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TOXICOLOGICAL EVALUATIONS

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TOXICOLOGICAL EVALUATION

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2,5-Dimethoxy-4-chloroaniline

No. 121

CAS No. 6358-64-1

BG Chemie
Berufsgenossenschaft der chemischen Industrie

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2,5-Dimethoxy-4-chloroaniline

1 Summary and assessment

Oral LD_{50} values of 1260 and 4800 mg/kg body weight have been determined for 2,5-dimethoxy-4-chloroaniline in rats, on the basis of which the chemical can be considered harmful upon acute oral ingestion. It has been found that the clinical signs of acute oral intoxication with 2,5-dimethoxy-4-chloroaniline are unspecific and macroscopic examination at necropsy of deceased animals reveals lobular markings of the liver. Dermal application of 2,5-dimethoxy-4-chloroaniline is not toxic; 24-hour occlusive application of 2000 mg/kg body weight to the intact depilated skin of rats produces no abnormal findings (dermal LD_{50} > 2000 mg/kg body weight).

The toxic effects of 2,5-dimethoxy-4-chloroaniline following repeated administration have been investigated in Sprague-Dawley rats in a subacute oral study conducted in accordance with OECD guideline No. 408 and Directive 79/831/EEC, Annex V, Part B, Method B7. Gavage treatment with 2,5-dimethoxy-4-chloroaniline at daily dose levels of 100 or 500 mg/kg body weight for 29 days gave rise to dose-related alterations in haematological parameters as signs of anaemia, including reductions in red blood cell counts, haemoglobin levels and haematocrit values, mean corpuscular volume and mean corpuscular haemoglobin concentration, increased reticulocyte counts, polychromasia and slight anisocytosis as well as increased early and late normoblast counts in the bone marrow. Furthermore, 2,5-dimethoxy-4-chloroaniline caused dose-related damage to the liver and kidneys at the dose levels stated above, including increased organ weights, alterations in clinical chemistry parameters and histopathological findings in the form of centrilobular hepatocyte enlargement and necrosis of the papillary tubules. In the absence of a histopathological correlate, a marked increase in spleen weight was also noted at 500 mg/kg body weight. The lowest dose tested, 20 mg/kg body weight, which was associated only with occasional post-gavage increase in salivation and slightly increased water consumption in males, was evaluated as the *no observed adverse effect level* (NOAEL).

Exposure of the skin and eyes to 2,5-dimethoxy-4-chloroaniline causes no irritation in rabbits.

2,5-Dimethoxy-4-chloroaniline shows no skin-sensitising potential in the Magnusson and Kligman maximisation test in the guinea pig.

In vitro, the Salmonella/microsome assay, conducted as a standard plate incorporation test on *Salmonella typhimurium* strains TA 98, TA 100, TA 1535, TA 1537 and TA 1538, has shown 2,5-dimethoxy-4-chloroaniline to be clearly mutagenic in strain TA 100 and slightly mutagenic in strain TA 98 in the presence of metabolic activation with S-9 mix from Aroclor 1254-induced rat livers. The test was negative in the absence of metabolic activation. In *Escherichia coli* WP2uvrA and in the HPRT test on V79 cells of the Chinese hamster, no mutagenicity was detected for 2,5-dimethoxy-4-chloroaniline either in the presence or absence of metabolic activation (S-9 mix from Aroclor 1254-induced rat livers). In vivo, the mouse micronucleus assay also revealed no genotoxic effect following a single oral administration of 2,5-dimethoxy-4-chloroaniline at 1200 mg/kg body weight. Thus, 2,5-dimethoxy-4-chloroaniline is devoid of genotoxic potential.

In the Federal Republic of Germany, the Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area ("MAK-Kommission") of the Deutsche Forschungsgemeinschaft has worked on 2,5-dimethoxy-4-chloroaniline on the suggestion of BG Chemie. The MAK-Kommission has assigned 2,5-dimethoxy-4-chloroaniline in the List of MAK and BAT Values 2004, to Category 3B of carcinogenic substances (i.e. "Substances that cause concern that they could be carcinogenic for man but cannot be assessed conclusively because of lack of data. The classification in Category 3 is provisional. Substances for which in vitro or animal studies have yielded evidence of carcinogenic effects that is not sufficient for classification of the substance in one of the other categories. Further studies are required before a final decision can be made. A MAK or BAT value can be established provided no genotoxic effects have been detected."). Furthermore 2,5-dimethoxy-4-chloroaniline has been designated with "H" because of the danger of percutaneous absorption.

2 Name of substance

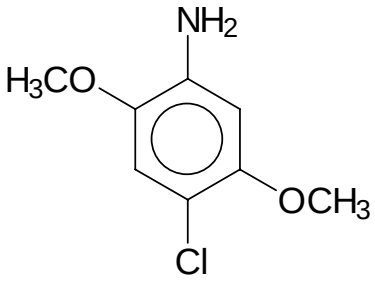
2.1	Usual name	2,5-Dimethoxy-4-chloroaniline
2.2	IUPAC name	2,5-Dimethoxy-4-chloroaniline
2.3	CAS No.	6358-64-1
2.4	EINECS No.	228-782-0

3 Synonyms, common and trade names

1-Amino-4-chlor-2,5-dimethoxybenzol
Aminochlorhydrochinondimethylether
2-Amino-5-chlorhydrochinondimethylether
2-Amino-5-chlorohydroquinone dimethyl-ether
Aniline, 4-chloro-2,5-dimethoxy-
Benzenamine, 4-chloro-2,5-dimethoxy-
Benzolamin, 4-Chlor-2,5-dimethoxy-
5-Chlor-2-amino-1,4-dimethoxybenzol
Chloraminohydrochinondimethylether
4-Chlor-2,5-dimethoxyanilin
4-Chlor-2,5-dimethoxybenzolamin
Chloro-4-dimethoxy-2,5-aniline
4-Chloro-2,5-dimethoxyaniline
4-Chloro-2,5-dimethoxybenzenamine
CMEB
CME-Base
2,5-Dimethoxy-4-chloranilin

4 Structural and molecular formulae

4.1 Structural formula



4.2 Molecular formula $C_8H_{10}ClNO_2$

5 Physical and chemical properties

5.1	Molecular mass, g/mol	187.63	
5.2	Melting point, °C	117.5	(EC, 2000)
5.3	Boiling point, °C	Decomposition at 25 °C	(EC, 2000)
5.4	Vapour pressure, hPa	0.00001 (at 20 °C) 0.0933 (at 90 °C)	(EC, 2000)
5.5	Density, g/cm³	1.3 (at 20 °C)	(Hoechst, 1986 a, b)
5.6	Solubility in water	4 g/l (at 20 °C)	(EC, 2000)
5.7	Solubility in organic solvents	Soluble in ethanol, toluene, acetone, xylene, benzene and ether	(Hoechst, 1986 a, b)
5.8	Solubility in fat	Partition coefficient log P_{ow}: 1.8 and 1.88 (calculated)	(EC, 2000)
5.9	pH value	7–8	(Hoechst, 1991)
5.10	Conversion factor	1 ml/m³ (ppm) ≙ 7.66 mg/m³ 1 mg/m³ ≙ 0.13 ml/m³ (ppm) (at 1013 hPa and 25 °C)	

6 Uses

Intermediate in the manufacture of pigments and dyestuffs (Hoechst, 1986 a, b, 1991).

7 Experimental results

7.1 Toxicokinetics and metabolism

No information available.

7.2 Acute and subacute toxicity

Acute toxicity

The acute oral toxicity of 2,5-dimethoxy-4-chloroaniline (purity not specified) was studied in female Wistar rats (strain Hoe: WISKf(SPF71)). Groups of 10 animals received 800, 2000 or 5000 mg/kg body weight by gavage as a 25-percent suspension in sesame oil. The observation period was 14 days. An LD_{50} value of 1260 (798 to 1850) mg/kg body weight was ascertained. Clinical signs of toxicity included drowsiness, imbalance, squatting posture, crawling position or stooped posture, abdominal position, lateral position, piloerection, narrow palpebral fissures, increased lacrimation, irregular or intermittent breathing, narcosis and dark-brown yellow discoloration of the urine. Necropsy of the animals that died revealed lobular markings of the liver and full urinary bladder containing brown urine as macroscopic findings. Terminal necropsy yielded no remarkable findings (Hoechst, 1979).

In a further study conducted to determine the oral LD_{50}, 2,5-dimethoxy-4-chloroaniline in corn oil was administered by gavage to groups of 10 male Wistar rats at dose levels of 1080, 1950, 3510, 4720 or 6330 mg/kg body weight. The observation period was 14 days. No necropsies were carried out. The LD_{50} value was calculated to be 4800 (3800 to 6000) mg/kg body weight. Clinical signs of toxicity, which included, *inter alia*, lethargy, prostration, ptosis, piloerection, diarrhoea, chromorhinorrhoea and chromodacryorrhoea, were unspecific (MB, 1979).

The dermal LD_{50} of 2,5-dimethoxy-4-chloroaniline of $\geq$ 99.0% purity was determined in 5 male and 5 female Wistar rats (strain Hoe: WISKf(SPF71)) in a limit test performed in accordance with OECD guideline No. 402. A dose of 2000 mg/kg body weight was applied to the intact depilated dorsal skin under occlusive cover. After 24 hours, the skin was washed with water to remove residual substance. No deaths or signs of intoxication occurred du-

ring the 14-day observation period. Necropsy was without remarkable findings. Thus the dermal LD_{50} value for 2,5-dimethoxy-4-chloroaniline in the rat was > 2000 mg/kg body weight (Hoechst, 1988 a).

Subacute toxicity

A preliminary study for a 4-week oral study (see below; HRC, 1993 b) was conducted in groups of 5 male and 5 female Sprague-Dawley rats (strain Crl: CD® SD BR VAF PLUS; mean initial weights approx. 163 and approx. 145 g, respectively) given 2,5-dimethoxy-4-chloroaniline (87.7% pure) at dietary concentrations of 0 (control), 2000, 4000 or 8000 ppm for 14 days. The study was carried out in accordance with OECD guideline No. 407. Food consumption was used to calculate daily dietary intake of 2,5-dimethoxy-4-chloroaniline in males and females, which was found to be 0 (control), 240, 469 or 915 mg/kg body weight and 0 (control), 225, 460 or 906 mg/kg body weight, respectively. All animals survived. Food consumption and body weight gain showed dose-dependent decreases during the first week of the study. Fur loss from the back and shoulder region occurred in animals of all dose groups, and piloerection was additionally noted in the top dose group. Red stains were observed on the cage tray paper in all groups treated with 2,5-dimethoxy-4-chloroaniline. There were no such stains in the controls, suggesting that staining was due to urinary excretion of the pink-coloured test substance. The top dose group, in particular, exhibited changes in haematological parameters as signs of anaemia; haemoglobin levels, red blood cell counts and packed cell volume levels were lowered and there was polychromasia of the red blood cells. In addition, blood clotting was affected (lowered thrombotest times) in males and females and higher platelet counts were recorded from males. To a lesser extent, polychromasia was noted in the animals in the two lower dose groups and clotting was reduced in the 4000 ppm males. With regard to the clinical chemistry parameters studied, cholesterol and bilirubin levels were increased in the top dose group (8000 ppm) whilst alkaline phosphatase and aspartate aminotransferase (glutamic-oxaloacetic transaminase) levels were decreased, as were alanine aminotransferase (glutamic-pyruvic transaminase) levels in females only. Moreover, males exhibited lower albumin/globulin ratios. The 4000 and 2000 ppm doses also reduced alkaline phosphatase levels; the 4000 ppm dose increased cholesterol levels and, in fe-

males only, bilirubin levels while reducing the albumin/globulin ratio in males. Relative liver weights were increased in all dose groups. Relative kidney weights were increased in top-dose males but decreased in females from the two upper dose groups, as were adrenal weights. Four out of 10 animals in the low dose group, 5 out of 10 in the intermediate dose group and 6 out of 10 in the top-dose group showed macroscopic enlargement of the liver. Treatment-related minimal centrilobular hepatocyte enlargement occurred in all dose groups together with minimal aggregation of organelles in centrilobular hepatocytes. A *no observed effect level* could not be achieved. Diet analysis revealed that 2,5-dimethoxy-4-chloroaniline was not stable at dietary levels lower than 50 ppm (HRC, 1993 a).

In the subsequent 4-week study, the animals were dosed by gavage because the stability of 2,5-dimethoxy-4-chloroaniline appeared to be insufficient in dietary administration (see above; HCR, 1993 a). The study was conducted in accordance with OECD guideline No. 408 and Directive 79/831/EEC, Annex V, Part B, Method B7. Groups of 5 male and 5 female Sprague-Dawley rats (strain Crl: CD® SD BR VAF PLUS, respective mean initial weights 147.2 and 137 g) received daily treatment with a corn oil suspension containing 2,5-dimethoxy-4-chloroaniline (77.9% pure, 18.5% water) at 0 (control), 20, 100 or 500 mg/kg body weight for 29 days. All animals survived until necropsy on day 30 of the study. Body weight gains were depressed from the first week of the study in the top-dose males and at study week 4 in the top-dose females. Food consumption was significantly reduced in top-dose males, though only during the first half of the study, whilst water consumption was dose-dependently increased in all male dose groups and from 100 mg/kg body weight in females. Only males in the top dose group showed significantly lower terminal body weights than control. Clinical signs of toxicity noted in animals in the 100 and 500 mg/kg groups included piloerection, increased salivation and, intermittently, abnormal gait, which were dose-related. Animals in the 500 mg/kg group also exhibited hunched posture and intermittent lethargy and ptosis. The treated animals' cage tray paper showed a reddish-brown staining which did not occur in the controls. The animals in the low dose group treated at 20 mg/kg body weight by gavage exhibited an increase in post-dose salivation on a number of occasions during the study. At 500 mg/kg body weight the following significant alterations in haematological parameters were recorded as signs of anaemia: decreases in red blood cell count, haemoglobin, haema-

tocrit, MCV (mean corpuscular volume; in females only) and MCHC (mean corpuscular haemoglobin concentration; in males only), an increase in reticulocyte count; polychromasia and slight anisocytosis; additionally, bone myelograms revealed significant increases in early and late normoblasts in males whereas total erythroid cells tended to be increased, though not statistically significantly, in males and females. Many of the haematological changes evident in animals treated at 500 mg/kg body weight were also noted in a milder form following administration of 100 mg/kg body weight. Significant changes at that dose level included decreases in red blood cell counts, haemoglobin and haematocrit, the latter in males only, as well as higher reticulocyte counts in females and slight polychromasia in both sexes. Females in the two higher dose groups had slight reductions in thrombotest time as a measure of blood clotting. No statistically significant changes in red cell parameters were noted in animals treated at 20 mg/kg body weight. Changes in clinical chemistry parameters were evident in the upper two dose groups and comprised increased bilirubin concentrations in both sexes and reduced aspartate aminotransferase activity in males. Additionally, but restricted to the top dose group, cholesterol concentrations were increased in both sexes and plasma protein and creatinine levels were elevated in females, as were the sodium and chloride levels and alkaline phosphatase activity. There were increases in absolute and relative liver weights in both sexes in the intermediate and high dose groups, increases in relative kidney weights in the intermediate-dose females and the top-dose males and females as well as increases without histopathological correlates in relative and absolute spleen weights in both sexes in the top dose group. Furthermore, absolute testes weights were reduced in all dose groups in the absence of dose-dependence and histopathological correlates. Histological examination revealed centrilobular hepatocyte enlargement in 1 out of 5 intermediate-dose males and females, 5 out of 5 top-dose males and 4 out of 5 top-dose females as well as kidney degeneration in the form of papillary necrosis in 2 out of 5 intermediate-dose males and in 4 out of 5 males and 3 out of 5 females in the top dose group. The lowest dose tested, 20 mg/kg body weight, which was associated only with occasional post-gavage salivation and slightly increased water consumption in males, was evaluated by the investigators as representing the *no observed adverse effect level* (NOAEL; HRC, 1993 b).

7.3 Skin and mucous membrane effects

An acute skin irritation study, carried out in rabbits in accordance with OECD guideline No. 404 and Directive 84/449/EEC, found 2,5-dimethoxy-4-chloroaniline (98% pure) to be nonirritating. A 500 mg dose of the chemical was semi-occlusively applied to the intact depilated skin of the trunk of 3 New Zealand rabbits for 4 hours. All examinations at 30 and 60 minutes and 24, 48 and 72 hours after the end of exposure revealed no abnormal skin findings in any of the animals (Hoechst, 1986 a).

In an eye irritation study of 2,5-dimethoxy-4-chloroaniline (98% pure), conducted in accordance with OECD guideline No. 405 and Directive 84/449/EEC, 3 New Zealand rabbits each had 100 mg of the chemical (99.5% pure) administered into the conjunctival sac of one eye. Irritancy was assessed at 1, 24, 48 and 72 hours after administration. Examination one hour after administration revealed slight swelling of the conjunctivae and marked hyperaemia to diffuse crimson colouration of the conjunctivae. The signs of irritation were accompanied by clear ocular discharge. The conjunctival swelling was reversible in all animals after 24 hours, whereas the reddening of the conjunctiva cleared up after 48 hours in 2 animals and after 72 hours in one. Based on the individual scores for the readings at 24, 48 and 72 hours, a mean score of 0.0 was calculated for clouding of the cornea, iritis and conjunctival swelling while a mean score of 0.4 was obtained for reddening of the conjunctivae. Based on the classification criteria set forth in Directive 83/467/EEC, the chemical was evaluated as nonirritating (Hoechst, 1986 b).

7.4 Sensitisation

2,5-Dimethoxy-4-chloroaniline showed no skin-sensitising potential in a Magnusson and Kligman maximisation test in the guinea pig performed in accordance with OECD guideline No. 406 and Directive 96/54/EC, Annex IV C, Method B6. In preliminary skin irritation studies, a 5-percent formulation of 2,5-dimethoxy-4-chloroaniline (99.1% pure) in hydroxyethylcellulose (Tylose H 4000 G4 PHA), injected intradermally with 50-percent Freund's complete adjuvant, caused well-defined erythema and slight oedema. A 1-percent and a 0.2-percent formulation gave rise to slight erythema and oedema. Occlusive 24-hour dermal exposure of the intact depilated dorsal

skin to up to 25-percent formulations after intradermal injection of the adjuvant gave no abnormal findings. In the actual sensitisation test, 10 female Pirbright-White guinea pigs (strain HsdPoc:DH) were injected twice intradermally into the intact depilated dorsal skin with 50-percent adjuvant, a 5-percent formulation of 2,5-dimethoxy-4-chloroaniline in hydroxyethylcellulose and a mixture of the latter formulation with the 50-percent adjuvant. Well-defined erythema and oedema as well as encrustations developed at the site of application, for which reason administration of 10-percent sodium dodecylsulphate was omitted. One week after intradermal induction, dermal induction was carried out with a 25-percent formulation of 2,5-dimethoxy-4-chloroaniline in hydroxyethylcellulose, which was occlusively applied to the dorsal skin for 48 hours and gave rise to erythema and oedema in the areas treated with the adjuvant at the first induction. Dermal challenge was achieved by occlusive application of a 25-percent formulation to the intact depilated skin of the flank for 24 hours 14 days after the second induction. None of the animals showed positive skin reactions at 24 or 48 hours after application (Aventis, 2001).

7.5 Subchronic and chronic toxicity

No information available.

7.6 Genotoxicity

7.6.1 In vitro

In the Salmonella/microsome test with metabolic activation (S-9 mix from Aroclor 1254-induced rat livers), 2,5-dimethoxy-4-chloroaniline (99.9% pure) had a mutagenic effect on *Salmonella typhimurium* strains TA 98 and TA 100. The test was negative in the absence of metabolic activation. The study was conducted as a plate incorporation test in which *Salmonella typhimurium* strains TA 98, TA 100, TA 1535, TA 1537 and TA 1538 and the *Escherichia coli* WP2uvrA strain were incubated with a DMSO formulation of 2,5-dimethoxy-4-chloroaniline at 4 to 10000 µl/plate. Two independent test series were carried out, each with three plates/concentration. At levels of 5000 µg/plate and above, 2,5-dimethoxy-4-chloroaniline precipitated in the plating medium, and 10000 µg/plate proved toxic to most strains. In the

presence of metabolic activation, revertant counts for strain TA 100 were markedly increased in a concentration-dependent manner from 4 µg/plate. Strain TA 98 exhibited a slight and not clearly concentration-dependent increase in revertant counts from 4 µg/plate in the presence of metabolic activation, the increase reaching no more than about twice the spontaneous revertant count. In the absence of metabolic activation, incubation of *Salmonella typhimurium* strains and the *Escherichia coli* strain with 2,5-dimethoxy-4-chloroaniline did not result in any significant increase in revertant counts. Tests with the positive controls sodium azide, 9-aminoacridine, 2-nitrofluorene, N-methyl-N'-nitro-N-nitrosoguanidine, benzo[a]pyrene and 2-aminoanthracene gave the expected results (Hoechst, 1986 c).

In the HPRT test performed in V79 cells of the Chinese hamster, 2,5-dimethoxy-4-chloroaniline showed no mutagenicity either in the presence or in the absence of metabolic activation (S-9 mix from Aroclor 1254-induced rat livers). The test was performed with 2,5-dimethoxy-4-chloroaniline of approx. 99% purity in accordance with OECD guideline No. 476. Preliminary studies showed that cytotoxicity occurred at 300 µg/ml (solubility limit) in the absence of metabolic activation and at as little as 2 µg/ml in the presence of metabolic activation. The main study tested concentration levels of 0 (negative controls), 37.5 75, 150 and 300 µg/ml without metabolic activation and levels of 0 (negative controls), 0.25, 0.5, 1.0, 1.25 and 1.5 µg/ml in the presence of metabolic activation. 2,5-Dimethoxy-4-chloroaniline did not induce any increase in the incidence of 6-thioguanine-resistant mutants in two independent experiments carried out under these conditions and therefore was devoid of genotoxicity. In the main study, the concentrations tested without metabolic activation were not cytotoxic. However, in the presence of metabolic activation, the PE values (relative plating efficiencies) noted for the highest concentration levels tested in the two substudies were reduced to 53.3 and 74.2%, which was indicative of cytotoxicity. Ethylmethane sulphonate and 9,10-dimethyl-1,2-benzanthracene served as positive controls and produced the expected mutagenic effect (Hoechst, 1988 b).

7.6.2 In vivo

2,5-Dimethoxy-4-chloroaniline was also found to be devoid of genotoxicity in a micronucleus assay performed in accordance with OECD guideline No. 474. Groups of 5 male and 5 female NMRI mice (strain Hoe: NMRKf

(PFF71), respective mean initial weights: 36.8 and 26.6 g) per dose level and sampling time were dosed by oral gavage with a single dose of the chemical in sesame oil at 0 (control) or 1200 mg/kg body weight. Treatment with 2,5-dimethoxy-4-chloroaniline (technical product “4-Chlor-2,5-dimethoxyanilin TF” of 77.3% purity) at 1200 mg/kg body weight had a lethal effect in one male and caused signs of intoxication, such as reduced spontaneous activity, uncoordinated or ataxic gait, abdominal position, irregular breathing and reduced or negative righting reflex. The animals were free of clinical signs of toxicity 48 hours after administration. Animals were sacrificed and their femoral bone marrow isolated at 24, 48 and 72 hours after administration. The ratio of polychromatic erythrocytes to normochromatic erythrocytes was determined for 1000 erythrocytes/animal, and 1000 polychromatic and 1000 normochromatic erythrocytes/animal were examined for micronuclei. The ratio of polychromatic to normochromatic erythrocytes in the bone marrow remained unaffected and there was no increase in the frequency of micronucleated erythrocytes from the bone marrow. Positive controls treated with cyclophosphamide (Endoxan®) exhibited the expected increases in micronucleus frequency (Hoechst, 1993).

7.7 Carcinogenicity

No information available.

7.8 Reproductive toxicity

No information available.

7.9 Effects on the immune system

No information available.

7.10 Neurotoxicity

No information available.

7.11 Other effects

No information available.

8 Experience in humans

According to company experience, methaemoglobinaemia may occur (no further details; Hoechst, 1994).

9 Classifications and threshold limit values

In the Federal Republic of Germany, the Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area ("MAK-Kommission") of the Deutsche Forschungsgemeinschaft has worked on 2,5-dimethoxy-4-chloroaniline on the suggestion of BG Chemie. The MAK-Kommission has assigned 2,5-dimethoxy-4-chloroaniline in the List of MAK and BAT Values 2004, to Category 3B of carcinogenic substances (i.e. "Substances that cause concern that they could be carcinogenic for man but cannot be assessed conclusively because of lack of data. The classification in Category 3 is provisional. Substances for which in vitro or animal studies have yielded evidence of carcinogenic effects that is not sufficient for classification of the substance in one of the other categories. Further studies are required before a final decision can be made. A MAK or BAT value can be established provided no genotoxic effects have been detected."). Furthermore 2,5-dimethoxy-4-chloroaniline has been designated with "H" because of the danger of percutaneous absorption (DFG, 2004).

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