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p-Chloroaniline

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on Existing Chemicals of Environmental Relevance (BUA)

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S. Hirzel

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Foreword

The German Chemicals Act (Chemikaliengesetz - ChemG) of 1980 stipulates that certain existing chemicals must be reported to the competent authority, if they exhibit properties which indicate that they may be hazardous, either alone or in combination with other substances.
In the summer of 1982, an Advisory Committee on Existing Chemicals of Environmental Relevance (BUA) was set up by the German Chemical Society (Gesellschaft Deutscher Chemiker - GDCh). It brings together representatives from the scientific community, the chemical industry and the governmental authorities. This Advisory Committee is responsible for elaborating appropriate solutions for substances of relevance for health and the environment on the basis of voluntary measures. It selects and examines existing chemicals from the aforementioned angles. The testing and evaluation are based on scientific criteria alone.
It was, therefore, necessary to develop priority setting procedures. In a first phase reports were only prepared for priority chemicals. Within the framework of a first priority setting procedure, chemicals were compiled from several priority lists and 135 chemicals were selected for detailed substance reports.
In a second priority setting procedure the survey of the German Chemical Industry Association (VCI) on all substances with a production volume of more than 10 tons per year was used as a starting list. Since this survey covered 4,600 chemicals, BUA decided to process the corresponding list in several stages. The first stage included approx. 1,050 substances with a production volume of more than 1,000 tons per year.
Detailed reports are drawn up on chemicals suspected of having a hazard potential and abridged reports on those presenting only a minor hazard potential, according to the current state of knowledge.
The detailed BUA reports take in both the published literature and data from industry. If data for the evaluation of the chemicals are not available, additional studies are recommended and the results are published as updates to the reports. The reports serve as a basis for the instigation of administrative measures, when there are indications of risks to health or the environment.

Tübingen, May 1993

Ernst Bayer
Chairman of the Advisory Committee
on Existing Chemicals
of Environmental Relevance

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Summary and conclusions

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Manufacture, usage and distribution among environmental compartments (discharge, occurrence)

In 1990 about 1350 tonnes of 4-chloroaniline were produced in the Federal Republic of Germany, of which about 350 tonnes were exported. 85 % of the 4-chloroaniline produced and retained in the Federal Republic of Germany were further processed by the manufacturers. No information is available on Imports of 4-chloroaniline or on production in the former German Democratic Republic and the ‘new federal states‘, respectively.

Of the 4-chloroaniline produced and retained in the Federal Republic of Germany (ca. 1000 tonnes), about 600 tonnes are used as an intermediate in the synthesis of the active ingredients of plant protection products, about 200 tonnes as an intermediate in the cosmetics industry and about 75 tonnes as a precursor in the production of dyes. No further information is available on the use pattern of the remaining ca. 125 tonnes of 4-chloroaniline produced and retained in the Federal Republic of Germany.

From production of 4-chloroaniline only a few kilogrammes per annum are emitted into the atmosphere and hydrosphere. From processing of 4-chloroaniline, at each of the four German plants concerned, less than 25 kg/a are emitted into the atmosphere, while in total about 240 kg/a are emitted into the hydrosphere. For the 3 isomeric monochloroanilines emissions of 1.5 tonnes from production and 5.5 tonnes from processing were given for 1987 without specifying the amount of 4-chloroaniline alone. There are no emissions of 4-chloroaniline into the geosphere and biosphere from production and processing. Waste from production and processing is disposed of by incineration. Emissions into air and water or into waste from the use of products based on 4-chloroaniline cannot be estimated. About 25 - 50 kg of 4-chloroaniline per annum enter the geosphere from the use of the crop protection agent Monolinuron. Discharges into the environment from the use of structural analogous crop protection agents or from the reformation of daughter products (crop protection agents, dyes), respectively, are conceivable but not quantifiable.

No data are available on the occurrence of 4-chloroaniline in the atmosphere. Since 1973 numerous measurements have been carried out in the River Rhine and its tributaries in the Federal Republic of Germany. In the majority of cases, at detection limits of 0.1, 0.5 and 1 µg/l, no 4-chloroaniline was detected. Detected concentrations in the River Rhine between 1973 and 1990 ranged from 0.087 µg/l to a maximum of 0.6 µg/l, while those found in Rhine tributaries ranged from 0.18 µg/l (Main, 1973/74) to 4.1 µg/l (Emscher, 1984) and 3.8 µg/l (Wupper, 1990). In the Dutch section of the Rhine (1971 to 1986) concentrations of 4-chloroaniline ranged between <0.1 µg/l (detection limit) and 1.1 µg/l (monthly average, January/February 1973), while in Rhine tributaries concentrations ranged from 0.02 µg/l to a maximum of 0.29 µg/l (Ijssel, 1979). In the Federal Republic of Germany (1973/74), 4-chloroaniline concentrations of 0.08 µg/l and 0.007/0.008 µg/l, respectively, were detected in Rhine bank filtrate and the drinking water produced from it. Corresponding concentrations for the River Main (1973/74) were 0.15 µg/l (bank filtrate) and 0.013 µg/l (drinking water from bank filtrate).

Following application of the insecticide Diflubenzuron (Finland 1984), 4-chloroaniline could not be detected in ground water (detection limit, 0.2 µg/l); while at a detection limit of 0.01 - 0.02 µg/l no significant amounts were found in forest fungi, bilberries (*Vaccinium myrtillus*) or cranberries (*Vaccinium vitis-idaea*).

Based on the calculated value of Henry‘s Law constant for 4-chloroaniline, at the most only a small degree of transfer from hydrosphere to atmosphere is to be expected.

Under aerobic conditions most of the 4-chloroaniline entering the soil will be bound covalently to the organic soil fraction, whereby the degree of soil sorption will depend on the content of organic matter, clay content and pH value of the soil.

Transport of 4-chloroaniline from soil into the ground water with leachate, particularly in soil with a low content of organic matter and a high pH, is to be expected.

Degradability

In respect to the photochemical-oxidative degradation of 4-chloroaniline by OH-radicals in the troposphere, half-lives of 4.7 - 9.6 hours have been determined experimentally.

4-Chloroaniline which has entered surface waters should be subject to direct phototransformation in the top layers (experimentally determined half-lives: 1 - 7.5 hours).

In the hydrosphere 4-chloroaniline is inherently biodegradable under aerobic conditions, whereby a large degree of elimination, however, is due to adsorption effects. Thus, under conditions which are unfavourable for photo- or biodegradation, an accumulation of 4-chloroaniline in the sediment of surface waters is to be expected. Under anaerobic conditions no significant degree of biodegradation is to be expected in the hydrosphere. Thus, considering the adsorptive properties of 4-chloroaniline, in this environmental compartment extremely long residence times must be reckoned with.

According to the results of laboratory tests, biodegradation of 4-chloroaniline in soil seems to be possible under aerobic but not under anaerobic conditions, whereby even under aerobic conditions degradation might occur only hesitantly after a lenghty period of adaptation.

Bioaccumulation

4-Chloroaniline can be taken up by plants and incorporated, particularly in their roots. Depending on concentration and the stage of the plant growth, translocation to parts of the shoot also occurs. In monocots, residual 4-chloroaniline is mainly found bound to the cell wall in the lignin and pectin fraction, while in dicots it is found in the starch and protein fraction.

Experimentally determined bioaccumulation factors for fish between 4 and <20 (based on fresh weight) are given, and for green algae between 240 and 260 (based on fresh weight) or 1200 (based on dry weight). For activated sludge accumulation factors of 280 and 1300 have been determined (ratio of conc. in dry weight of sludge to final concentration in water). Together with experimentally determined log P_{OW} in the range of 1.83 - 2.05, these values indicate a low bioaccumulation potential for 4-chloroaniline.

Ecotoxicological effects

In a 16-hr cell proliferation inhibition test with the bacterium *Pseudomonas putida*, an EC_{10} of 72 mg/l was determined for 4-chloroaniline.

In a static test of cell proliferation with *Escherichia coli* a 24-hr minimum inhibitory concentration (MIC) of 370 mg/l and an IC_{50} of 382.7 mg/l were determined. For the bacterium *Mycobacterium smegmatis* a 96-hr MIC of 65 mg/l was determined.

In a static cell proliferation inhibition test with the freshwater yeast *Rhodotorula rubra*, incubated for 24 hours, an IC_{50}-value of 109.0 mg/l was determined, while for two yeast strains isolated from the activated sludge of a sewage plant (*Pichia sp.* and *Rhodotorula sp.*) IC_{50}-values of 78.7 mg/l and 127.6 mg/l, respectively, were found (measured parameter: turbidity).

For brewers yeast (*Saccharomyces cerevisiae*) an IC_{50}-value of 357.2 mg/l was determined with regard to cell proliferation inhibition in the exponential growth phase. For inhibition of the electrical properties of the cell membrane (transport capability) *in vivo*, of purine transport *in vivo* and of proton transport *in vitro* by 4-chloroaniline, IC_{50}-values between 1,454.3 and 2,296.3 mg/l have been determined.

4-Chloroaniline concentrations of up to 5 mg/kg had no inhibitory effect on nitrification in loamy soil (addition of ammonium sulphate or sodium nitrite). On addition of 100 mg 4-chloroaniline/kg soil, complete oxidation of NH_4-N to NO_3-N took 22 days compared to 10 days in the controls. In parallel experiments a reduction of the 4-chloroaniline concentration (30 mg/kg) was observed, corresponding to a drop of 45 % in the effective concentration after 2 weeks incubation.

In a 2-day anaerobic suspension test, concentrations of 50, 100 and 200 mg 4-chloroaniline/l had no inhibitory effect on the denitrification of 70 mg NO_3-N/l by a strain of bacterium isolated from soil.

The effect of 4-chloroaniline on the activity of microorganisms from the top soil (A-horizon) of various soil types was investigated in a 5-day anaerobic Fe(III)-reduction test. With increasing 4-chloroaniline concentration (0 - 500 mg/kg soil added as aqueous solution, with yeast extract as additional substrate) microbial activity decreased which could be quantified by determination of microbial reduction of easily reducible Fe(III)-oxides to soluble Fe^{2+}-ions (AAS analysis). EC_{10}-values deduced from dose-response relationships ranged from 85 to 1,000 mg/kg and EC_{50}-values from 725 to 1000 mg/kg (medians >1000 mg/kg).

The effect of 4-chloroaniline on the activity of soil microorganisms in fresh soil from the Ap-horizon of an area under cultivation was examined using measurements of CO_2 production, fluorescein-diacetate (FDA) hydrolysis and ATP-determination. At concentrations of 2 and 20 mg 4-chloroaniline/kg soil (based on wet weight at 50 % of maximum water-holding capacity) the ATP content increased on most days, while at 200 mg/kg there was an almost constant reduction in ATP. CO_2 production was increased compared to the control at all of the applied concentrations. During the first week of the experiment FDA hydrolysis was stimulated at all of the applied 4-chloroaniline concentrations, subsequently, however, it fell, until at the end of the experiment (day 48) it was below that in the control.

In the Microtox test involving inhibition of bioluminescence in the luminescent marine bacterium *Photobacterium phosphoreum*, IC_{50} values of 3.2 mg/l (5 min.), 3.8 mg/l (15 min.) and 5.1 mg/l (30 min.) were determined for 4-chloroaniline.

In the cell proliferation inhibition test, in which the detrimental effect of 4-chloroaniline on the freshwater ciliate *Tetrahymena pyriformis* was investigated, a 24-hr IC_{50}-value of 10 mg/l was obtained.

Cell proliferation of the unicellular green alga *Scenedesmus subspicatus* was inhibited after 48 - 96 hours exposure to 4-chloroaniline with an IC_{10} of 0.4 mg/l and IC_{50} of 2.2 - 8.0 mg/l, while after 7 days exposure an IC_{10} of 0.02 mg/l and an IC_{50}-value of 2.1 mg/l were obtained. In respect to the effect of 4-chloroaniline on the fluorescence of *Scenedesmus subspicatus* following illumination with a flash of light in a flow-through cuvette, an IC_{10} (here defined as the lowest statistically significant effective concentration) of 0.003 mg/l and an IC_{50}-value of 1.14 mg/l were found (exposure time: 30 minutes).

Seven days exposure of the green alga *Chlorella zofingiensis* to a 4-chloroaniline concentration of 12.8 mg/l resulted in 24 % inhibition of chlorophyll biosynthesis.

Three hours exposure of the flagellated alga *Euglena gracilis* to 4-chloroaniline concentrations of 10 - 200 mg/l resulted in inhibition of cell proliferation between 8 % (10 mg/l) and 40 % (200 mg/l) (determined by optical measurement of cell density).

In a test of the effect of 4-chloroaniline in respect to immobilization on the water flea *Daphnia magna*, 24-hr EC_{50}-values of 0.06 - 12.7 mg/l and a 48-hr EC_{50}-value of 0.31 mg/l were determined.

In an extended daphnia test of reproduction rate, within 21 days of exposure to 4-chloroaniline, an NOEC of 0.01 mg/l (nominal value) was determined.

In a static, 48-hr immobilization test with larvae of the mosquito *Chironomus plumosus* an EC_{50} of 43 mg/l was determined (95 % confidence interval 36 - 51 mg/l).

For the rotifer *Brachionus rubens*, in a closed system a 24-hr LC_{50} value of 100 mg/l was determined. In a 21-day test under semistatic conditions, increasing 4-chloroaniline concentrations (1 - 40 mg/l) resulted in a general decrease in the population parameters ‘natural growth‘ (offspring/female/hour) and ‘population density‘ (individuals/15 ml medium).

The chronic effect of 4-chloroaniline on the population dynamics of two size classes of the zooplankton fraction (rotifera, daphnia, copepods etc.) was studied in both sides open-ended cylinders which had been pressed vertically into the sediment of a 15 year old pond so that the upper ends were above the water surface, thus preventing exchange with the pond water. From strips of impregnated polyethylene hanging in the water enclosed by the cylinders incorporated 4-chloroaniline was slowly released until after about 12 days a concentration of 0.08 - 0.09 mg/l and after 35 days a concentration of 0.03 mg/l was reached within the cylinders. An initial reduction in individual numbers of both size classes, which was explained as resulting from the installation of the cylinders and from temperature effects, was followed, after about 2 weeks exposure, by relatively constant population densities. From day 21 to day 35 of exposure the number of smaller rotifers was 9 - 40 % below that in the control, while the number of larger rotifers was lower by about 13 - 20 %. A reduction in oxygen content and in chlorophyll fluorescence provided evidence of a slight decline in autotrophic plankton, while a higher total carbon

content indicated an insignificant increase in the rate of mineralization in the cylinders contaminated with 4-chloroaniline.
In a 10-hr semistatic test with the shrimp *Crangon septemspinosa* a lethal threshold concentration of 12.5 mg/l was determined (here defined as the geometric mean of the highest measured 4-chloroaniline concentration at which all of the test animals survived and the lowest measured concentration at which all the animals died). For the vivalve *Mya arenaria* a lethal threshold concentration of 15.1 mg/l was found after 29 hours of exposure to 4-chloroaniline.

In tests of the acute toxicity of 4-chloroaniline towards various freshwater fish, the lowest LC_{50}-value (2.4 mg/l) was determined after 96 hours exposure for the blue-gill sunfish (*Lepomis macrochirus*). For other species the 24 to 96-hr LC_{50}-values were between 12 and 46 mg/l.

In a 3-week test of the sublethal effect of 4-chloroaniline on the zebra fish *Brachydanio rerio*, a NOEC of 1.8 mg was determined.

In studies of the acute physiological effect of 4-chloroaniline on rainbow trout (*Oncorhynchus mykiss*), within the first hours of exposure to the 24-hr lethal concentration of 22.4 mg/l there was a significant increase in cough frequency and in blood haematocrit, while ventilation volume, total oxygen consumption, total arterial O_2 and CO_2 content, as well as the pH of arterial blood were significantly reduced. No significant changes were found in ventilation frequency, the efficiency of 0_2 uptake by the gills, in heart beat or in the haemoglobin content of the blood. At this concentration the average time of survival was 5.7 ± 3.2 hours.

In studies of the chronic effect of 4-chloroaniline on growth and reproduction of *Brachydanio rerio* over 3 generations (F_0 to F_2) 17 weeks of exposure to concentrations of 0.04, 0.2 and 1 mg/l had no effect in the F_0 generation (adult, 6 months old) on spawning, fertilization, behaviour, growth or mortality. In the 22nd week of exposure, eggs were taken from each group and subjected to further exposure to the same concentrations of 4-chloroaniline. In the F_1

generation, while fertilization, growth and mortality were unaffected at all the tested concentrations, after 19 weeks of exposure the fish subjected to 0.04 and 0.2 mg/l, but not those subjected to 1 mg/l, were found to be significantly heavier than those in the control group. More than 90 % of the F_1 animals exposed to a concentration of 1 mg/l showed an increase in abdominal swellings and spinal deformations between the ages of 5 weeks and sexual maturity. At all tested concentrations the numbers of eggs deposited by F_1 females were significantly below those in the controls. In addition, at 1 mg/l the rate of fertilization was reduced. Subsequent exposure of the F_2 generation yielded similar results.

Exposure, from the egg stage of development on, of the clawed toad (*Xenopus laevis*) in a semistatic, 90-day test to a concentration of 100 mg 4-chloroaniline/l, resulted in the death of all the animals within 3 weeks. At 1 mg/l a weak delay and at 10 mg/l a marked delay in larval development was observed.

In the test according to OECD-Guideline 208, an EC_{50} of 140 mg/kg soil was determined for oat (*Avena sativa*) and of 66.5 mg/kg soil for the wild turnip (*Brassica rapa*), both values based on dry weight.

In order to establish the effect of 4-chloroaniline on germination and early growth stages of various monocot and dicot species of cultivated plants, 4-chloroaniline was added to the soil (loamy sand) at concentrations of 1, 10, 100 and 1,000 mg/kg before sowing. The 14-day period of incubation had a clear effect on germination and growth only at a concentration of 1000 mg/kg. While at this concentration 11 of the exposed species showed 100 % inhibition of germination, 4 species showed strong inhibition of early growth.

The effect of 4-chloroaniline on photosynthesis in protoplasts of the vetch *Vicia faba* was investigated in a ribulose-bisphosphate carboxylase inhibition test (determination of $^{14}CO_2$ fixation). After 36 hours of exposure to 4-chloroaniline, an IC_{10}-value of 12.8 mg/l and an IC_{20}-value of 38.3 mg/l were determined. In a test of inhibition of oxygen-uptake, the lowest concentration at which any effect was observed after 15 - 20 minutes exposure (given here as IC_{10} was 9.6 x 10^{-5} mg/l, while an IC_{20}-value of 6.4 mg/l is given.

In a 5-week test of the effect of various 4-chloroaniline concentrations on the growth of tomatoes, at concentrations of 5, 10, 15 and 20 mg/l in the watering solution (single application at 6- to 8-leaf stage of development) the plants produced fruits after 5 weeks. Only at concentrations of 25 mg/l and above growth inhibition was observed: at 25 mg/l the plants only reached the stage of flowering, while concentrations of 50 and 100 mg/l caused the roots of the plants to rot and the shoot remaining at the stage of development it was at the time of treatment. In respect to germination, the formation of root or shoot anomalies or the number of rotted seeds, 4-chloroaniline concentrations of 1 - 25 mg/l showed no effect on summer barley (*Hordeum vulgare*), oat (*Avena sativa*), summer wheat (*Triticuni aestivum*) or rape (*Brassica napus*).

An LC_{50} of 540 mg/kg dry substrate was determined for the earth worm *Eisenia fetida* in the test according to OECD-Guideline 207. At 340 - 510 mg/kg the worms showed a clear increase in skin moisture and in slime secretion, while at concentrations above 510 mg/kg they showed loss of weight and strongly reduced activity. The minimum weight of 300 - 600 mg prescribed for the worms in the guideline was not adhered to in 32 % of the tests. Exposure to 4-chloroaniline, which was mixed with the defined substrate, occurred via ingestion and contact with the body surface.

After administration of a single oral dose of 4-chloroaniline, an LD_{50} of 1000 mg/kg body weight was found for the starling (*Sturnus vulgans*) and of 237 mg/kg body weight for the quail (*Coturnix coturnix*).

Toxicological aspects*)

After a single oral dose, p-chloroaniline is rapidly and almost completely absorbed by the organism. The main metabolites in the blood are p-chloroanilide and 2-amino-5-chlorophenyl sulfate. The radio activity reaches a maximum in the plasma one hour after administration of ^{14}C-labelled p-chloroaniline, and is enriched in the erythrocytes within 24 hours. In the urine of mice, rats and monkeys, 80, 81 to 87 and 55 %, respectively, of p-chloroaniline and its metabolites are excreted within 24 hours, while in the faeces, only 5.2, 8.3 and 1.2 %, respectively, are excreted within 4 days. The main metabolite in the urine at 49 % (mice), 54 % (rats) and 36 % (monkeys) is 2-amino-5-chlorophenyl sulfate. The total excretion in 24-hour urine is 80 % in mice, 88 % in rats and 56 % in monkeys, and the total excretion after 4 days (urine and faeces) is 91 % (mice), 101 % (rats) and 82 % (monkeys). p-Cloroaniline is eliminated from the tissues in 2 phases with half-lives of less than 10 minutes and 3 to 4 hours, respectively. In humans, p-chloroaniline is mainly excreted in the urine. Conjugated p-chloroaniline and conjugated 2-amino-5-chlorophenol have also been found as major metabolites in the urine in a case of acute poisoning.

Like aniline, p-chloroaniline primarily damages the erythrocytes, causing methaemoglobinaemia with cyanosis and its secondary effects (anaemia, increases in Heinz bodies, reticulocytosis). In this respect it appears to have even more severe effects than aniline. Kidney damage due to p-chloroaniline has also been described in rats.

p-Chloroaniline is of moderate acute toxicity on oral and dermal administration to rats (LD_{50} oral 300 to 425 mg/kg body weight; LD_{50} dermal 335 mg/kg body weight) and on dermal administration to rabbits (LD_{50} dermal 360 mg/kg body weight). Based on its acute dermal

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*) With permission of BG Chemie taken from:
Toxikologische Bewertungen Nr. 9 “p-Chloroaniline“.
Berufsgenossenschaft der chemischen Industrie.
Heidelberg (1994),
Kap. 1: Summary and assessment.

toxicity, it appears to be well absorbed through the skin. The acute inhalation toxicity in the rat is 2.34 mg/l (4-hour LC_{50}). On subacute oral administration for 28 days, the tolerable no effect dose for rats is less than 10 mg/kg body weight; the no effect level for increases in Heinz bodies in rats is 1 mg/m^3 air after inhalation exposure for a month.

According to early studies, p-chloroaniline is irritating to the skin and eyes of the rabbit, while other studies which have been carried out in accordance with OECD guidelines suggest that it is not.

p-Chloroaniline is a weak sensitizer in the maximization test in guinea-pigs.

After oral administration to rats and mice for 3 months, dose-dependent methaemoglobinaemia occurred down to the lowest doses tested of 7.5 mg/kg body weight/day in the mouse and 5 mg/kg body weight/day in the rat. This was associated with secondary anaemia as well as histopathological effects on the liver, spleen and kidneys which could be attributed to these blood effects. In 6-month subchronic inhalation studies in rats, 15 mg/m^3 was toxic and 1.5 mg/m^3 was the "threshold dose", while an exposure for 3 months, 0.15 mg/m^3 was without effect. The dose having an effect in dogs after oral administration for 3 months was 5 to 15 mg/kg body weight/day (a no effect level was not established). The findings in this study were similar to those described above.

The genotoxicity data are contradictory. p-Chloroaniline is mainly negative in the Salmonella/microsome test up to the concentration of 1000 µg/plate. The same applies to reversion tests in *Escherichia coli*. Other genotoxicity tests (Pol A test in *Escherichia coli*, mitotic recombination in *Saccharomyces cerevisiae* and reversion tests in *Aspergillus nidulans*) have sometimes been positive and sometimes negative. In rat hepatocytes *in vitro*, p-chloroaniline has shown both positive and negative results, but was negative in the UDS test. p-Chloroaniline is positive in the mouse lymphoma test, but does not cause DNA strand breaks in mouse lymphoma cells. No clear results have been obtained in tests for chromosome aberrations and sister chromatid exchange in Chinese hamster ovary (CHO) cells. Overall, the substance should be evaluated as being genotoxic, based on the in vitro studies. *In vivo*, p-chloroaniline is negative in the micronucleus test in the mouse at the maximum tolerated oral dose (180 mg/kg body weight) and positive in the somatic mutation and recombination test in *Drosophila melanogaster*.

With regard to the carcinogenicity of p-chloroaniline, several studies are available in rats and mice, with both negative and positive results. A 78-week feeding study in rats and mice gave no clear results, while a 103-week gavage study produced clear evidence of carcinogenic activity in male rats and no evidence of carcinogenic activity in female mice. The evidence in female rats was equivocal, while there were some indications of carcinogenic activity in male mice. All of the studies primarily involved partly-metastasized spleen tumours (fibromas, fibrosarcomas, sarcomas, carcinomas, haemangiosarcomas), as well as liver tumours in the mice (hepatocellular adenomas, carcinomas, haemangio-sarcomas). These tumours, the spontaneous incidence rate of which is very low, are also seen after chronic administration of aniline, and are viewed as a consequence of the haematotoxic effect of p-chloroaniline, although a genotoxic mechanism for tumour induction cannot be excluded.

p-Chloroaniline was mainly positive in four cell transformation tests.

In vitro studies with human skin (from surgical procedures) show that p-chloroaniline is well absorbed by intact skin, and even more so by abraded skin.

In humans as well as animals, the acute effect of p-chloroaniline (methaemoglobin formation) is more severe than that of aniline. Alcohol can lead to augmentation of the effect.

With regard to the acute toxicity of p-chloroaniline, case reports are available on industrial poisonings, one of which was fatal. One patient survived after appropriate therapy (vitamin C, methylene blue), despite a maximum methaemoglobin level of 70 %.

It is reported from a production unit that p-chloroaniline concentrations of ca. 60 mg/m^3 air have led to methaemoglobin concentrations of 1.6 to 2.8 g/100 ml blood, to cyanosis, anaemia and even to acute intoxication. However, in this case, dermal absorption of the substance was thought to have contributed to the effects. Other reports indicate that a p-chloroaniline concentration of 44 mg/m^3 air leads to severe toxic effects in man after short exposures, and 22 mg/m^3 air leads to signs of illness on longer exposure.

p-Chloroaniline has a strong tendency to form haemoglobin adducts, and their determination can therefore be used in biomonitoring of employees exposed to the effects of p-chloroaniline in the workplace.

p-Chloroaniline is classified in category C2 (substances that should be regarded as carcinogenic in humans).

Recommendations

Ecological aspects

Available data on the ecotoxicology and behaviour of 4-chloroaniline in the environment are considered sufficient for an evaluation of its environmental relevance. Thus, at the moment no further studies are necessary.

Toxicological aspects

Data are available on all the important toxicological end points, so, that an assessment of 4-chloroaniline‘s toxicological effects can be made. Thus, for the time being, further studies are not considered to have a high priority.