 50 a $PNEC_{plant}$ of 6 µg/m³ was derived.

Secondary poisoning

Concerning the assessment of secondary poisoning a PNECoral of 2.3 mg/kg food was derived from a repeated dose toxicity study in rats.

3.3 RISK CHARACTERISATION

3.3.1 Aquatic compartment

Production and processing

Production

The PEC/PNEC ratio for two production sites is above 1, thus a risk to the aquatic environment is expected: **conclusion (iii)**. The exposure scenario is based on site-specific emission data.

Processing to MDA

The PEC/PNEC ratio for three sites processing aniline to MDA is above 1, thus a risk to the aquatic environment is expected: **conclusion (iii)**. The exposure scenarios for the three sites are based on site-specific emission data.

Processing to rubber chemicals

The PEC/PNEC ratio for two sites processing aniline to rubber chemicals is above 1, thus a risk to the aquatic environment is expected: **conclusion (iii)**. The exposure scenarios for the two sites are based on site-specific emission data.

The exposure scenarios for two other sites processing aniline to rubber chemicals are largely based on default parameters. The PEC/PNEC ratio is above 1, thus a risk to the aquatic environment is expected: **conclusion (iii)**. Industry was asked repeatedly for the missing data, without success.

Processing to dyes

The PEC/PNEC ratios for the aquatic compartment are below 1 for all sites processing aniline to dyes, thus a risk to the aquatic environment is not expected: **conclusion (ii)**.

Processing to plant protection products

The PEC/PNEC ratios are below 1 for all sites processing aniline to plant protection products, thus a risk to the aquatic environment is not expected: **conclusion (ii)**.

Processing to pharmaceuticals

The PEC/PNEC ratio for the site processing aniline to pharmaceuticals is above 1. The technical description of the processes reveals that the releases via wastewater origin primarily from MDA production: **conclusion (ii)**.

Rubber chemicals

In a first rough approach, a PEClocal of 0.63 µg/l was estimated for emissions of rubber manufacturers. So far, the database for the exposure estimation is extremely poor, and the resulting PECs cannot be considered as safe.

Data about the formation of aniline from different precursors, the releases into the wastewater and wastewater treatment, which are representative for the European rubber industry are needed: **conclusion (i)**.

Coal and oil industry

The present information is not sufficient to carry out a risk characterisation for this emission source. The releases resulting from coal and oil industry are not covered by the life-cycle of aniline produced or imported into the EU. Data improvement sufficient for risk assessment purposes is judged disproportionate within the scope of this programme. Therefore, no formal conclusion is drawn for this emission scenario.

Plant protecting agents

Releases of phenylureas and -carbamates and their metabolisation to aniline in the hydrosphere are probably of minor importance: **conclusion (ii)**.

Sediments

Production

The PEC/PNEC ratio for two production sites is above 1, thus a risk to the benthic environment is expected: **conclusion (iii)**. The exposure scenario is based on site-specific emission data.

However, as the PEC/PNEC ratio for surface water is higher for these sites than the PEC/PNEC ratio for sediment, any risk reduction measure that has to be applied for surface water will cover also the sediment compartment. Therefore, no further risk reduction measures are necessary for the sediment compartment.

Processing to MDA

The PEC/PNEC ratio for two sites processing aniline to MDA is above 1, thus a risk to the benthic environment is expected: **conclusion (iii)**. The exposure scenarios for the two sites are based on site-specific emission data.

However, as the PEC/PNEC ratio for surface water is higher for these sites than the PEC/PNEC ratio for sediment, any risk reduction measure that has to be applied for surface water will also cover the sediment compartment. Therefore, no further risk reduction measures are necessary for the sediment compartment.

Processing to rubber chemicals

The PEC/PNEC ratio for one site processing aniline to rubber chemicals is above 1, thus a risk to the benthic environment is expected: **conclusion (iii)**. The exposure scenarios for this site are based on site-specific emission data.

However, as the PEC/PNEC ratio for surface water is higher for these sites than the PEC/PNEC ratio for sediment, any risk reduction measure that has to be applied for surface water will cover also the sediment compartment. Therefore, no further risk reduction measures are necessary for the sediment compartment.

The exposure scenarios for two other sites processing aniline to rubber chemicals are largely based on default parameters. The PEC/PNEC ratio is above 1, thus a risk to the benthic environment is expected: **conclusion (iii)**. Industry was asked repeatedly for the missing data, without success.

However, as the PEC/PNEC ratio for surface water is higher for these sites than the PEC/PNEC ratio for sediment, any risk reduction measure that has to be applied for surface water will cover also the sediment compartment. Therefore, no further risk reduction measures are necessary for the sediment compartment.

Processing to dyes

The PEC/PNEC ratios are below 1 for all sites processing aniline to dyes, thus a risk to the benthic environment is not expected: **conclusion (ii)**.

Processing to plant protection products

The PEC/PNEC ratios are below 1 for all sites processing aniline to plant protection products, thus a risk to the benthic environment is not expected: **conclusion (ii)**.

Processing to pharmaceuticals

The PEC/PNEC ratio for the site processing aniline to pharmaceuticals is above 1. The technical description of the processes reveals that the releases via wastewater origin primarily from MDA production: **conclusion (ii)**.

3.3.2 Atmosphere

Production and processing

The exposure scenarios for one production site are based on a limited number of measured concentrations. The PEC/PNEC ratio for the atmosphere is above 1, thus a risk to plants exposed via the vapour phase is expected: **conclusion (iii)**.

The PEC/PNEC ratio for all sites processing aniline to MDA is below 1, thus a risk to plants exposed via the vapour phase is not expected: **conclusion (ii)**.

The PEC/PNEC ratio for all sites processing aniline to rubber chemicals is below 1, thus a risk to plants exposed via the vapour phase is not expected: **conclusion (ii)**.

The PEC/PNEC ratios for all sites processing aniline to dyes is below 1, thus a risk to plants exposed via the vapour phase is not expected: **conclusion (ii)**.

The PEC/PNEC ratios for all sites processing aniline to plant protection products is below 1, thus a risk to plants exposed via the vapour phase is not expected: **conclusion (ii)**.

The PEC/PNEC ratio for the site processing aniline to pharmaceuticals is below 1, thus a risk to plants exposed via the vapour phase is not expected: **conclusion (ii)**.

Rubber industry

For the rubber industry, only an initial exposure estimation with an unsafe data basis was possible. More representative information on aniline releases is necessary, especially whether exhaust air purification techniques are commonly applied, together with their effectiveness: **conclusion (i)**.

Thermal degradation of polyurethanes

Aniline was detected in the working place atmosphere in foundries where it is formed by thermal degradation of MDI-based polyurethane bound foundry core materials. There are no data about pollution of the outer atmosphere by these sources. Compared with aniline production and processing plants with releases above 1 t/a, this source is expected to be of minor importance.

The present information is not sufficient to carry out a risk characterisation for the environment for this emission source. As these releases are expected to be of minor importance, data improvement is not of high priority. No formal conclusion is drawn for this scenario.

3.3.3 Terrestrial compartment

Production and processing

Aniline emitted into the atmosphere is deposited into the soil near the source. With a $PNEC_{soil}$ (related to dry weight) of 33 µg/kg, a PEC/PNEC ratio below one is calculated for the site with the highest submitted emission: **conclusion (ii)**.

Rubber chemicals

A first rough exposure assessment for the rubber industry resulted in a PEC/PNEC ratio below 1: **conclusion (ii)**.

Plant protecting agents

With a PNEC of 33 µg/kg dw, the PEC/PNEC ratios are above 1 for the use of plant protecting agents.

The result of the effects assessment was that it is not possible to derive a PNEC which considers the realistic exposure situation. The risk characterisation is only a rough initial approach. For an improved effects assessment, tests with terrestrial organisms with pre-incubated aniline should be performed. Long-term tests with plants, earthworms and microorganisms are proposed to enable a proper effects assessment. It is proposed that this problem should be considered for the assessment of plant protection agents within the frame of Council Directive 91/414/EEC. **Conclusion (i)**.

3.3.4 Secondary poisoning

Because of the low accumulation of aniline in fish via water, the exposure route water - fish -fish eating bird or mammal is likely to be not relevant.

However, the reaction product of aniline with humic acids accumulates in sediments and soils and is probably bioavailable. A bioaccumulation via the route sediment or soil - sediment or soil dwelling worm – worm-eating mammal or bird cannot be excluded. However, the result of a recently performed bioaccumulation study with the benthic oligochaete *Lumbriculus variegatus* indicates that also for sediment and soil dwelling organisms bioaccumulation of aniline is low: **conclusion (ii)**.

4 HUMAN HEALTH

4.1 HUMAN HEALTH (TOXICITY)

4.1.1 Exposure assessment

4.1.1.1 Occupational exposure

Aniline is exclusively used as a chemical intermediate which is mainly (76%) processed to MDA, a starting product for polyurethane plastics. Minor amounts are used to produce initial dye products (6.4%) and rubber chemicals (14%) (percentages estimated for 1998).

Based on the available information three sources of exposure were identified:

- chemical industry (production and further processing),
- release of aniline as a decomposition product during thermal degradation of plastics,
- use of products with residual aniline (dyes, adhesives).

The following occupational exposure limits apply in the EU:

- DK, S: 4 mg/m^3 (1 ml/m^3)
- FIN, B: 7.6 mg/m^3 (2 ml/m^3)
- D: 8 mg/m^3 (2 ml/m^3)
- UK, F: 10 mg/m^3 (2 ml/m^3)

In Germany, the short-term exposure limit amounts to 32 mg/m^3 (8 ml/m^3, 4·occupational exposure limit (MAK), 15 min, duration 1 hour). Up to the end of 1996 it amounted to 40 mg/m^3 (10 ml/m^3, 5·MAK, during 30 minutes, 2 times per day).

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 are to be regarded as reasonable worst-case estimates representing the highly exposed workers of a scenario. If a sufficient number of measured results is available, the 90th or 95th percentiles are taken. In case of limited number of measured results, the highest result is used for exposure assessment.

With regard to dermal exposure, measured results are not available. For most occupational exposure scenarios, the regular use of suitable PPE (Personal Protective Equipment) at the workplaces is not probable. Therefore, actual dermal exposure is generally assessed based on the EASE model without considering that PPE might be worn by a part of the exposed collective. For certain scenarios, dermal exposure is assessed in addition using expert judgement taking into account the regular use of suitable gloves. In general, dermal exposure is assessed for as exposure to part of hands and forearms. The results for the different scenarios are summarised in **Table 4.1**. All shift averages should be regarded as representing the reasonable worst-case situation.

Chemical industry

For the large-scale chemical industry, it is assumed that the production and further processing of aniline is mainly performed in closed systems. Exposure occurs if the closed systems are breached for certain activities e.g. filling, cleaning and maintenance. The assessment of inhalation exposure for the production (Scenarios 1 and 2) is made based on the provided measured data. Since it could not be judged whether the data are representative for all companies, inhalation exposure is additionally assessed using the EASE model for those companies which did not submit data (Scenario 3). Inhalation exposure during further processing of aniline is estimated in Scenario 4.

For the production and further processing of aniline (Scenarios 1 – 4) dermal exposure is assessed in consideration that aniline is manufactured and further processed primarily in closed systems and that the use of PPE (here gloves) is highly accepted within the chemical industry. Taking into account the available information, two estimates are made for each scenario (1 – 4), showing the exposure reducing effect of suitable gloves:

- Scenario 1a – 4a: On condition that suitable gloves are worn, dermal exposure is assessed as low. One manufacturer performed tests of several glove types according to DIN EN 374. The measurement results revealed that the materials butyl rubber, fluorocarbon rubber and layers of LLDPE are stable against penetration of aniline for at least 8 hours.
- Scenario 1b – 4b: Since the knowledge on the used glove materials is incomplete and there is still a lack of information with regard to the suitability of all recommended materials, dermal exposure is assessed for the unprotected worker additionally. The limited effect of unsuitable protective gloves cannot be considered.

In the case of occasional (not daily) cleaning and maintenance of plants (e.g. during "shut down" of the plant), larger skin areas than during usual daily work may be exposed (see **Table 4.1**, footnote 1).

Release of aniline as a decomposition product during thermal degradation of plastics

Inhalation exposure to aniline not resulting from the life-cycle of the substance may be caused by the release of aniline during thermal decomposition in the areas

- of rubber processing, e.g. due to decomposition of vulcanisation accelerators (Scenario 5),
- of foundries due to pyrolysis of polyurethane foam binders in casting moulds (Scenario 6)
- in other branches, e.g. due to the decomposition of polyurethane plastics (Scenario 7).

For the latter, only data summarised from different workplaces are available, e.g. the grinding of thermoplastic polyurethane materials which are used in injection moulding machines, the baking of polyurethane lacquers and welding of materials coated with polyurethane. Industries and activities involved are the production and processing of plastics, electrical engineering, cable production, dismantling, screwing using cooling lubricants and sewerage sanitation. Because aniline is released during thermal processes (Scenarios 5 – 7), dermal exposure is restricted to touching contaminated surfaces and is assessed as low (here: < 1 mg/person/day).

Use of products with residual aniline (dyes, adhesives)

Based on sparse but reliable information, it is known that residual aniline is contained in adhesives and dyes in low concentrations (up to 0.3%). However, within the framework of the risk assessment of aniline, Spain provided the information that dyes containing aniline are

produced in Spain and are used as consumer products for the purpose of dyeing shoes. The content of aniline has recently been reduced from 9% to 2%. This concentration is taken forward to model estimations since it could not be excluded that similar dyes are used at the workplace, e.g. in the textile industry. The exposure assessment is made for dyes being used as liquids (Scenario 8a) or as powders (Scenarios 8b, 8c) and for the application of liquid adhesives (Scenario 9).

Summary of exposure data

If no other information is given, the presented shift averages in **Table 4.1** represent exposure of reasonable worst-case situations. In case of exposure estimates based on measured data, 95th percentiles derived from the available data are given.

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/person/day]
Chemical industry			
Production, reduction of nitrobenzene 1) By means of H_2 [1)] 2) By means of Fe [1)]	 shift length, daily shift length, daily	 2.5 (measured data) 1.5 (highest measured result)	 a) low [2)] b) 42 – 420 [3)] a) low [2)] b) 42 – 420 [3)]
3) Production (companies which did not submit any data) [1)]	shift length, daily	2 – 12 (EASE)	a) low [2)] b) 42 – 420 [3)]
4) Further processing to various products [1)]	shift length, daily	2.0 (measured data, worst case)	a) low [2)] b) 42 – 420 [3)]
Release of aniline as a decomposition product			
5) VulcaniSation of rubber plastics and rubber processing	shift length, daily (assumed)	0.8 (measured data)	low [4)] (expert judgement)
6) Iron, steel and aluminium foundries	shift length, daily (assumed)	6.4 (literature data, highest result)	low [4)] (expert judgement)
7) Different branches (e.g. plastics processing, electrical engineering)	shift length, daily (assumed)	0.1 (measured data)	low [(4)] (expert judgement)
Use of products with residual aniline			
8) Use of dyes with residual aniline (2%), used e.g. in the textile industry 8a) Liquid dyes 8b) Powdery dyes 8c) Powdery dyes	 shift length, daily (assumed) shift length, daily (assumed) shift length, daily (assumed)	 0 – 0.08 [5)] (expert judgement) 0 – 0.02 (EASE, with LEV) 0 – 0.1 (EASE, without LEV)	 17 - 84 (EASE, no gloves) 17 (EASE, no gloves) 17 (EASE, no gloves)
9) Use of adhesives with residual aniline (0.3%) in engineering, device and tool construction industries	shift length, daily (assumed)	0 – 0.08 [5)] (expert judgement)	0.06 – 0.6 (EASE, no gloves)

1) Separation of cleaning and maintenance performed daily (included in the scenario production) and cleaning and maintenance performed only occasional, e.g. during shut down of a plant; for the latter case the shift average amounts to 130 – 1,300 mg/p/day
2) Exposure assessment based on expert judgement taking into account the regular use of suitable gloves (see text)
3) Use of unsuitable gloves, exposure assessment for the unprotected worker (no gloves) based on model estimates (EASE) (see text)
4) Rough estimation: aniline is released during heating, secondary contact with contaminated surfaces (< 1 mg/person/day)
5) Estimation in comparison with the saturation concentration

4.1.1.2 Consumer exposure

Presumably, direct use of aniline by consumer does not exist. Only scarce information is available on the use of aniline as a component of consumer products. The Spanish authorities provided data that aniline is a component of a product used for dyeing shoes. Severe health hazards have been attributed due to the exposure with such aniline-containing products. Previous data reported a content of aniline of up to 9%, whereas recent information is on an amount of 1-2%. The worst-case calculation of the dermal exposure of consumers due to wearing shoes dyed with an aniline-containing product leads to an internal exposure to aniline of $1.0 \cdot 10^{-4}$ mg/kg bw/d (adults) and of $4.3 \cdot 10^{-5}$ mg/kg bw/d (children).

Aniline may occur in rubber articles in small amounts in the rubber matrix. As a result of migration and leaching, consumer exposure to aniline in low concentrations is conceivable but not quantifiable.

4.1.1.3 Humans exposed via the environment

Humans can be exposed indirectly to aniline via emissions into the hydrosphere and atmophere from industrial sites and via releases from plant protecting products via the terrestrial compartment.

The total daily dose is estimated to 0.74 mg/kg bw/d for the emissions from industrial sources on a local scale and $4.4 \cdot 10^{-6}$ mg/kg bw/d on a regional scale. The main contributions to the intake in the case of the local exposure are the $DOSE_{stem}$ and the $DOSE_{air}$ with fractions of 64% and 35%, respectively, of the total daily dose. This is caused by the high releases into the air at the main source. On the regional scale, a relevant exposure is expected only for the hydrosphere. In this case, the fraction of the $DOSE_{drw}$ is 84% and of $DOSE_{fish}$ is 13%.

Concerning the intake of aniline from plant protecting agents, there are no data available about the uptake of the bound aniline by plants. Therefore, the indirect exposure caused by the plant protecting agents cannot be modelled. However, from a few measured data a daily dose of 0.11 mg/kg bw/d is calculated.

4.1.2 Effects assessment

Toxicokinetics, metabolism and distribution

Aniline is well absorbed after oral, dermal and inhalation exposure. The extent of absorption after oral intake amounts 89-96% for rats. The corresponding figures for mouse, sheep and pig are 72%, 80% and 56%, respectively. From studies with human volunteers dermal absorption rates are reported in the range of 0.2 – 3.0 mg/cm²/h depending on the experimental conditions (exposure time, temperature, and moisture). Based on these results dermal absorption in humans was estimated to amount up to 38%.

In rats treated for one day with radioactively labelled aniline the distribution of radioactivity in different tissues showed highest concentration in RBCs, followed by plasma, spleen, kidney, lung, heart, brain and fat. Repeated administration leads to accumulation of radioactivity in spleen.

The major contributors to aniline clearance appear to be a combination of acetylation and hydroxylation reactions. Acetanilide may be either deacetylated back to aniline or 4-hydroxylated to 4-hydroxyacetanilide. The glucuronide and sulfate conjugates of 4-hydroxyacetanilide represent the major urinary metabolites of aniline. The N-acetylation of aniline is catalysed by hepatic N-acetyl-transferase, while the aromatic hydroxylation of aniline involves the cytochrome P-450 enzyme system. N-hydroxylation of aniline to N-phenylhydroxylamine (which may be further oxidised to nitrosobenzene, conjugated with glutathione, or re-reduced back to aniline) is the principal route by which aniline produces toxic effects, including methemoglobinaemia. The formation of methemoglobin (MetHb) after single oral administration to dogs is one to six times higher than after inhalation exposure.

Acute toxicity

Acute intoxication of humans with aniline/aniline vapours is reported frequently. In humans 60 ml of orally administered aniline causes death. 0.4-0.6 mg/l air may be borne without much harm for an exposure up to one hour, but 0.1-0.25 mg/l for several hours produces slight symptoms. Average lethal inhalation dose for humans is reported to be 25 mg/l air or 0.35-1.43 g/kg bw. With respect to methemoglobin formation the no-effect dose of aniline in adult man is in the range of 15 mg/man (about 0.21 mg/kg bw). In experiments in rats and rabbits the acute toxicity of aniline is moderate, independent of the way of application: In rats oral LD50 values of 780 mg/kg bw in females and 930 mg/kg bw in males were determined. Inhalation LC50 values in rats are different depending on the kind of exposure: For head-only exposure 3.3 mg/l/4 hours and for whole-body exposure 1.86 mg/l/4 hours were detected. Acute dermal toxicity of aniline is characterised by LD50 values of 1,540 mg/kg bw for rabbits and 1,290 mg/kg bw for guinea pigs. Cats however, react much more sensitive, with a dermal LD50 of 254 mg/kg bw and death following oral application of as low as approximately 50-100 mg/kg. In dogs 3 hours after oral treatment with 15 mg aniline/kg bw methaemoglobin levels were in the range of 19-29%. The normal range of about 0.7% MetHb was reached after 24 hours. In an acute inhalation test with the same species peak methaemoglobin levels of 3–24% were determined within 3 hours after the start of the exposure which declined to normal levels (<1%) after approximately 20 hours. Methaemoglobin was restituted at a half time of 100 minutes. In rats an oral dose of 20 mg aniline/kg bw resulted in a small increase of MetHb levels (3.3% versus 2.4% in controls). In adult man the no-effect dose after oral treatment for three consecutive days resulted in a no-effect dose in the range of 15 mg/man (about 0.21 mg/kg). Taking into account all available data on animals and humans aniline is classified as “T, toxic” and labelled as “R 23, 24, 25, toxic by inhalation, in contact with skin and if swallowed”.

Irritation

Human data on irritation to the skin and eyes are not available. Aniline causes only weak irritation to the skin of rabbits, but long lasting severe irritation with pannus formation to the eyes of rabbit. Accordingly, aniline is classified as "Xi, Irritant" and labelled with "R 41, Risk of serious damage to eyes".

Sensitisation

In humans aniline causes contact allergy, often associated with para-group cross reactivity. Aniline causes mild to moderate skin sensitisation in guinea pigs. Animal data revealed a mild to moderate sensitisation rate. In 2/3 guinea pig tests positive rates of 10% and 50% are documented. Respiratory sensitisation has not been observed. However, based on the observed

skin sensitisation, the occurrence of respiratory sensitisation cannot be ruled out. Based on animal and human data, aniline is labelled with the R-phrase R 43 “May cause sensitisation by skin contact”.

Repeated dose toxicity

Repeated aniline administration to rats has been shown to damage erythrocytes followed by haemolytic anaemia, cyanosis and methaemoglobinemia at doses from 7 mg/kg bw/d in rats after oral administration (LOAEL) or 5 ppm (19 mg/m³) after inhalation. Corresponding effects were haemosiderin deposits in the spleen and to a lower degree or at higher doses in the kidneys and the liver, respectively, increased erythropoeitic activity in the bone marrow and the spleen. The spleen of treated animals showed congestion of the red pulp sinuses and increased weight. Chronic testing resulted in excessive fibrosis and fatty metamorphosis of splenic stroma and chronic capsulitis. Treatment-related adverse effects of minor relevance were also reported to occur in the adrenals (cortical hyperplasia) and ovaries (reduced organ weights).

Overt haemotoxicity or indication on this is the relevant toxic effect consisting of haemolytic anaemia and its consequential alterations. This was seen in repeated dose studies with oral administration at dosages which need classification as toxic and labelling with T, R 48/25. Although the parameters examined, the sensitivity of examination and the quantification of the results were very different between the studies performed, the toxic profile observed after prolonged aniline exposure was very consistent within the rat studies. Experience from humans after repeated oral uptake also give indications on haemotoxicity (besides methemoglobin formation) at dosages from 0.4 mg/kg bw/d. The data basis on the inhalation route is insufficient. However, the limited studies give also indications that aniline is haemotoxic at very low concentrations (5 ppm (19 mg/m³)/26 weeks and ≥ 30 ppm (approx. 120 mg/m³)/2 weeks. Although no dermal study is available, the dermal route is also included in labelling because aniline is well absorbed after all exposure routes. According to the present data aniline has been classified as "T, toxic" and labelled with the R-phrases R 48/23/24/25 “Danger of serious damage to health by prolonged exposure through inhalation, in contact with skin and if swallowed”.

Mutagenicity

Aniline is negative in routine bacterial mutation tests. In mammalian cell cultures positive effects were obtained with respect to chromosomal effects, sister chromatide exchanges, and possibly for gene mutations. In general, stronger effects are induced in the presence of an exogenous metabolic activation system than in the absence. *In vivo*, aniline is an inducer of micronuclei in mouse and rat bone marrow cells. Whereas in mice positive effects occur only at high doses in the toxic range, in rats a positive dose-related response can be seen in non-toxic doses. The mutagenicity *in vitro* and *in vivo* of aniline is supported by *in vivo* studies showing DNA strand breaks and DNA adducts in different organs.

Mutagenicity data of a metabolite (4-aminophenol) and a structurally related substance (azobenzene) strengthen the evidence for mutagenicity of aniline in somatic cells of animals. Available data on germ cell mutagenicity, which are negative (sperm head anomalies) or equivocal (dominant lethal assay), are of limited predictive values due to relatively poor sensitivities of the test systems. The available data of mutagenicity are not sufficient to classify aniline as a category 2 mutagen, however, due to the positive findings in several *in vitro* and i*n vivo* tests, especially in the bone marrow micronucleus test with rats aniline has been classified as a category 3 mutagen and labelled “R 68, possible risk of irreversible effects”.

Carcinogenicity

At this time data on carcinogenicity in humans are inadequate. No clear tumour response could be associated with aniline exposure to humans. In two carcinogenicity studies on F344 rats, aniline produced dose-dependently higher incidences of spleen sarcomas in males. A few splenic tumours observed in female rats were also considered to be related to aniline treatment. A carcinogenic effect could not be demonstrated in mice. Aniline is genotoxic *in vivo* in rats and in mice. It can be assumed that the genotoxicity is responsible for tumour initiation and development, but this did not necessarily include a scientific plausible proof that the underlying mechanism of carcinogenicity is based on the genotoxic activity. Other mechanisms are also discussed to be involved in tumour development. Until now, it is not possible to demonstrate a plausible mode of action indicating the existence of a threshold mechanism. Further studies are necessary to investigate mechanisms involved in aniline carcinogenicity especially to elucidate further the possible mechanisms of formation of spleen tumours in rats.

As far as known aniline is metabolised similarly in rats and humans. Aniline is carcinogenic in rats, together with the knowledge on metabolism and positive *in vivo* genotoxicity a relevant concern on carcinogenicity in humans is concluded. From the limited human data basis a final assessment of human cancer risk is not possible. Aniline is considered to be a non-threshold carcinogen. The current classification of aniline as a category 3 (low) carcinogen is considered to be appropriate until further data are available.

Toxicity for reproduction

Concerning reproductive toxicity, data from valid epidemiological studies are not available. Animal data on functional testing for fertility (e.g. generation studies) are not available. In lifetime studies with repeated oral administration of doses of 7, 22 and 72 mg/kg bw/d organ weight determinations as well as histopathological evaluations had been performed for both sexes and at periods relevant for reproduction. Testes weights and histology had not been affected during this study. Also female reproductive organs were not affected by continuous aniline exposure up to the age of more than 52 weeks. The reported observations from studies with rats concerning female sex organs (reduced ovary weight, uterine endometrial polyps) are not considered to be of significance in relation to female reproductive capacity and capability. At the highest dose severe chronic toxic effects and carcinogenicity occurred in the study. The results concerning reproductive organs are interpreted as giving no indication for an impairment of fertility up to doses which induce toxic and tumourigenic effects.

In a developmental toxicity study in rats with oral doses of approximately 10, 30 and 100 mg aniline hydrochloride/kg bw/d maternal toxicity occurred at all dose levels. No indications for significant impairment of pre- or postnatal development were obtained. However, based on some indications for interference of aniline with the hematopoietic system of the conceptus and with postnatal viability, a NOAEL of 21 mg aniline/kg/day concerning developmental toxicity was derived. The available developmental studies did not give evidence for a specific embryotoxic, fetotoxic or teratogenic potential of aniline.

4.1.3 Risk characterisation

4.1.3.1 Workers

Exposure routes to be considered for risk assessment at the workplace are inhalation against aniline vapour and skin contact with the liquid substance and its formulations. Aniline seems to be readily absorbed via the oral, dermal and inhalation route. The actual percentage of absorption at work, however, is difficult to address. Therefore in a first approximation similar availability of aniline by all routes is assumed. Combination of both exposure routes is not especially addressed in this summary risk assessment report because it does not lead to additional scenarios of concern.

For toxicological endpoints with relevant quantitative data MOS values are calculated as quotients of experimental NOAEL (or LOAEL) and workplace exposure assessments. For dose transformation a breathing volume of 10 m^3 per day is assumed at work. Concerning carcinogenicity, MOE values are determined on the background of T25. Scientifically based assessment factors describe the stepwise extrapolation of animal data to the worker population. The value of the minimal MOS, as decision mark between conclusion (ii) and (iii), results from the multiplicative combination of the different assessment factors. In a parallel procedure, which gives identical but more direct results, a "critical exposure level" is identified for each endpoint, indicating concern if occupational exposure levels exceed this value.

For extrapolation between different species (rat to human) an overall factor of 10 is derived for the oral route based on a comparison of rat and human effect data. This factor includes correction for metabolic rate differences which does not apply for inhalation. Species extrapolation at that route therefore uses a factor of 2.5. For each toxicological endpoint an additional uncertainty factor is determined which takes into account aspects like the reliability of the database, the biological relevance of the observed effects, the slope of the dose response curve or the variability of the human population. Intraspecies differences are not accounted for with an extra assessment factor.

In the following risks at the workplace are considered specifically for each toxicological endpoint. Summary tables containing all scenarios at risk are given at the end of this section.

Acute systemic toxicity

As starting point for worker risk assessment the human NOAEL concerning methaemoglobin formation of 15 mg/person is chosen, the according air concentration at the workplace would be 1.5 mg/m3 for exposure duration of 8 hours. For risk evaluation no further aspects have to be considered. The minimal MOS concerning acute toxicity simply is 1. The critical exposure levels are identified as 1.5 mg/m3 for inhalation (8 hours) or 15 mg/person for dermal or combined exposure.

For some inhalation exposures especially during production and further processing in the large-scale chemical industry concern is indicated. Dermal exposure scenarios beeing in the concern range are production and further processing if unsuitable glove material is provided and use of dyes with residual anilin. **Conclusion (iii)**.

Irritation/Corrosivity

Aniline causes weak irritation to the skin of rabbits. This was not sufficient for classification, no concern for humans is derived.

After instillation in the eyes long lasting severe damage was observed in rabbits, it is assumed that preparations containing ≥ 5% aniline are irritating to human eyes. On the grounds that control measures exist for aniline, which should be able to efficiently minimise exposure thereby similarly mitigating concern, conclusion (ii) is proposed. However, these control measures must be implemented and complied with to reduce the risk of damage to the eyes.

Although there is a lack of data concerning local effects in the respiratory tract severe airway damage is not anticipated at concentrations below those relevant for systemic toxicity. Thus specific risk reduction measures concerning this toxicological endpoint are not considered to be necessary: **conclusion (ii)**.

Skin sensitisation

Aniline causes skin sensitisation in guinea pigs and positive reactions in humans have been reported. For risk assessment purposes at the workplace it is assumed that preparations containing ≥ 1% aniline are sensitising to human skin. In several occupational exposure scenarios dermal contact is either expected to be low by technical reasons in combination with PPE or because the aniline content of the formulation which leads to skin contact is below 1%. However, in the chemical industry it cannot be excluded that in rare cases unsuitable glove material might be used which only provides limited protection. In addition during use of dyes considerable dermal exposure might occur. For these scenarios, even if only occasional contact is assumed, the risk of workers to develop a contact allergy is of concern: **conclusion (iii)**.

Sensitisation by inhalation

Data on respiratory sensitisation in humans (e.g. case reports) and in experimental animals is not available. At the background of occupational exposure in former years aniline seems at least not to be a strong respiratory sensitiser in humans since no case reports are recorded. No concern is expressed: **conclusion (ii)**.

Repeated dose toxicity, systemic effects

The most relevant study for MOS calculation is considered to be the 2-year oral study by CIIT. Its results are confirmed by a 14-day inhalation study by EPA. As starting point the rat LOAEL of 7 mg/kg/day is taken. The corresponding human dose is identified as 490 mg/person/day, the according air concentration at the workplace is 49 mg/m^3. Evaluation of the MOS values accounts for species extrapolation, differences between study duration and occupational exposure, the fact that a LOAEL is used as a starting point, uncertainty considerations. Altogether a minimal MOS of 107 is identified for chronic toxicity of aniline. The according critical exposure level is 4.6 mg/person/day or 0.5 mg/m^3.

Several inhalation or dermal MOS values are below the minimal MOS (see **Tables 4.2** and **4.3**) and risk reduction measures should be initiated: **conclusion (iii)**.

Mutagenicity

Under certain circumstances aniline is able to induce genotoxic effects in soma cells *in vivo*. Thus for aniline possible risks by heritable damage cannot be excluded. With the available data, a more differentiated risk estimation concerning different exposure situations is not possible. Since the nature of the effect in general is considered to be severe, concern is raised for all exposure scenarios. A high degree of uncertainty is associated with this decision. **Conclusion (iii)**.

Carcinogenicity

In two carcinogenicity studies aniline caused increasing incidences of spleen sarcomas in male F344 rats. It can be assumed, that genotoxicity might be responsible for tumour initiation and development, but other mechanisms might also be involved. From the rat carcinogenicity data the dose resulting in a tumour rate of 25 % (T25) is obtained as 46 mg/kg/day. As starting point for MOE calculation the corresponding human dose is identified as 3,220 mg/person/day, the according air concentration at the workplace calculates to 322 mg/m^3.

For the time being, risk characterisation as a whole is limited by the uncertainties concerning the mechanism of tumour formation and its relevance for humans. Since a genotoxic mechanism cannot be excluded concern is expressed for all exposure scenarios: **conclusion (iii)**. However, high MOE values indicate, that cancer risks are already very low and might not need immediate further action thus leading to **conclusion (iii) (low)**. The respective evaluation of MOE values accounts for the risk level at T25, which from the results of a multistage model is 460 times higher than $1 \cdot 10^{-4}$, species extrapolation and differences between "standard life span humans" and duration of exposure at work. The minimal MOE is identified as 1,620. The according critical exposure level is 2 mg/person/day or 0.2 mg/m^3.

For several inhalative and dermal scenarios MOE values below 1,620 lead to conclusion (iii) (see **Tables 4.2** and **4.3**). It should be noted that for repeated dose toxicity the same working areas are identified to be of concern: **conclusion (iii)**.

Reproductive toxicity, fertility impairment

The available results are interpreted as giving no indication for reproductive toxicity of aniline up to doses which induce chronic toxic effects and carcinogenicity. For significant higher exposure levels fertility risks cannot be excluded on the basis of the available data. **Conclusion (ii)**.

Reproductive toxicity, developmental toxicity

Although no significant impairment of development was detected in an according study, some indications for less important changes were obtained. With a conservative approach the animal NOAEL of 21 mg aniline/kg/day is used as starting point for MOS calculation. The corresponding human dose is identified as 1,470 mg/person/day, the according air concentration at the workplace is 147 mg/m^3. Evaluation of the MOS values only accounts for species extrapolation because the NOAEL is derived with sufficient precaution. The minimal MOS for developmental toxicity is 10. The according critical exposure level is 150 mg/person/day or 15 mg/m^3.

Dermal contact during production and further processing in the large-scale chemical industry in the case of unsuitable gloves leads to a **conclusion (iii)**.

Summary tables

Tables 4.2 and 4.3 give a summary of the most critical exposure scenarios in the order of risk with respect to inhalation and dermal exposure, respectively. For mutagenicity **conclusion (iii)**, associated with a high degree of uncertainty, applies for all scenarios (not shown).

Table 4.2 Ranking of the most critical inhalation exposure scenarios for aniline and associated health risks

Scenario [1]		Exposure level in mg/m³	Carcino-genicity	Repeated dose toxicity	Acute toxicity	Developmental toxicity
			Critical exposure level in mg/m³			
			0.2	0.5	1.5	15
3a,b	Production by means of H_2 or by means of Fe	12	**iii**	**iii**	**iii**	ii
6	Iron, steel and aluminium foundries	6.4	**iii**	**iii**	**iii**	ii
1a,b	Production, reduction of nitrobenzene by means of H_2	2.5	**iii**	**iii**	**iii**	ii
4a,b	Further processing to various products	2	**iii**	**iii**	**iii**	ii
2a,b	Production, reduction of nitrobenzene by means of Fe	1.5	**iii**	**iii**	**iii**	ii
5	Vulcanisation of rubber plastics and rubber processing	0.8	**iii**	**iii**	ii	ii
Other scenarios		≤ 0.1	**iii** (low)	ii	ii	ii

1) 1a-4a: suitable gloves, 1b–4b: unsuitable gloves

Table 4.3 Ranking of the most critical dermal exposure scenarios for aniline and associated health risks

Scenario [1]		Exposure level in mg/p/d	Carcino-genicity	Repeated dose	Acute toxicity	Sensiti-sation	Developmental toxicity
			Critical exposure level in mg/p/d				
			2	5	15	n.d.[2]	150
1b	Production, reduction of nitrobenzene by means of H_2	420	**iii**	**iii**	**iii**	**iii**	**iii**
2b	Production, reduction of nitrobenzene by means of Fe	420	**iii**	**iii**	**iii**	**iii**	**iii**
3b	Production by means of H_2 or by means of Fe	420	**iii**	**iii**	**iii**	**iii**	**iii**
4b	Further processing to various products	420	**iii**	**iii**	**iii**	**iii**	**iii**
8a	Use of dyes with residual aniline (2%), used e.g. in the textile industry, Liquid dyeing formulations	84	**iii**	**iii**	**iii**	**iii**	ii
8b,c	Use of dyes with residual aniline (2%), used e.g. in the textile industry, Powdery dyes	17	**iii**	**iii**	**iii**	**iii**	ii
Other scenarios		≤ 1	**iii** (low)	ii	ii	ii	ii

1) 1a-4a: suitable gloves, 1b–4b: unsuitable gloves
2) For skin sensitisation a critical exposure level cannot be determined. However in several scenarios dermal exposure is expected to be low enough not leading to concern, either by technical reasons in combination with the use of personal protective equipment or because the aniline content of the formulation which leads to skin contact is below 1%.

For inhalation aniline exposures at the workplace on the background of cancer risks air concentrations of 0.2 mg/m^3 should not be exceeded. By this measure risks from several other endpoints as repeated dose toxicity, acute toxicity or reproductive toxicity would similarly and

effectively be mitigated, too. Special emphasis has to be given to reduce dermal contact with aniline. Aniline easily penetrates human skin and risk assessment shows that the according risks might actually be higher than those from inhalation exposure. Even a significant lower dermal absorption as assumed would not sufficiently reduce the estimated risks. Therefore effective risk reduction measures should be implemented and complied with at all working places. As a minimum standard it seems self-evident that suitable gloves should be provided.

In **Table 4.4** occupational exposure scenarios are listed in the order of scenario numbers to give an overview for all situations with concern. All toxicological endpoints are listed which at least in one case lead to a conclusion (iii). Irritation, respiratory sensitisation and fertility, giving no reason for concern, are not included.

Table 4.4 Summary of exposure scenarios with concern for aniline

Scenario		Acute toxicity		Sensitisation	Repeated dose toxicity		Mutagenicity	Carcino-genicity		Develop-mental toxicity	
		Inhalation	Dermal	Dermal	Inhalation	Dermal	Inhalation or dermal	Inhalation	Dermal	Inhalation	Dermal
Production and further processing in the large-scale chemical industry [1]											
1a	Production, reduction of nitrobenzene by means of H_2	**iii**	ii	ii	**iii**	ii	**iii**	**iii**	**iii** (low)	ii	ii
1b		**iii**	**iii**	**iii**	**iii**	**iii**	**iii**	**iii**	**iii**	ii	**iii**
2a	Production, reduction of nitrobenzene by means of Fe	**iii**	ii	ii	**iii**	ii	**iii**	**iii**	**iii** (low)	ii	ii
2b		**iii**	**iii**	**iii**	**iii**	**iii**	**iii**	**iii**	**iii**	ii	**iii**
3a	Production by means of H_2 or by means of Fe	**iii**	ii	ii	**iii**	ii	**iii**	**iii**	**iii** (low)	ii	ii
3b		**iii**	**iii**	**iii**	**iii**	**iii**	**iii**	**iii**	**iii**	ii	**iii**
4a	Further processing to various products	**iii**	ii	ii	**iii**	ii	**iii**	**iii**	**iii** (low)	ii	ii
4b		**iii**	**iii**	**iii**	**iii**	**iii**	**iii**	**iii**	**iii**	ii	**iii**
Release of aniline as a decomposition product											
5	Vulcanisation of rubber plastics and rubber processing	ii	ii	ii	**iii**	ii	**iii**	**iii**	**iii** (low)	ii	ii
6	Iron, steel and aluminium foundries	**iii**	ii	ii	**iii**	ii	**iii**	**iii**	**iii** (low)	ii	ii
7	Different branches (e.g. plastics processing, electrical engineering)	ii	ii	ii	ii	ii	**iii**	**iii** (low)	**iii** (low)	ii	ii

Table 4.4 continued overleaf

Table 4.4 continued Summary of exposure scenarios with concern for aniline

Scenario			Acute toxicity		Sensitization	Repeated dose toxicity		Mutagenicity	Carcino-genicity		Develop-mental toxicity	
			Inhalation	Dermal	Dermal	Inhalation	Dermal	Inhalation or dermal	Inhalation	Dermal	Inhalation	Dermal
Use of products with residual aniline												
8a	Use of dyes with residual aniline (2%), used e.g. in the textile industry	liquid dyes formulations	ii	**iii**	**iii**	ii	**iii**	**iii**	**iii** (low)	**iii**	ii	ii
8b		powdery dyes (+ LEV)	ii	**iii**	**iii**	ii	**iii**	**iii**	**iii** (low)	**iii**	ii	ii
8c		powdery dyes (- LEV)	ii	**iii**	**iii**	ii	**iii**	**iii**	**iii** (low)	**iii**	ii	ii
9	Use of adhesives (0.3%) engineering, device and tool construction industries		ii	ii	ii	ii	ii	**iii**	**iii** (low)	**iii** (low)	ii	ii

1) In the large-scale chemical industry normally suitable gloves are worn (Scenarios 1a-4a), however it cannot be excluded that the use of unsuitable glove material provides only limited protection (Scenarios 1b-4b)

4.1.3.2 Consumers

There is scarce information from Spain, that aniline is a component of a product used for dyeing shoes. The calculation of the dermal exposure of consumers due to wearing shoes dyed with an aniline-containing product leads to an internal exposure to aniline of $1.0 \cdot 10^{-4}$ mg/kg bw/d (adults) and of $4.3 \cdot 10^{-5}$ mg/kg bw/d (children).

Repeated dose toxicity

From all studies with chronic administration of aniline to rats a NOAEL could not be derived. The LOAEL of systemic toxic effects (nonneoplastic lesions) of 7 mg/kg bw/d from the carcinogenicity study in rats was considered to be the most appropriate value for risk assessment. The margin of safety between the estimated exposure levels and the oral LOAEL is judged to be sufficient, even if special considerations on intra- and interspecies variation, nature and severity of the effects and possible human populations at risk are taken into consideration and being aware that the exposure calculation is based on a worst-case model calculation. Thus, there is no concern in relation to dermal exposure of consumers from wearing dyed leather shoes regarding nonneoplastic effects: **conclusion (ii)**.

Mutagenicity

Aniline is positive in mammalian cell cultures with respect to gene and chromosomal mutations. *In vivo*, aniline is an inducer of micronuclei in mouse and rat bone marrow cells. In rats a positive dose-related response can be seen in non-toxic doses. Aniline is classified as category 3 mutagen and labelled "R 68, possible risks of irreversible effects". Taken together, a possible risk cannot be excluded and an exposure level without effect cannot be stated. Thus, there remains concern on mutagenicity for consumers: **conclusion (iii)**.

Carcinogenicity

Data on carcinogenicity in humans are inadequate. No clear tumour response could be associated with occupational aniline exposure to humans. Aniline is clearly carcinogenic in rats, together with the knowledge on metabolism and positive *in vivo* genotoxicity a relevant concern on carcinogenicity in humans is concluded. Aniline is considered to be a non-threshold carcinogen. It is classified as a category 3 carcinogen. Thus, there is concern on carcinogenicity for consumers: **conclusion (iii)**.

Toxicity for reproduction / Fertility

Conclusive fertility studies are not available for aniline, but in a chronic toxicity feeding study with doses of up to 72 mg/kg/day no significant effects were observed for male or female reproductive organs, however, at the highest dose severe chronic toxic effects and carcinogenicity occurred. The results concerning reproductive organs are interpreted as giving no indication for an impairment of fertility up to doses which induce toxic and tumourigenic effects. Taking into account the low exposure it can be concluded that there is no concern in relation to fertility regarding dermal exposure of consumers from wearing dyed leather shoes: **conclusion (ii)**.

Toxicity for reproduction / Developmental toxicity

The available data from animal studies did not give evidence for a specific embryotoxic, fetotoxic or teratogenic potential of aniline (NOAEL 21 mg aniline/kg bw/d). The margin of safety between the estimated low exposure levels of adults and children and the NOAEL is judged to be sufficient. Thus, the substance is of no concern in relation to dermal exposure of consumers from wearing dyed leather shoes: **conclusion (ii)**.

4.1.3.3 Humans exposed via the environment

Indirect exposure via the environment is calculated using data for oral intake via food, drinking water, and air. Following the local scenario data (at a point source) an intake of a total daily dose of 0.74 mg/kg bw/d is calculated with the main contributions of the $DOSE_{stem}$ and $DOSE_{air}$ with fractions of 64% and 35%, respectively. Following the data for the regional scenario, the total daily dose is lower ($4.4 \cdot 10^{-6}$ mg/kg bw/d) with a fraction of the $DOSE_{drw}$ of 84%. Due to the removal of aniline in the waterworks the total daily intake is reduced to $0.7 \cdot 10^{-6}$ mg/kg bw/d. A daily intake of aniline via plants of 0.11 mg/kg bw/d has been calculated.

Repeated dose toxicity

Local scenario

A NOAEL has not been established; the LOAEL of systemic toxic effects (nonneoplastic lesions) of 7 mg/kg bw/d is derived from the lifetime carcinogenicity study in rats. The margin of safety between the estimated exposure level of 0.74 mg/kg bw/d and the oral LOAEL of 7 mg/kg bw/d is judged to be not sufficient**.** Taking into account the nature and severity of the effects and being aware that the exposure calculation is based on measured data there is need for limiting the risks: **conclusion (iii)**.

Regional scenario

The total calculated internal dose after combined exposure is $0.7 \cdot 10^{-6}$ mg/kg bw/d (regional scenario). The margin of safety between the exposure level and the oral LOAEL of 7 mg/kg bw/d is judged to be sufficient. Thus, the substance is of no concern in relation to regional exposure via the environment: **conclusion (ii)**.

Intake from plants

The calculated intake from plants amounts to 0.11 mg/kg bw/d. The margin of safety between the exposure and the oral LOAEL of 7 mg/kg bw/d is judged to be not sufficient taking into account the nature and severity of the effects and being aware that the exposure calculation is based on measured data. Thus, there is need for limiting the risks: **conclusion (iii)**.

Mutagenicity

Aniline is positive in mammalian cell cultures with respect to gene and chromosomal mutations. *In vivo*, aniline is an inducer of micronuclei in mouse and rat bone marrow cells. In rats a positive dose-related response can be seen in non-toxic doses. Aniline is classified as category 3 mutagen and labelled "R 68, possible risks of irreversible effects". Taken together, a possible risk cannot be excluded for the different exposure scenarios via the environment. Thus, there is need for limiting the risks: **conclusion (iii)**.

Carcinogenicity

There is clear evidence on carcinogenicity in rats. Occupational aniline exposure is not clearly associated with a tumour response in humans. DNA adduct formation was demonstrated in the spleen as target organ of carcinogenicity. Aniline is considered to be a non-threshold carcinogen. It is classified as a category 3 carcinogen. Animal data and i*n vivo* genotoxicity data give concern that aniline is carcinogenic to humans, too. Thus, there is need for limiting the risks for the different exposure scenarios via the environment: **conclusion (iii).**

Toxicity for reproduction / Fertility

Conclusive fertility studies are not available for aniline, but in a chronic toxicity feeding study with doses of up to 72 mg/kg bw/d no significant effects were observed for male or female reproductive organs, however, at the highest dose severe chronic toxic effects and carcinogenicity occurred. The results are interpreted as giving no indication for an impairment of fertility up to doses which induce toxic and tumourigenic effects. As consequence of carcinogenicity and chronic toxicity risk reduction measures have to be taken into account for aniline. Thus, exposure will be at a level which is clearly below concern with respect to fertility: **conclusion (ii)**.

Toxicity for reproduction / Developmental toxicity

Local scenario

The total internal dose after the combined exposure is 0.74 mg/kg bw/d for the local scenario. The available animal data did not give evidence for a specific embryotoxic, fetotoxic or teratogenic potential of aniline (NOAEL 21 mg aniline/kg bw/d). The margin of safety is judged

to be not sufficient. Thus, the substance is of concern in relation to local exposure via the environment: **conclusion (iii)**.

Regional scenario

The total calculated internal dose after combined exposure is $0.7 \cdot 10^{-6}$ mg/kg bw/d (regional scenario). The margin of safety between the exposure level and the NOAEL of 21 mg/kg bw/d is judged to be sufficient. Thus, the substance is of no concern in relation to regional exposure via the environment: **conclusion (ii**).

Intake from plants

The calculated intake from plants amounts to 0.11 mg/kg bw/d. The margin of safety between the calculated exposure and the NOAEL of 21 mg/kg bw/d is judged to be sufficient. Thus, there is no concern in relation to indirect exposure via plants: **conclusion (ii)**.

4.2 HUMAN HEALTH (PHYSICO-CHEMICAL PROPERTIES)

In view of its chemical structure, aniline is not expected to have an oxidising potential. The substance is neither explosive nor flammable. Therefore with regard to the physico-chemical properties and with regard to the occupational and consumer exposure aniline is not expected to cause specific concern relevant to human health: **conclusion (ii).**

5 RESULTS

5.1 ENVIRONMENT

Aquatic compartment (incl. sediment)

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

This conclusion is reached because of the need for better information to adequately characterise the risks for the aquatic ecosystem as a consequence of exposure arising from rubber production sites.

The information and/or test requirements are:

- data about the formation of aniline from rubber chemicals, the releases into the wastewater and wastewater treatment processes which are representative for the European rubber industry.

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 effects on the aquatic environmental spheres including sediment as a consequence of exposure arising from aniline production and further processing (4,4'-methylenedianiline and rubber chemicals) sites.

Atmosphere

Conclusion (i) There is a 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 the atmosphere.

The information and/or test requirements are:

- data about releases into the atmosphere and the applied exhaust air purification techniques which are representative for the European rubber industry.

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 effects on plants as a consequence of exposure via the air compartment arising from one aniline production site.

Terrestrial compartment

Conclusion (i) There is a 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 agricultural soils from aniline as a degradation product of phenylurea and carbamate derivatives used as plant protection products.

The information and/or test requirements are:

- long term tests with plants, earthworms and micro-organisms.

However, since the risk to soil from the breakdown of plant protection agents is not covered by Regulation 793/93 it is proposed that this be considered within the frame of Council Directive 91/414/EEC.

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 acute toxicity as a consequence of:
  - inhalation exposure and/or dermal contact in case of unsuitable gloves arising from production and further processing in the large-scale chemical industry;
  - inhalation exposure arising from thermal degradation of plastics in iron, steel and aluminium foundries;
  - dermal exposure arising from the use of dyes containing residual aniline;
- concerns for skin sensitisation as a consequence of dermal exposure arising from production and further processing in the large-scale chemical industry (in case of unsuitable gloves), and the use of dyes with residual aniline;
- concerns for systemic toxic effects as a consequence of
  - inhalation exposure and/or dermal contact in case of unsuitable gloves arising from production and further processing in the large-scale chemical industry;
  - inhalation exposure arising from vulcanisation of rubber chemicals, and from thermal degradation of plastics in iron, steel and aluminium foundries;
  - dermal exposure arising from the use of dyes containing residual aniline;
- concerns for mutagenicity and carcinogenicity in all workplace scenarios, as the substance is identified as a non-threshold carcinogen. However, for the following specific working scenarios risks are already low:
  - release of aniline as a decomposition products in different industrial sectors (e.g. plastics processing, electrical engineering);
  - use of products with residual aniline (e.g. adhesives, engineering, device and tool construction industries);

This should be taken into account when considering the adequacy of existing controls and the feasibility and practicability of further specific risk reduction measures.

- concerns for developmental toxicity as a consequence of dermal exposure in case of unsuitable gloves arising from production and further processing in the large-scale chemical industry.

5.2.1.2 Consumers

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

This concusion is reached because of:

- concerns for mutagenicity and carcinogenicity as a consequence of exposure arising from use of products containing the substance, as aniline is identified as a non-threshold carcinogen.

5.2.1.3 Humans exposed via the environment

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 systemic toxic effects, developmental toxicity, mutagenicity and carcinogenicity as a consequence of exposure arising from point sources.
- concerns for mutagenicity and carcinogenicity as a consequence of possible exposures at a regional level, as aniline is identified as a non-threshold carcinogen. However, exposures are already very low and this should be taken into account when considering the adequacy of existing controls and the feasibility and practicability of further specific risk reduction measures.

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 for risk reduction measures beyond those which are being applied already.

This conclusion is reached because:

- The risk assessment shows that risks are not expected. Risk reduction measures already being applied are considered sufficient.