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The Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals

125. Toluene

Grete Østergaard

Nordic Council of Ministers

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Co-editors: Mikael Bergenheim, Anders Kjellberg, Birgitta Meding, Gunnar Rosén och Ewa Wigaeus Tornqvist

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Preface

The Nordic Council of Ministers is an intergovernmental collaborative body for the five countries, Denmark, Finland, Iceland, Norway and Sweden. One of the committees, the Nordic Senior Executive Committee for Occupational Environmental Matters, initiated a project in order to produce criteria documents to be used by the regulatory authorities in the Nordic countries as a scientific basis for the setting of national occupational exposure limits.

The management of the project is given to an expert group. At present the Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals consists of the following members:

Gunnar Johanson (chairman)	National Institute for Working Life, Sweden
Vidir Kristjansson	Administration of Occupational Safety and Health, Iceland
Kai Savolainen	Finnish Institute of Occupational Health, Finland
Vidar Skaug	National Institute of Occupational Health, Norway
Leif Simonsen	National Institute of Occupational Health, Denmark

For each document an author is appointed by the Expert Group and the national member acts as a referent. The author searches for literature in different data bases such as Toxline, Medline, Cancerlit and Nioshtic. Information from other sources such as WHO, NIOSH and the Dutch Expert Committee on Occupational Standards is also used as are handbooks such as Patty's Industrial Hygiene and Toxicology. Evaluation is made of all relevant scientific original literature found. In exceptional cases information from documents difficult to access is used. However, only literature judged as reliable and relevant for the discussion is referred to in this document.

The document aims at establishing dose-response / dose-effect relationships and defining a critical effect based only on the scientific literature. The task is not to give a proposal for a numerical occupational exposure limit value.

The evaluation of the literature and the drafting of this document on toluene was made by Dr Grete Østergaard, Danish Veterinary and Food Administration, Institute of Food Safety and Toxicology. The draft document was discussed within the Expert Group and the final version was accepted by the Nordic Expert Group August 18, 2000, as its document.

Editorial work was performed by the Group's Scientific Secretary, Jill Järnberg, and technical editing by Karin Sundström both at the National Institute for Working Life in Sweden.

We acknowledge the Nordic council for its financial support of this project.

Jill Järnberg
Scientific Secretary

Gunnar Johanson
Chairman

Abbreviations

FSH	follicle stimulating hormone
GLP	good laboratory practice
NOAEL	no observed adverse effect level
LC_{50}	lethal concentration for 50% of the exposed animals
LD_{50}	lethal dose for 50% of the exposed animals
LH	luteinising hormone
LOAEL	lowest observed adverse effect level

Contents

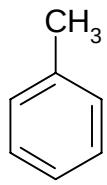
1. Introduction

Toluene is a component of crude oil and is produced by different petroleum distillation conversion processes. Isolated toluene is used in industry as a chemical intermediate and as a solvent. Toluene is a high production volume substance. Workers in the chemical industry and paint industry, and workers using products containing toluene (*e.g.* painters) may be occupationally exposed.

2. Substance identification

CAS No.	108-88-3
EINECS No.	203-625-9
IUPAC name	Toluene
Synonyms	methyl benzene, phenyl methane, toluol methyl benzol, methacide
Molecular formula	C_7H_8
Molecular weight	92.13 g/mol

Structural formula



3. Physical and chemical properties

Boiling point at 101.3 kPa	110.6°C
Melting point at 101.3 kPa	-95°C
Vapour pressure at 25°C	3.73 kPa
Density at 20°C	0.876 g/ml
Vapour density (air=1)	3.20
Saturation concentration (in air at 25°C)	142 000 mg/m^3
Explosive limits (vol% in air)	1.17 - 7.10
Log partition coefficient (octanol/water)	2.69
Flame point	4.4°C

Odour threshold	1.5 - 3.2 mg/m^3 (48)
	17.5 -262.5 mg/m^3 (135)
	11 ± 6 mg/m^3 (3)
Conversion factors at 25°C	1 mg/m^3 = 0.267 ppm
	1 ppm = 3.75 mg/m^3

Toluene is a colourless, flammable liquid with unpleasant aromatic odour. Water solubility at 20°C is approximately 6.5 mmol/l. Toluene is soluble in acetone and carbon disulphide, and miscible with most ethers, ketones, alcohols, esters, and aliphatic and aromatic hydrocarbons. Toluene forms azeotropic mixtures with many of the solvents mentioned above. Toluene is used as solvent in a number of products such as bitumen, tar, paints, lacquers, greases, and natural and synthetic resins.

4. Occurrence, production and use

Toluene occurs naturally and natural sources are volcanoes and forest fires. Toluene is naturally present in small amounts in crude oil. In the petroleum refinery process, this toluene will be present in low concentrations in straight-run gasoline products. By different petroleum conversion processes (catalytic reforming, powerforming, catalytic cracking, hydrocracking, steam cracking etc.) the yield of useful products from crude oil is upgraded, producing olefinic and aromatic rich streams containing benzene, toluene and xylenes in varying concentrations. Most of the refinery / cracker streams containing toluene are used as a base or blending feedstock to produce motor gasoline. In order to produce the commercial product toluene, a fraction of the toluene-rich streams is segregated, distilled and purified.

As an intermediate in the chemical industry, toluene is used as a raw material in the organic synthesis of other chemicals e.g. benzaldehyde, benzene, benzoic acid, benzyl chloride, phenol, toluene diisocyanate, xylene and other derivatives used as dye intermediates, resin modifiers and germicides. Toluene is also used in the synthesis of explosives (TNT), vinyl toluene, cresols and flavouring agents.

Toluene is used as a solvent for paints, lacquers, gums, resins, and in the extraction of various substances from plants. Approximately 20% of isolated toluene sold as solvent is used in paints, inks, thinners, coatings, adhesives, degreasers and other formulated products requiring a solvent carrier.

Because of the vast amount of products in which toluene is used, either as intermediate or as solvent, toluene is found in most industrial categories. The main exposure to toluene occurs by inhalation of vapours and liquid aerosols and via dermal exposure to liquids. Further, toluene is used as an additive in cosmetic products.

A large part of the annually produced toluene is used as a constituent of gasoline. Toluene increases the octane number.

In Denmark, the Danish Product Registry (1996) data on toluene registered approximately 2 700 products with an annual use of 19 000 tonnes toluene. The Danish product types covering more than 50 functions / uses include solvents, adhesives and binding agents, paints, lacquers and varnishes, and intermediates. The industry groups were chemical industry, manufacture of metal articles, textile and clothing industry, reprographic industry, wood and furniture industry, and construction industry distributed in 28 trades.

In Norway, 880 toluene-containing products were registered in 1996, with a total toluene tonnage of 370 000. From 1992 to 1998 the number of products containing toluene has risen from 517 to (estimated) 875. The estimated tonnage for 1998 was 410 000 (Information from the Norwegian Product Register 1999).

5. Occupational exposure data

Occupational exposure may occur during:

Production of toluene, including storage and handling (i.e. transfer from one container to another), sampling and analysis of quality control samples, cleaning, repair and maintenance of the equipment.

Production, storage and handling of toluene-containing products (semi-products as well as products for sale), sampling and analysis of quality control samples, cleaning, repair and maintenance of the equipment.

Use of toluene-containing products (occupational exposure and consumer exposure) sampling and analysis of quality control samples, cleaning, repair and maintenance of the equipment.

Commonly, maintenance workers may be exposed to high exposure concentrations, but of short duration. Workers performing sampling for product control usually experience high exposure concentrations of very short duration, but exposures may be frequent.

Within production of toluene in the chemical industry, a reasonable worst case short term exposure level is 100 mg/m^3, while the typical full shift exposure level is low, 3 mg/m^3. For production of toluene-containing products, a reasonable worst case short-term exposure level is 200 mg/m^3, while the typical full shift exposure level is low, 4 mg/m^3. Occupational use of toluene-containing products can lead to high exposure levels. For use of toluene-containing adhesives and inks the typical full shift exposure level is 75 mg/m^3. These values derive from the EU risk assessment of toluene (31).

6. Measurements and analysis of workplace exposure

The most widely used analytical technique for quantifying toluene in environmental samples is gas chromatography. Air samples may be collected and concentrated on adsorbent or in canisters for subsequent analysis. Sampling

techniques include collection in sample loops, on adsorbents, in canisters, and by cryogenic trapping. Detection limits depend on the amount of air sampled (158).

7. Toxicokinetics

7.1 Uptake

7.1.1 Skin

Liquid toluene can be absorbed through the skin. In five volunteers exposed to toluene by immersing a hand up to the wrist in liquid toluene for 30 minutes, maximum concentrations of toluene in blood (0.17 mg/l) were found 30 minutes after start of the exposure. The maximum blood toluene concentration was maintained for 10-15 minutes after exposure had ended and was a quarter of that achieved in a two-hour inhalation exposure to 100 ppm (375 mg/m^3) toluene vapour (139).

Ten male volunteers were exposed in a dynamic exposure chamber, with respiratory protection, to toluene vapour (2250 mg/m^3 (600 ppm)). To keep the skin practically unprotected, the subjects wore only thin pyjamas and socks. The exposure was therefore to the skin of the whole body. Steady state occurred after 30 minutes with a toluene concentration of 1.08 µmol/l (100 µg/l) in venous blood. The total duration of exposure was 3.5 h. Based on average values for lung retention and lung excretion of toluene it was estimated that the percutaneous uptake of toluene vapour amounted to approximately 1% of the respiratory uptake at the identical air concentration (130). A similar relation between lung and percutaneous uptake of toluene vapour is given elsewhere (117).

The capability of toluene to penetrate the skin was investigated in isolated rat skin. At steady state a penetration of 8.5 nmol/cm^2/min (0.78 µg/cm^2/min) was determined (157).

In conclusion, dermal uptake after skin exposure to liquid toluene occurs to a limited degree. Dermal exposure to toluene vapours is not likely to be an important route.

7.1.2 Lungs

The major uptake of toluene vapour is through the respiratory system. A number of investigations in humans (21, 22, 110, 178) have shown that at rest a three-hour exposure to toluene vapour will result in an uptake amounting to approximately 50% of the inhaled toluene across the exposure levels tested (300-400 mg/m^3, approximately 100 ppm).

The concentration of toluene in alveolar air and in arterial and venous blood rises quickly during the first 10-15 minutes of exposure (21, 179). After only 10 seconds of exposure toluene can be detected in blood from brachial arteries (179).

Data from experimental exposure of voluntary study subjects show that physical work results in increased toluene uptake (21, 163). Using a 50 W work load, exposure to 300 mg/m^3 (80 ppm) toluene for 2 hours did not result in steady

state of the blood concentration of toluene in 12 study subjects. The toluene uptake was 2.4 times higher than the uptake at rest. During the work, lung ventilation was increased 2.8 times. Concentrations of toluene in alveolar air and blood increased with increasing work loads (0-150 W in periods of 30 minutes) (21). However, at higher workloads the proportion of toluene taken up decreased (only 29% at 150 W compared with 52% at rest), indicating that the uptake is limited by the rate of removal of toluene from the lungs via blood (89). The amount of toluene absorbed increased with greater amounts of body fat (23).

In nine male volunteers exposed to 200 mg/m^3 (53 ppm) toluene for 2 hours during a workload of 50 W the total uptake of toluene was 50% of that inhaled (91).

7.1.3 Gastro-intestinal tract

Case reports of accidents and attempted suicides, and clinical trials involving toluene administration to leukaemia patients (14) show that toluene is absorbed via the alimentary system in humans.

In rats, uptake of toluene via the alimentary system is slower than the respiratory uptake. Toluene concentration in blood reached maximum values two hours after an oral dose (126). About 76% was recovered as hippuric acid in the urine (76), and approximately 18% was excreted as toluene vapour through the respiratory system (145), suggesting that absorption is nearly 100%.

7.2. Distribution

The blood/air partition coefficient for toluene is 11.2-15.6 at 37°C (87, 137, 138, 141, 159).

The distribution of toluene is among other factors dependent on the tissue partitioning and the metabolism. In rabbits, the following tissue/blood partition coefficients have been found: brain, heart, liver, and intestine: 2.3, muscle tissue: 1.6, adipose tissue: 74.3, bone, connective tissue, and lung tissue: 1.9 (140). In rats, brain/blood ratios of 1.2 (74) and 1.7 (175) have been determined. In humans, the adipose tissue/blood partition coefficient of toluene is determined to be 81-83 (140, 141).

Whole body autoradiography of mice after acute inhalation of ^{14}C toluene (9) showed high radioactivity in adipose tissue, bone marrow, spinal nerves, spinal cord, and in the white parts of the brain, and somewhat lower activities in blood, liver, and kidneys. One hour after exposure nerve tissue showed no radioactivity. In adipose tissue nearly all radioactivity had disappeared after four hours, and only traces of non-volatile radioactivity could be found in the liver. After 24 hours all radioactivity had disappeared from the body.

Toluene passes the placental barrier. Two hours following exposure of rats via inhalation to 1375 or 2700 mg/m^3 (367 or 720 ppm) for 24 hours, foetal blood had a toluene concentration of 74% of that found in the dam's blood. The amniotic liquid contained a toluene concentration of 5% of that in the dam's blood. Four

and six hours after exposure, similar relative toluene concentrations were found (Ungvary 1984, quoted from (62)).

Groups of four mice (11, 14 or 17 days pregnant) were killed 0, 30, 60 and 240 minutes after having inhaled 7500 mg/m^3 (2000 ppm) ^{14}C-toluene for ten minutes. Radioactivity as volatile and non-volatile was measured in lung, liver, kidney, brain, cerebellum, fat, plasma, amniotic fluid, placenta, and foetus. It was shown that toluene immediately after inhalation was taken up in the foetal tissue at a concentration of about 10% of that found in the maternal lungs. It was suggested by the authors that this could be due to the fact that the foetus does not contain any lipid-rich tissue. At four hours after exposure the toluene radioactivity was decreased to 2% of the original value (44).

Toluene has been found in human breast milk. In 12 pooled samples from four urban areas in the United States, toluene was identified qualitatively in at least 7 samples (Pellizzari et al., 1982, quoted from (67)).

7.3 Biotransformation

Biotransformation of toluene occurs mainly by oxidation. The endoplasmatic reticulum of liver parenchymal cells is the principal site of oxidation that involves the cytochrome P-450 system. Analysis of blood and urine samples from workers and voluntary study subjects exposed to toluene via inhalation in concentrations ranging from 100 to 600 ppm (375-2250 mg/m^3) indicate that approximately 99% of the biotransformed toluene is oxidised via benzyl alcohol and benzaldehyde to benzoic acid. The remaining 1% is oxidised in the aromatic ring, forming ortho-, meta- and para-cresol (172, 173).

Water solubility of the biooxidation products is achieved through linkage with suitable substances (phase 2 reaction). Benzoic acid is linked to either glycine or glucuronic acid forming either hippuric acid or benzoyl glucuronide. Cresols and benzyl alcohol are linked to glucuronic acid or sulphate (62). At heavy toluene exposures there may not be enough glycine available for conjugation with the toluene metabolite benzoic acid to form hippuric acid. Benzoic acid may then be conjugated with glucuronic acid, and excreted as benzoyl glucuronide.

7.4 Excretion

7.4.1 Lungs

Data from experimental inhalation exposure of voluntary subjects show that the toluene concentration in expired air decreases rapidly during the first 10 to 20 minutes after cessation of exposure to toluene via inhalation (21, 33, 162). Two to four hours later, very low toluene concentrations are found in expired air (21). Of the toluene absorbed, 15-20% is exhaled during the first few hours after exposure has stopped (110). The cumulative excretion of toluene via the lungs amounts to 4-8% and 7-14% after 2 and 20 hours, respectively (21). The cumulative excretion (in per cent) of toluene via the lungs appears to increase with increasing amounts of toluene taken up (21).

7.4.2 Kidney

The majority (80-90%) of absorbed toluene is biotransformed and excreted from the body via the kidneys. At an exposure level of 750 mg/m^3 (200 ppm), the excretion is mainly as hippuric acid. About 1% of the biotransformed toluene is excreted as glucuronides or sulphates of o-, m-, or p-cresol (62).

p-Toluylmercapturic acid and S-benzylmercapturic acid have been identified as urinary metabolites of toluene in human studies (158).

A very small proportion, approximately 0.06% of the toluene absorbed via inhalation, is excreted unchanged in the urine in man (168).

7.4.3 Gastro-intestinal tract

In rats, a small proportion, less than 2%, of the absorbed toluene is excreted via the bile to the intestine. The substances excreted are reabsorbed in the intestine. Thus, very small amounts are excreted in faeces (2).

7.5 Biological half-lives

In humans, two hours' inhalation of 375 mg/m^3 (100 ppm) and determination of the time course of toluene in blood and expired air after exposure gave a three-phasic decay curve. Biological half-lives of 2 minutes, approximately 30 minutes, and approximately 3.5 hours, respectively, were calculated (140). Half-lives of 22 minutes and 175 minutes for the two last phases have also been determined (136).

In a study of workplace accidents with coma as a result of exposure to high toluene concentrations, a fourth phase with a 20-hour half-life was found. This phase is taken to represent toluene elimination from adipose tissue (16). Nise et al. (108) have found elimination curves for toluene in venous blood to contain at least three exponential components with median half-lives of nine minutes, 2 hours and 90 hours in rotogravure printers exposed to a time weighted median concentration of toluene of 75 mg/m^3 (range 8-416 mg/m^3) during a 5-day working week. The third component reflected the decline of toluene in adipose tissue, which had a median half-life of 79 hours as measured in subcutaneous adipose tissue. According to the authors the slower elimination from blood compared to fat could be due either to an overestimate of the half time in blood or to a decay of the biotransformation of toluene towards the end of the study period. The median venous blood toluene concentration was found to be 2.3 µmol/l at the end of a week's last shift. After 72 hours the blood toluene concentration had fallen to 0.16 µmol/l. In another part of the same study toluene concentrations were determined in venous blood and subcutaneous adipose tissue at 0, 63, and 135 hours. In venous blood an initial median toluene concentration of 1 µmol/l was found. After 135 hours the toluene concentration had decreased to 0.06 µmol/l. In subcutaneous adipose tissue the corresponding median toluene concentrations were 4 mg/kg fat and 1 mg/kg fat, respectively. Carlsson & Ljungquist (23) reported that the half-life of toluene from subcutaneous adipose tissue increased with increasing amounts of body fat. The range of values for the half-life was from 0.5 to 2.7 days. The variation in half-lives may be a matter of sample

collection strategies, and related to variations in exposure levels and durations. An important point is that the slow elimination of toluene from adipose tissue may result in accumulation of the chemical in adipose tissue in humans after repeated daily exposure. In rats, the rate of elimination from fat seems to be much higher than in humans, as only a few percent of the toluene concentration found in perirenal fat immediately after end of exposure to 100 ppm was recovered 12 hours later (175).

7.6 Metabolic (toxicokinetic) interactions

In the previous version of the NEG criteria document on toluene (66) inhibition of toluene metabolism by ethanol is described. Toluene excretion was independent of previous toluene exposure, age, body weight, and previous alcohol consumption. Smokers showed a tendency to faster excretion of blood toluene via the lungs.

Volunteers were exposed to toluene via inhalation for 4 h (300 mg/m^3) with or without prior ingestion of paracetamol (14 mg/kg), or with or without prior ingestion of acetylsalicylic acid (14 mg/kg) (90). Paracetamol, but not acetyl-salicylic acid, reduced the apparent blood clearance by 13%, while urinary excretion of hippuric acid was not affected.

In a recent review (89) investigations in humans of toxicokinetic interactions between toluene and other industrial solvents are described. The solvents may decrease each other's biotransformation rates resulting in increased toluene levels in blood and delayed excretion of urinary metabolites. This has been shown for xylene and benzene co-exposure with toluene, while no effect was seen after exposure to methyl ethyl ketone and toluene.

8. Methods of biological monitoring

8.1 Biological markers

Measurements of toluene in blood, urine and exhaled air provide reliable markers of exposure to toluene. Measurement of toluene metabolites is also utilised for monitoring toluene exposure in humans. Hippuric acid is formed in the body by the metabolism of toluene. High performance liquid chromatography (HPLC) with ultraviolet detection is usually used for detection of hippuric acid in urine. Other metabolites such as o-cresol, benzylmercapturic acid, or S-p-toluyl-mercapturic acid may also be measured (158).

A good correlation was found between toluene exposure (air concentration multiplied by time) and concentration of hippuric acid in post exposure urine. However, a background level of hippuric acid is present in human urine, as a product of endogenous metabolism, and of metabolism of substances present in food. In the Western part of the world, at exposure levels below 100 ppm (375 mg/m^3) hippuric acid in post exposure urine cannot be used to separate an exposed person from an unexposed one because the difference between the back-

ground level and the toluene-generated level is too small (84). However, hippuric acid background levels in urine vary geographically. In some countries (e.g. Taiwan and Croatia) a low urinary hippuric acid background level is found. Thus, in these parts of the world it is possible to use this metabolite as a biological marker for toluene exposure even at exposure levels lower than 100 ppm (25, 158, 164, 166).

9. Mechanisms of toxicity

The exact toxicological mechanism of toluene is not known. Several mechanisms have been proposed. Toluene alters the lipid structures of cell membranes and thereby changes intercellular communication and the movement of ions and/or biomolecules between cells and the interstitial fluid. Toluene interacts with the hydrophobic portions of cell proteins to alter either membrane-bound enzyme activity or receptor-site specificity. The metabolic path in which toluene is metabolised into o-cresol and p-cresol includes an arene oxide intermediate, which binds to cell proteins and RNA, thereby modifying their function (158).

10. Effects in animals and in vitro studies

10.1 Irritation and sensitisation

10.1.1 Skin irritation

The skin irritancy of toluene in rabbits was tested by four different methods, including the OECD guideline 404 method (46). The same scoring system was used to measure results from all four methods. Toluene was found slightly irritating by the OECD guideline method, and moderately irritating by the other methods.

10.1.2 Eye irritation

In a rabbit eye irritation study toluene was judged to be a moderate to severe irritant with corneal involvement or irritation that persisted for more than 24 hours but recovered within 21 days after treatment (149).

Toluene was also found to be an eye irritant in another study, which appears to have been performed by a method resembling the OECD guideline method (47).

10.1.3 Sensitisation

No published data have been found.

10.1.4 Respiratory irritation

In mice, RD-50[1] values of 12 590 mg/m^3 (98), 12 650 mg/m^3 (3373 ppm) (32), and 19 875 mg/m^3 (5300 ppm) (106) have been determined, suggesting that

[1] Respiratory rate depression

Table 1. Acute lethality data for toluene compiled from various sources

Species	Exposure route	LC_{50} (inhalation) LD_{50} (oral, dermal, intra-peritoneal application)	Reference
Rat	Inhalation 1 h	>100 000 mg/m^3	8
Rat	Inhalation 6 h	22 000 - 23 500 mg/m^3	11
Rat	Inhalation 6.5 h	45 800 mg/m^3	19
Mouse	Inhalation 6 h	24 000 - 27 900 mg/m^3	11
Mouse	Inhalation 6 h	26 000 mg/m^3	12
Mouse	Inhalation 7 h	19 900 mg/m^3	154
Rat	Oral	7.5 g/kg	146
Rat	Oral	5.9 g/kg	161
Rat	Oral	5.5 g/kg	73
Rat	Oral	5.6 g/kg	171
Rat	Oral	7.0 g/kg	174
Rabbit	Dermal	12.4 g/kg	146
Rat	Intraperitoneal	1.6 g/kg	34, 61, 88
Mouse	Intraperitoneal	2.15 g/kg	77

LC_{50} = lethal concentration for 50% of the exposed animals
LD_{50} = lethal dose for 50% of the exposed animals

toluene can cause irritation to the respiratory tract at these high concentrations. The irritative effect of lower toluene concentrations has not been examined.

10.2 Effects of single exposure

10.2.1 Inhalation

Toluene has low acute toxicity via inhalation and the oral route (Table 1). In rats, inhalatory LC_{50} values in the range of 20 000-50 000 mg/m^3/6h, and oral LD_{50} values of 5.5-7.5 g/kg have been reported. A dermal LD_{50} of 12.4 g/kg has been determined in the rabbit. Via the intraperitoneal route LD_{50}s of approximately 2 g/kg for rats and mice have been found.

10.3 Effects of short-term exposure

10.3.1 Liver

In mice, rats, and rabbits exposed via inhalation to 2000 mg/m^3 or 3000 mg/m^3 toluene, either for 24 hours or 8 hours per day for 1-3 weeks, the cytochrome P450 and cytochrome b_5 concentrations were increased (161).

10.4 Effects of long-term exposure and carcinogenicity

10.4.1 General toxicity, inhalation

Rats, 15 weeks

Groups of ten male and ten female F344/N rats were exposed via inhalation to 0, 100, 625, 1250, 2500, or 3000 ppm toluene 6.5 h/day for 5 days/week for 15 weeks (56). Effects included dyspnea, ataxia, body weight reduction, increased relative liver, brain, heart, lung, kidney, and testes weight. The leukocyte count

was decreased for female rats at 1250 ppm or higher. No compound-related effects were seen on sperm or oestrous cycle. Among the high-dose males 8 deaths occurred during the second week of exposure. Overall, a no observed adverse effect level (NOAEL) of 625 ppm toluene (2350 mg/m^3) for 15 weeks' inhalation exposure of rats can be derived from this study. At 1250 ppm and above, a decrease in leukocyte count in females was found. Also, at and above 1250 ppm weight changes in a number of organs were detected.

Rats, 2-year exposure
Groups of 120 male and 120 female Fisher F344 rats were exposed via inhalation to toluene 6.5 h per day/5 days/week for up to 24 months in concentrations of 0, 112, 375 or 1125 mg/m^3 (0, 30, 100, 300 ppm) (45). No substance related adverse changes were found with respect to clinical signs, body weight, haematology, blood chemistry or urinalysis. No gross pathological or histopathological changes related to toluene exposure were seen. The NOAEL was 300 ppm.

Rats, 15-month and 2-year exposure
Groups of 60 male and 60 female F344N rats were exposed by inhalation to 0, 600, or 1200 ppm toluene 6.5 hours/day 5 days/week for two years in a GLP (good laboratory practice) study. At 15 months, 10 male and 10 female rats at each dose level were terminated (56).

Rats, 15-month and 2-year exposure: 15-month exposure. In the nasal cavity, mild to moderate degeneration of the olfactory and respiratory epithelium was more obvious in toluene-exposed rats and goblet cell hyperplasia was somewhat increased whereas other lesions (necrosis, metaplasia) were seen in a few exposed rats. The incidences and severity of chronic inflammation were greater in exposed females than in controls. Hyperplasia of the alveolar and bronchiolar epithelium was found in two males and three females in the 1200 ppm group and in one control female. In this study, the lowest exposure level (600 ppm) caused toxic effects in the nasal epithelium (56).

Rats, 15-month and 2-year exposure: 2-year exposure. Mean body weights of rats exposed to 1200 ppm were 4-8% lower than those of controls. No compound-related clinical signs were recorded, and no significant differences in survival were observed between any groups of either sex. In the nose, erosion of the olfactory epithelium and degeneration of the respiratory epithelium were significantly increased in exposed rats. Inflammation of the nasal mucosa and respiratory metaplasia of the olfactory epithelium were observed at significantly ($P < 0.05$) increased incidences in exposed female rats. Forestomach ulcers were marginally increased in exposed male rats. The severity of nephropathy was increased with exposure concentration in both sexes. The lowest observed adverse effect level (LOAEL) was 600 ppm for nasal toxicity, forestomach ulcers, and kidney damage (56).

Mice, 14-week exposure
Groups of 10 male and 10 female B6C3F1 mice were exposed to 0, 100, 625, 1250, 2500, or 3000 ppm toluene 6.5 hours/day, 5 days/week for 14 weeks. Effects included deaths at 625 ppm and above, body weight decrease, dyspnea, increased relative weight of liver, lung, and kidney. Centrilobular hepatocellular hypertrophy was observed in all male mice at 2500 ppm and 4/6 male mice at 3000 ppm. No effect on sperm count or motility or on oestrous cycle were seen.

Mice, 15-month and 2-year exposure
Groups of 60 male and 60 female B6C3F1 mice were exposed by inhalation to 0, 120, 600, or 1200 ppm toluene 6.5 hours/day, 5 days/week for 2 years in a study of GLP quality. Ten female mice at each exposure level were terminated after 15 months (56). In female mice exposed for 15 months no toluene-induced effects were seen on body weight, absolute or relative organ weights of brain, kidney or liver. Haematological parameters were unaffected by exposure. Minimal hyperplasia of the bronchial epithelium was seen in females at 1200 ppm.

In the 2-year study, body weights in female mice were slightly lower at 1200 ppm compared with controls. No significant differences in survival were observed between any groups of either sex.

10.4.2 General toxicity, oral
Groups of 10 male and 10 female F344N rats received 0, 312, 625, 1250, 2500, or 5000 mg toluene/kg body weight in corn oil by gavage for 13 weeks (56). Effects included death, body weight reduction, prostration, hypoactivity, ataxia, pilo-erection, lacrimation, and excessive salivation. Liver and heart weights were increased, while brain weight was reduced in both sexes at 2500 mg/kg. Neuro-pathological changes in the brain, consisting of neuronal cell necrosis in the dentate gyrus and Ammons horn of the hippocampus, were seen in male and female rats that received 2500 or 1250 mg/kg. In addition to the hippocampal lesions, necrosis and/or mineralisation was present in the granular layer of the cerebellar cortex. Haemorrhage was present in the mucosa, submucosa, or muscularis layer of the urinary bladder of males and females of the two highest dose groups. The dose level 625 mg/kg is considered the NOAEL. At doses of and above 1250 mg/kg, neurone necrosis in the brain was found, which is clearly an adverse effect (56).

Groups of 10 male and 10 female B6C3F1 mice received 0, 312, 625, 1250, 2500 or 5000 mg toluene/kg in corn oil by gavage for 13 weeks (56). All mice that received 5000 mg/kg died during the first week, 4 male and 4 female rats that received 2500 mg/kg and one female mouse that received 1250 mg/kg died before termination of the study. Effects included body weight decrease, subconvulsive jerking, prostration, impaired grasping reflex, bradypnea, hypothermia, hypo-activity, and ataxia. Liver, brain, testis, and kidney weight were increased with no accompanying histopathology mentioned. The NOAEL is considered to be 625 mg/kg (56).

10.4.3 Specific organ toxicity

Liver

In rats exposed via inhalation to 1000 mg/m^3, 1500 mg/m^3, 3000 mg/m^3, 3500 mg/m^3 or 6000 mg/m^3 toluene 8 hours/day for up to 6 months, reversible dose-dependent increases in relative weight of the liver, succinate dehydrogenase activity, and concentration of cytochrome P-450 and b_5, and a decrease in glycogen content were reported (160).

Nervous system

Groups of male rat pups were exposed to 0, 100, or 500 ppm (0, 375, or 1875 mg/m^3) toluene for 12 hours/day on postnatal days 1-28. Histological and volumetric examination of the hippocampus on postnatal day 28 (n=7) revealed a reduced volume of various subregions in the area dentata at both exposure levels. However, the difference at 100 ppm may be due to an atypical value in the control group for this exposure group and is therefore not considered reliable. On day 120 (n=6) no differences were apparent in the volumes of the dentata components (143, 144).

Groups of six rats were exposed to 0 or 1500 ppm (5625 mg/m^3) toluene via inhalation for 6 h/day, 5 days/week for 6 months. A statistically significant neuron loss of 16% was found in the regio inferior (CA3 and CA2) of the hippocampus in exposed rats after an exposure-free period of 4 months (78).

Groups of 36 rats were exposed to 0, 500, or 1500 ppm (0, 1875, or 5625 mg/m^3) toluene via inhalation 6 h/day, 5 days/week for 6 months followed by an exposure-free period of two months prior to testing and sacrifice. The weight of the hippocampus was dose-dependently reduced (statistically significant at 1500 ppm), and an increase in perikaryal volume and nuclear volume in the neocortex was found at 500 ppm. Noradrenaline, dopamine and 5-hydroxytryptamine levels were significantly changed in various brain regions at 500 and 1500 ppm (80).

Groups of 8 male Wistar rats were exposed to 0, 100, 300, or 1000 ppm (0, 375, 1125, 3750 mg/m^3) toluene 8 hours/day, 6 days/week for 16 weeks (54). Measurement of the content of various neuronal and glial marker proteins revealed dose-related changes in some brain regions. The changes were interpreted by the authors as possible first steps in toluene neurotoxicity. The biological significance of these changes in marker proteins is not known, and it is considered that they are not directly adverse effects.

Auditory system toxicity

Auditory impairment of toluene-exposed rats has been demonstrated in a number of studies as behavioural and electrophysiological changes at exposure concentrations between 900 and 1400 ppm 14h/day, 7 days/week, for 5-14 weeks (123, 124, 127).

The dose-response relationship between toluene and hearing loss in rats was investigated in a series of experiments in male Fischer rats. Toluene ototoxicity was manifest only at relatively intense schedules of exposure. The toluene concentration and the duration of exposure must be above a certain level before

hearing loss will occur. A LOAEL of 1000 ppm (14h/day, 2 weeks) and a NOAEL of 700 ppm (14h/day, 16 weeks) was found (125).

There was no control for noise in any of the above-mentioned studies.

A group of 13 male Sprague-Dawley rats inhaled 1400 ppm toluene 16 h/day for a maximum of 8 days (48). Light microscopy or scanning electron microscopy examination of the cochlea revealed a progressive severe loss of hair cells. The auditory brainstem response threshold was increased with an average loss of auditory sensitivity of about 20-40 dB compared with control rats, and the loss was greater with increasing number of days of exposure (68)

Further descriptions of the morphological appearance of toluene-induced cochlear damage have been published (20, 83, 150).

Interaction with toluene on auditory function: Noise.
Groups of 8-12 male Sprague-Dawley rats were exposed to ambient air, to 1000 ppm toluene 16 h/day, 5 days/week, for 2 weeks, to noise (105 dB Sound Pressure Level (SPL)) 10 h/day, 7 days/week, for 4 weeks, or to toluene followed by noise (same dose and schedule) (69). The decrease in auditory sensitivity in rats exposed to toluene followed by noise was greater than the summated effects of each factor alone, indicating a synergistic rather than additive toxic effect of toluene and noise on auditory functions.

Synergism of simultaneous exposure to toluene and noise was found in a study, which also described the different nature of the cochlear damages induced by noise alone or by toluene alone (83). Noise induces injury to stereocilia, while toluene induces outer hair cell loss.

Interaction with toluene on auditory function: Ethanol
Rats were exposed to ambient air, to toluene alone (1000 ppm, 21 h/day, 8 weeks), to toluene plus ethanol, or to ethanol alone (112). Auditory function was reduced in the toluene-exposed groups, but not in the group exposed to ethanol alone. Ethanol counteracted the effect of toluene on auditory sensitivity.

Interaction with toluene on auditory function: n-Hexane
Groups of 18 male Sprague-Dawley rats were exposed to air, n-hexane, toluene, or toluene plus n-hexane, each solvent in a concentration of 1000 ppm; for 21 h/day, 7 days/week for 28 days (111). Neurophysiological recordings were made 2 days, 3 months, and one year after end of the exposure. Loss of auditory sensitivity measured by auditory brain stem response was observed 2 days after exposure in the two toluene-exposed groups. At the two subsequent recordings no improvement was observed in the group exposed to pure toluene. In the group exposed to toluene plus hexane a synergistic loss of auditory sensitivity was observed at 3 months. After one year hearing function had not recovered.

10.4.4 Carcinogenicity
Groups of 120 male and 120 female Fischer F344 rats inhaled toluene 6.5 h per day, 5 days/week for up to 24 months in concentrations of 0, 112, 375 or

1125 mg/m^3 (0, 30, 100, 300 ppm) (45). No increase in tumour frequency was seen, however, the exposure level may have been inadequate since the maximum tolerable dose was not reached.

Groups of 60 male and 60 female F344N rats were exposed by inhalation to 0, 600, or 1200 ppm toluene 6.5 hours/day, 5 days/week for two years in a GLP study (56). No significant differences in survival were observed between any groups of either sex. There were no substance-related increases in any tumour types.

Groups of 60 male and 60 female B6C3F1 mice were exposed by inhalation to 0, 120, 600, or 1200 ppm toluene 6.5 hours/day, 5 days/week for two years in a study of GLP quality (56). Toluene caused a marginal increase in the occurrence of non-malignant pituitary tumours (adenomas) in mice. A single adenoma occurred in each of the three exposed groups of female mice (2%). The occurrence in the control group was zero, and the historical incidence in chamber control female B6C3F1 mice was reported as 1/370 (0.3%).

The carcinogenic potential of toluene has been evaluated by IARC. IARC has evaluated toluene as not classifiable as to its carcinogenicity to humans (IARC Group 3). The evaluation report describes that toluene has been used as vehicle control in a number of dermal cancer studies in mice. No clear increase of skin tumours attributable to toluene was noted (60).

10.5 Mutagenicity and genotoxicity

There are extensive data available on the lack of mutagenicity of toluene to the standard Salmonella typhimurium test strains (TA1535, TA1537, TA1538, TA98 and TA100) and other Salmonella typhimurium test strains in the plate incorporation assay (13, 28, 52, 65, 103, 148). Toluene is volatile with a boiling point of 110.6°C, and the standard plate assay is not considered to be able to accommodate volatile substances without modifications, such as taping of the plates or use of a dessicator. However, toluene has been found negative in a preincubation test with the standard Salmonella typhimurium test strains, which may be considered to be adequate for the test of compounds with boiling points from 107°C to 132°C (57). Thus, toluene can be considered negative for bacterial mutagenicity in the Ames Salmonella typhimurium mutation assay.

Toluene has not been found to induce DNA repair mediated toxicity to various bacteria, gene conversion in the yeast Saccharomyces cerevisiae or genotoxic effects in Drosophila melanogaster (65, 93, 94, 102, 131, 132, 170).

The genotoxicity of toluene *in vitro* has been evaluated in several types of mammalian cells, including cell lines with mouse lymphomas or Syrian hamster embryo cells, primary rat hepatocytes and human lymphocytes.

Toluene does not appear to induce biologically significant increases in mutations, sister chromatid exchanges, micronuclei or DNA damage *in vitro* in mammalian cells at non-cytotoxic doses (24, 43, 65, 129, 142, 147, 176). Significant levels of cytotoxicity have been reached in most studies, and toluene

therefore appears to have been adequately examined for genotoxic effects in mammalian cells *in vitro*.

Toluene has been tested for clastogenicity and other types of DNA interactions in several *in vivo* experiments.

Positive results have been obtained in three cytogenetic studies performed in the former USSR in the 1970s (60). It has, however, been implied that these significant cytogenetic responses might be due to contamination with benzene. In more recent studies, toluene has not induced biologically significant increases in micronuclei and chromosomal aberrations in the bone marrow of mice and rats or DNA damage in peripheral blood cells, bone marrow, and liver of mice (41, 65, 95, 119, 133). Toluene can be considered to be adequately tested and is considered non-genotoxic *in vivo*.

10.6 Reproductive and developmental toxicity

In a 15-week inhalation study (56) no toluene-related effects on sperm morphology and vaginal cytology in rats exposed to 100, 625, and 1250 ppm toluene 6.5 h/day, 5 days/week were found.

Significantly and dose-related decreased sperm count and reduced epididymal weight was found in rats exposed via inhalation to a concentration of 2000 ppm (7500 mg/m^3) during 6 h/day for 90 days (113). The NOAEL was 600 ppm (2250 mg/m^3).

Lower foetal weight, lower birth weight and delayed postnatal development have been reported in a number of studies (30, 51, 53, 55, 114, 156). The LOAELs are in the range of 1000-2000 ppm (3750-7500 mg/m^3), except in two studies where the LOAELs are below 300 ppm (1125 mg/m^3) (30, 55). These two studies, however, have limitations concerning experimental design and reporting and the results are not in agreement with the other well-reported and -performed studies.

The NOAELs are in the range of 400-750 ppm (1500-2812 mg/m^3). A NOAEL for effects on birth weight and postnatal development of 600 ppm (2250 mg/m^3) can reasonably be set.

Increased spontaneous activity and impairments of cognitive functions (learning and memory) after exposure to toluene during brain development have been found in two studies (51, 53). Increased spontaneous locomotor activity has been found after pre- and postnatal toluene exposure to 1200 ppm (4500 mg/m^3) (51). Prenatal exposure alone caused no significant effects on locomotor activity (24 h) (156). Investigations of short-term activity after prenatal exposure to 1800 (53) or 2000 ppm (114) (6750 mg/m^3 or 7500 mg/m^3) toluene have not shown significant effects on activity. Impairment of cognitive function measured in the Morris water maze has been found in one study where rats (especially females) prenatally exposed to 1800 ppm toluene (6750 mg/m^3) were examined as young adults (53).

In another study pre- and postnatal exposure to 1200 ppm of toluene (4500 mg/m^3) also caused deficits in exposed females in a similar cognitive task (51).

Thus, the LOAEL for the behavioural effects is 1200 ppm (4500 mg/m^3) and a NOAEL cannot be established since lower exposure levels were not investigated.

Courtney et al. (29) found some signs of foetotoxicity of toluene in mice at 400 ppm (1500 mg/m^3). There was no level without effect in this study. Jones & Balster (70) found lower birth weight, decreased postnatal weight gain, and delayed reflex development in the absence of maternal toxicity at 2000 ppm toluene (7500 mg/m^3). The NOAEL was 400 ppm (1500 mg/m^3), but the daily exposure periods were limited to 3 hours.

Effects on behaviour in the absence of maternal or general toxicity have been reported in mice after perinatal dosing with approximately 60 mg/kg/day toluene (79). The administration route was via drinking water.

In rabbits equivocal effects were found in a study comprising two teratology tests (75). In the first part of the study (n=14) slight delays in skeletal development were registered at 500 ppm (1875 mg/m^3). No effect was observed in the second part of the study at the same exposure level (n=20).

11. Observations in man

11.1 Effects by contact and systemic distribution

11.1.1 Skin

Toluene has a degreasing effect on the skin. After repeated exposures, irritative contact dermatitis may develop (15, 42).

11.1.2 Eye

Eye irritation in toluene-exposed human volunteers has been examined in two studies (4, 33). In one of the studies (4), 16 volunteers were exposed for 6 hours to 0, 10, 40 or 100 ppm on each of 4 test days in random sequence. No change in lung function or nasal mucus flow was found. At 100 ppm irritation in the eyes and the nose was experienced. There was a significant deterioration in the perceived air quality and a significant increased odour level at all toluene concentrations. At 150 mg/m^3 (40 ppm) no irritation was registered. In the other study comprising 42 subjects (33), twice as many complaints of eye irritation were registered at 150 ppm as at 0 ppm. The two studies show that complaints of eye irritation start at air concentrations around 100 ppm (375 mg/m^3).

11.2. Effects of repeated exposure on organ systems

11.2.1 Liver

In 47 toluene-exposed workers a significant increase in S-ALP (serum alkaline phosphatase) compared with a referent group of 46 non-exposed workers was found (153). The association was still significant when heavy alcohol consumers were excluded from the analysis. The exposure levels measured by personal sampling were generally below 80 ppm. Other liver function-related enzyme

levels were unaffected. There was no association with cumulative exposure. Because of possible confounding by alcohol and lack of supportive evidence of liver toxicity from animal studies, the findings in this study are considered of doubtful relevance.

11.2.2 Kidneys

Sniffing of toluene results in reversible kidney damage evidenced as renal tubular acidosis (158). In some cases sniffing resulted in irreversible kidney damage (tubular dysfunction and interstitial nephritis) (134).

A workplace accident with massive toluene exposure for 18 hours resulted in renal failure with oligouria probably caused by dehydration and myoglobinuria (128).

Inhalation of 382 mg/m^3 (100 ppm) toluene for 6.5 hours in an exposure chamber resulted in unchanged excretion of albumin and beta-2-microglobulin in 43 printers with occupational exposure to toluene as compared to 43 age-matched controls without occupational exposure to toluene (107).

No signs of renal damage in 118 painters were found compared with a control group. The painters had an average of 9 years occupational exposure to toluene and xylenes. At the time of investigation the exposure was approximately 94 mg/m^3 (25 ppm) as determined from metabolites in urine (38).

In 42 printers with an occupational toluene exposure averaging 300 mg/m^3 (range 100-900 mg/m^3) compared with 48 unexposed controls, no changes in glomerular filtration rate, renal concentrating ability, beta-2-microglobulin excretion, and excretion of erythrocytes and leukocytes were found (6).

11.2.3 Blood

Among 24 solvent abusers (21 males, 3 females), 8 long-term users had lymphocyte abnormalities (5 lymphopenia, 3 lymphocytosis). Three subjects (2 were women) had a normocytic-normochromic anaemia (36).

In a study including 38 female workers employed with shoe gluing and a control group of 16 women from the same plant, but not exposed to organic solvents, the values of blood density, haemoglobin content, haematocrit and number of leukocytes were not different. The toluene concentration was 60-100 ppm measured during a year. However, the Mommsen toxic granula in the peripheral neutrophils developed faster in the group exposed to toluene. Since other blood parameters were not affected, the latter finding is not considered adverse. Furthermore, the exposure may not have been purely to toluene, as it is stated in the publication that gasoline (20-50 ppm) was detected in some samples (92).

11.2.4 Cardiovascular system

In a study involving 325 printers, past toluene exposure was elucidated through a questionnaire and an interview. The mean exposure level was approximately 375 mg/m^3 (100 ppm) for twenty years preceding the investigation. The information was used to group the printers according to an exposure index. A slight

increase in systolic blood pressure showed correlation with increasing toluene exposure, as judged by the exposure index. For 133 of the printers systolic blood pressure was measured before and after an exposure-free period of six weeks. The exposure-free period resulted in a significant decrease in systolic blood pressure. No significant changes were observed in diastolic blood pressure (101).

11.2.5 Central nervous system

The results achieved by 16 volunteers in a number of performance tests were not influenced by 6-h inhalation of toluene in concentrations up to 375 mg/m^3 (100 ppm). At 375 mg/m^3 (100 ppm) headache, dizziness, and feeling of intoxication were more often reported by the study subjects than at the lower concentrations (0 mg/m^3, 37.5 mg/m^3 (10 ppm), 150 mg/m^3 (40 ppm)) (4).

A one-hour inhalation of toluene (472-588 mg/m^3 (126-157 ppm)) was found to affect nystagmus reflexes (visual suppression) in 15 volunteers (58).

For 12 volunteers inhaling 300 mg/m^3 (80 ppm) toluene for 4.5 hours, the results in 4 performance tests carried out after 2 and 3.5 hours of exposure were not significantly different from the results obtained from the same persons during exposure to clean air. Subjective complaints of headache and irritation were more frequent at toluene exposure, during which a small decrease in the pulse at rest was observed (64).

Among 8 male post-graduate students exposed to 80 ppm toluene for 4 hours no difference in results in four choice reaction time, four choice errors, simple reaction time, visual search, visual analogues and stressalyser could be found compared to the results obtained by the same subjects exposed to clean air for 4 hours (26).

For 20 volunteers inhaling 98 ppm toluene for 4 hours the results in the psychomotor tests finger tapping, reaction time, pursuit-rotor test and Purdue hand precision test did not differ from control values obtained by the same 20 volunteers (169).

Following chamber exposure to 375 mg/m^3 (100 ppm) toluene for 6.5 hours, 43 printers with 9 to 25 years of occupational toluene exposure did not show significantly different results in 10 performance tests compared with an equally sized group not previously exposed to toluene and matched for sex, age, education and smoking habits. Toluene chamber exposure was found to decrease manual dexterity, colour discrimination, and accuracy in visual perception in both groups (17).

Forty-two college students inhaled 0, 281 mg/m^3 (75 ppm) or 562 mg/m^3 (150 ppm) toluene for seven hours on each of three days. The students carried out a number of performance tests prior to exposure, and after three and seven hours of exposure. On each day students served as their own control. Toluene exposure resulted in significantly poorer results in digit span, pattern memory, pattern recognition, symbol digit, and one hole test. The number of symptoms recorded was found to increase with increasing toluene exposure for headache and mucosal irritation. A dose response relationship was found in the number of times subjects

slept increasing from 7% at 0 ppm, 14% at 281 mg/m^3 (75 ppm), to 22% at 562 mg/m^3 (150 ppm) (33).

A random population sample of 32 male and 39 female subjects were allocated into three groups, one exposed to clean air, one exposed to a constant toluene level (100 ppm), and one exposed to varying concentrations of toluene (fourteen 30-minute episodes/day, each episode starting with an increasing concentration reaching a peak of 300 ppm after 5 min and then decreasing to a stable period of about 15 min at 50 ppm, giving a time weighted average (TWA) of 100 ppm for the whole exposure period). Toluene caused throat and respiratory irritation, headache and dizziness. In performance tests only minimal effects were found. There was no difference between constant exposure and peak exposure (18).

Humans exposed to high levels of toluene as a result of toluene abuse or industrial accidents may experience serious nervous system effects including fatal CNS depression. Other effects include cerebellar, pyramidal and cognitive dysfunction such as tremor, ataxia and memory impairment (158).

In a study of hospitalised solvent abusers, 24 patients with a mean age of 23 $\pm$ 4.4 years and 6.3 $\pm$ 3.9 years of toluene sniffing were examined. Present toluene consumption was 160-425 mg toluene/day (36). Computed tomography (CT) scanning results from 14 subjects revealed significant brain atrophy when the study subjects were compared with 20 age-matched controls, who were investigated for other non-solvent related neurological disorders.

A study of four toluene-sniffing patients (85) showed, in addition to neurological symptoms and findings, severely affected brain stem auditory evoked potential in three of the four patients tested. Audiometry showed mild abnormality in one of three patients. Moderate to severe oculomotor abnormality was found in three out of the four, and moderate to severe atrophy of the cerebellum in two of the patients.

Several cross-sectional studies have been found, in which a toluene-exposed group of workers have been compared with a matched control group. The studies in which the exposure was predominantly to toluene, and where an estimate of exposure levels was made, are shown in Table 2. The studies have revealed increased prevalence of subjective complaints (fatigue, recent memory failure, concentration difficulty, mood lability, depressive feelings, irritability, headache, dizziness, sleep disturbances, paresthesia, chest oppression, sexual problems) (86, 177), neuropsychological impairments (10, 35, 39, 63), electrophysiological changes (1, 165), and increased prevalence of neurasthenic complaints, short-term memory complaints, and organic brain syndrome (177).

11.2.6 Auditory system

The hearing ability of 50 workers exposed to noise (88-98 dB (A), 51 workers exposed to noise and toluene (100-300 ppm), and 39 workers exposed to a mixture of solvents (toluene, xylene, methyl ethyl ketone) was compared with an unexposed control group of 50 workers by pure tone audiometry and immittance audiometry. The groups were comparable with respect to age, previous exposure to noise and chemicals, medical history (diabetes, hypertension, ear infections,

and ototoxic medication), and noise related life-style factors (hunting, shooting, motor sports, amplified music, power tools, and military service (96).

High-frequency bilateral hearing loss was found in 8% of the unexposed, 26% of the noise-exposed, 53% of the noise- and toluene-exposed, and 7% of the solvent-exposed. The group exposed to noise plus toluene had significantly more workers with mild high frequency hearing loss (30-40 dB) than did all the other groups ($p<0.001$). The acoustic reflex measurements showed that the reflex decay in the toluene plus noise group was significantly higher than in the other groups ($p<0.001$). A multiple logistic regression for occupational hearing loss carried out on the four groups revealed that the relative risk was highest in the toluene plus noise group (10.9), followed by the solvent group (5.0), and the noise group (4.1). The study strongly indicates that occupational exposure to toluene increases the risk of developing occupational noise-related high-frequency hearing loss (96).

A group of 124 printing workers, all of whom were exposed to various levels of noise and a mixture of toluene, ethyl acetate, and ethanol underwent pure-tone audiometry and immittance audiometry testing after having been interviewed according to a comprehensive questionnaire (97). A personal average exposure evaluation, based on air samples from the breathing zone of each subject, was conducted for all the subjects for toluene, ethanol, and ethyl acetate. The total toluene exposure was assessed by monitoring of hippuric acid in urine samples collected immediately after each workday. Ethanol levels ranged from 0.25 to 1240 mg/m^3, ethyl acetate from 1.1 to 2635 mg/m^3, and toluene from 0.14 to 919 mg/m^3. Noise levels, measured via personal noise dosimeters, were in the range of 71 to 93 dB (A).

Forty-nine percent of the workers had hearing loss. Numerous variables were analysed for their contribution to the development of hearing loss. Only age and hippuric acid in urine were significantly associated with hearing loss. The odds ratio for hearing loss relative to hippuric acid was calculated. However, hippuric acid is problematic as a marker of toluene exposure, because of the variability in the natural background level of this substance. Therefore the odds ratio calculations may be based on incorrect assumptions, but the study does still provide an indication that occupational exposure to toluene increased the probability of hearing loss in the study population.

11.3 Genotoxic effects

Equivocal results were obtained in a multitude of studies with biological monitoring of various genotoxic effects in peripheral blood lymphocytes from workers exposed to toluene in the occupational environment (Table 3). Confounding due to coexposure to ink, other solvents and various genotoxic substances in the environment cannot be excluded. Furthermore, a clear synergistic effect between toluene exposure and smoking was demonstrated (50).

Table 2. Epidemiological studies on workers exposed to toluene, in which the exposure was predominantly to toluene

Exposure level	Groups studied	Toluene-related effects	Ref.
150 ppm, reduced to 50 ppm, for an average of 16.3 years. Higher concentrations occurred occasionally	34 toluene-exposed rotogravure printers, 34 solvent mixture-exposed subjects, 34 non-exposed controls	Increased simple reaction time	63
100-500 ppm for an average of 9.4 years	59 toluene exposed workers, 59 non-exposed workers	No effect	27
117 ppm for 26 years, during last year 78 ppm	43 toluene-exposed rotogravure printers, 31 occasionally solvent-exposed controls	Inconclusive because of uneven distribution of heavy alcohol drinkers	5, 59, 71
50-80 ppm, concentrations exceeding 1000 ppm 5 years previously. No. of years of exposure >12	22 toluene-exposed rotogravure printers, 19 unexposed controls	Higher frequency of slight or moderate organic brain syndrome	82
1- >150 ppm	193 toluene-exposed female workers, 65 non-exposed workers	Increase in prevalence of subjective symptoms e.g. ocular and nasal irritation, unusual smell and taste, sore throat, drunken feeling, headache and heavy feeling in the head	86
Mean exposure levels 43 and 157 mg/m^3 (12 and 42 ppm) for a median no. of 29 years (range 4-43)	30 toluene-exposed rotogravure printers, 72 unexposed controls	Increase in prevalence of subjective symptoms. Impairment in spatial memory	177
330 mg/m^3 (88 ppm) for an average of 5-7 years	30 toluene exposed workers, 30 unexposed controls	Impaired manual dexterity, verbal memory, and visual cognitive ability	35
97 ppm for 12-14 years	40 selected toluene-exposed workers, 40 non-exposed controls	Alterations in auditory evoked response	1
Unknown, blood conc. of toluene ranging from <0.22 to 7.37 mg/l	59 rotogravure workers, no control group	No effect on colour vision in 5 tests	99

Table 2. Cont,

Exposure level	Groups studied	Toluene-related effects	Ref.
40-60 ppm for an average of 21.4 years	49 printing-press workers exposed to toluene, 59 non-exposed controls	Changes in visual-evoked potentials	165
Mean blood toluene level 1.25 mg/l vs. 0.16 mg/l in controls	29 toluene-exposed workers, 29 unexposed controls	Impairment in psychological test	10
80 mg/m^3 (21 ppm); mean blood toluene level 0.3 mg/l	1324 toluene-exposed rotogravure workers, 154 paper industry workers	Impairment in short-term memory	39

Table 3. Studies of genotoxic effects of toluene in workers

Exposure level	Groups studied	Effects in peripheral blood lymphocytes	Ref.
Average 200 ppm for 3-15 years	24 rotogravure workers, age 29-60 years, 24 controls	No increase in CA	(37)
100-200 ppm with occasional rises to 500-700 ppm for 1.5-26 years	14 rotogravure workers, age 23-54 years; 49 controls	Significant increase in CA	(40)
7-112 ppm for 3-35 years	32 rotogravure workers, age 21-50 years; 15 controls	No increase in CA or SCE	(100)
mixed solvent exposure, toluene 1-157 mg/m^3 (0-50 ppm)	17 paint industry workers, 17 controls	No increase in SCE, or in CA of 5 most heavily exposed workers	(49)
200-300 ppm toluene for >16 years	20 rotogravure workers, age 32-60 years, 24 controls	Significant increases in CA and SCE	(7)
104-1170 ppm (390-4388 mg/m^3) for 12 years	42 rotogravure workers, mean age 39 years, 28 office and technical employees, 32 controls	Significant increase in CA, not controlled for smoking or co-exposure to ink mist	(116)
40 ppm (150 mg/m^3)	21 rotogravure printers, 21 controls	Significant increases of MN, no increase in CA, not controlled for age and smoking	(109)
19 ppm (70 mg/m^3) for 18 years	20 shoe workers, age 29-56 years, 20 controls	Significant increase in SCE and DNA damage, no dose correlation	(121)
	65 filling station attendants, no control group	No increase in urinary 8-OHdG	(81)
benzene and toluene	38 and 45 shoe workers, control workers	Significant increase in SCE, possibly related to benzene exposure	(72)
benzene (up to 15 ppm) and toluene (up to 50 ppm)	49 shoe workers, mean age 38 years, 27 controls	Significant increase in dicentric chromosomes	(50)
38-88 ppm (141-328 mg/m^3) for 18.9 years	42 rotogravure workers, age 22-60 years, 45 controls	Significant increases in SCE, not controlled for co-exposure to ink mist	(50)
26-110 ppm (96-412 mg/m^3) for an average of 12 years	34 shoe workers, mean age 38 years, 19 controls	No difference in Comet assay	(118)

CA=structural chromosomal aberrations. SCE=sister chromatid exchanges. MN=micronuclei.

11.4 Carcinogenic effects

In the IARC evaluation of toluene (60), four case-control studies involving several anatomical sites of cancer are mentioned. The results could not be evaluated with regard to toluene itself, because the exposure was to mixtures of solvents and not to pure toluene.

A cohort of 1020 rotogravure printers exposed to toluene and employed for a minimum period of three months in eight plants during 1925-85 was studied (152). Based on the measurements in the 1940s and 1950s the maximum toluene concentration was about 450 ppm, but it was only about 30 ppm in the mid 1980s. Exposure to benzene had occurred up to the beginning of the 1960s. Compared with the regional rates, total mortality did not increase during the observation period 1952-86. There was no increase in mortality from non-malignant diseases of the lungs, nervous system, or gastrointestinal and urinary tracts. There was no overall excess of tumours in the years 1958-85. Among the specific cancers only those of the respiratory tract were significantly increased. However, statistical significance was not attained, when only subjects with an exposure period of at least five years and a latency period of at least 10 years were considered.

The mortality from various cancer forms in a cohort of 6830 male and 751 female workers in the German rotogravure industry has been investigated (167). A significantly higher mortality due to bone and connective tissue tumours was identified, based on a low number of cases. Also mortality due to lung tumours, brain tumours, and tumours of the nervous system was increased, but not to a level reaching statistical significance. Although it is not clear from the report, the basis for cancer diagnoses seems to be death certificates, which probably is not an accurate source for this information.

11.5 Reproductive and developmental effects

11.5.1 Effects on hormones

Twenty men from a rotogravure printing company with a mean duration of employment of 25 years (range 0.5-37) and a mean age of 48.2 years (range 30-63) were compared with 44 male industrial workers without exposure to organic solvents and a mean age of 39.0 years (range 23-63) for concentrations of ten hormones in serum (151). With respect to the printers, the individual time weighted average toluene concentration in air was 36 ppm (range 8-111), the toluene level in blood was 1.7 µmol/l (range 1.0-6.6) and in adipose tissue 5.7 mg/kg (range 2.5-21). There was a negative association between blood toluene and plasma levels of prolactin. The exposed group had significantly decreased concentrations of follicle stimulating hormone (FSH), luteinising hormone (LH), and free testosterone; and an increase in the concentration of triiodothyronine compared with the control group. No correlation was found between cumulative exposure and plasma hormone concentrations. In eight printers, the levels of FSH and LH increased during a 4-week vacation, indicating reversibility; while levels of thyroid stimulating hormone, free triiodothyronine, and free thyroxin de-

creased. The observed effects were rather small with most hormone levels being within the reference limits.

Forty-seven men from two rotogravure printing companies were studied for their hormone status (153). In company A, the 28 men had a mean duration of employment of 18.4 years (range 4-33 years). In company B, the 19 men had a mean duration of employment of 14.5 years (range 3-39 years). Twenty-three workers from a metal industry and 23 craftsmen from hospital workshops were used as referents. The mean age for the exposed group was 44.4 years (range 23-62 years), and for the referents it was 43.5 years (range 20-61 years). Occupational exposure to toluene was measured for each working shift over a week, and the workers were divided into exposure groups based on these data. In company A, the following exposure groups were found: <5 ppm, 5-10 ppm, 10-15 ppm, and in company B the following: 20-25 ppm, 35-45 ppm, and >45 ppm. The referents had no exposure to toluene or other solvents. No statistically significant differences were found in any of the hormone concentrations between the total exposed and referent groups, however, younger members of the exposed group had significantly lower plasma LH, FSH, and testosterone levels. Increasing exposures to toluene (at the present exposure level) were significantly associated with decreasing plasma concentrations of LH and testosterone. No correlation was found between cumulative exposure and plasma hormone concentrations.

The authors conclude that the results of the two above-mentioned studies indicate that low-level toluene exposure (below the Swedish occupational exposure limit; at the time of sampling 80 ppm) may affect the hypothalamus-pituitary axis. Possible explanations include a link to toluene-induced changes in neurotransmitter levels, or to dopamine-like activity of toluene or its metabolites. Also, the possibility of reduced pituitary function in connection with a general depression of brain functions in relation to organic brain syndrome (which was not diagnosed in any of the exposed workers) was mentioned by the authors (151, 153).

The effects identified in these studies cannot be regarded as directly adverse, since the hormone levels were within reference limits, and the effects seemed to be reversible. The studies do, however, give evidence of a possible interference with endocrine mechanisms by toluene.

11.5.2 Fertility

In a cross sectional study, a sample of 150 male and 90 female printing industry workers in Germany were interviewed retrospectively on reproductive experiences (120). There was no association between occupational exposure to toluene and subfecundity in men and their partners. In women who worked in exposed areas, a significant reduction of fecundability of about 50% was found compared with periods working in other industries. The women worked exclusively in the stacking and bookbinding process, where the overall exposure to toluene was classified as low (<10 ppm). As toluene has been exclusively used in the German printing industry since 1960, exposure to other chemicals can be excluded.

The finding of the study indicate that an adverse effect of toluene on male fecundity is unlikely but cannot be completely excluded. For women, after considering possible biases, low daily exposure to toluene seems to be associated with reduced fecundity. Other forms of exposure such as noise and stress were not examined in the study and cannot therefore be excluded as having produced part of the findings or the overall result in the women. Also, there is a potential for recall bias in this study, e.g. persons with undesirable outcome may have recall of exposure that are different from those who do not experience the outcome. This applies for men as well as women and it is therefore considered impossible to draw clear conclusions from this study.

Rates of menstrual disorders were studied in 231 female production workers exposed to toluene (mean 88, range 50-150 ppm) and compared with a control group of 58 production workers in other departments of the same factory where little or no exposure to toluene ocurred (0-25 ppm) (104). An external community control group of 187 working class women was also studied. There was no evidence that menstrual disorders were likely to result from exposure to toluene.

11.5.3 Developmental toxicity

Several case reports of mothers giving birth to children with so-called toluene embryopathy as a result of toluene sniffing during pregnancy have appeared. Microcephaly, narrow bifrontal diameter, short palpebral fissures, deep-set eyes, small midface, low-set, prominent ears, micrognathia, spatulate fingertips, small fingernails, hypotonia, and hyperreflexia were found in the children. In total about 45 cases have been described in the literature (115). These cases all very much resemble the foetal alcohol syndrome, and there might be a common mechanism.

Spontaneous abortions among women working in laboratories, and congenital malformations and birth weights of the children were examined in a retrospective case-referent study (155). The exposure to toluene was assessed on the basis of the reported frequency of the use of the chemical and classified as frequent if the chemical was handled at least 3 days a week and rare if the toluene was handled 1 or 2 days a week. Significant associations with spontaneous abortions were found for frequent exposure to toluene (odds ratio 4.7, confidence interval 1.4 to 15.9) after adjustment for various covariates (206 cases and 329 referents). No association with congenital malformation was found (36 cases and 105 referents), however, the number of persons in the malformation study was too small for drawing final conclusions.

Rates of spontaneous abortions were determined using a reproductive questionnaire in 55 women with 105 pregnancies exposed to toluene (mean 88 ppm, range 50-150 ppm) and 31 women (68 pregnancies) working in the same factory in departments where little or no exposure to toluene occurred (0-25 ppm) (105). An external community control group of 190 working class women with 444 pregnancies was also studied. Significantly higher rates of spontaneous abortions were noted in the toluene exposed women compared with those in the internal and external control groups (12.9% vs. 2.9-4.5%). The rate differences between groups were not likely to be confounded by classical risk factors such as maternal

age, gravidity, smoking, or alcohol, which were taken into account both in the study design and the analysis.

12. Dose-effect and dose-response relationships

The key studies for evaluation of the important effects of toluene are listed in Table 4 and Table 5. The animal studies presented in Table 4 have been selected because they are considered to be reliable in that a sufficient number of study subjects have been included, the endpoints are relevant for hazard identification, and appropriate test methods have been used. A number of other studies, including studies investigating the nervous system, examine endpoints which are less well established as predictive of human adverse health effects. Such studies have not been included in Table 4. With respect to auditory and reproductive toxicity, only one study reference is presented in the table for each of these endpoints. However, a large number of other studies have examined these endpoints and yielded similar results, and thus bring support to the selected key studies. General toxicity has been investigated in two 2-year studies. Although other studies with shorter duration have also been performed, it is believed that the studies of the longer duration are the most relevant for prediction of human long-term hazard.

Table 4. LOAELs and NOAELs from animal studies

Exposure level	Exposure duration	Species	Effects	Reference
30 000 mg/ m^3 8000 ppm	4-6.5 h	Rat	lethal (LD_{50})	11, 19, 122, 146
3750 mg/m^3 1000 ppm	2 weeks	Rat	LOAEL for auditory toxicity	125
3750 mg/m^3 1000 ppm	gestation day 9-21	Rat	LOAEL for reduced birth weight and retarded postnatal development	156
2625 mg/m^3 700 ppm	16 weeks	Rat	NOAEL for auditory toxicity	125
2250 mg/m^3 600 ppm	2 years	Rat	LOAEL for nasal toxicity and general toxicity (nasal toxicity and stomach ulcers)	56
2250 mg/m^3 600 ppm	gestation day 9-21	Rat	NOAEL for reduced birth weight and retarded postnatal development	156
1125 mg/m^3 300 ppm	2 years	Rat	NOAEL for general toxicity	45

Table 5. LOAELs and NOAELs from human studies

Exposure level	Groups studied	Exposure duration	Effects	Ref.
>3750 mg/m^3 (>1000 ppm), reduced to 180-300 mg/m^3 (50-80 ppm) 5 years preceding investigation	22 exposed, 19 controls	work place, >12 years	Higher frequency of slight or moderate organic brain syndrome	82
565 mg/m^3 150 ppm	42 experimentally exposed subjects, serving as their own control	7 h (test at 0, 3, and 7 h)	LOAEL for impaired verbal and visual memory (5% loss), perception (12% loss), psychomotor function (26% loss), manual dexterity (7% loss), and for increased number of sleeping episodes (tripling)	33
375-1125 mg/m^3 average exposure levels 1978-1980: 140-600 ppm 1990: 75-365 ppm	51 noise+toluene-exposed, 50 unexposed, 50 noise-exposed, 39 organic solvent mixture exposed	work place	Increased incidence of high-frequency bilateral hearing loss (in the presence of noise)	96
375 mg/m^3 100 ppm	16 experimentally exposed subjects, serving as their own control	6 h	LOAEL for irritation of the eyes and nose, headache, dizziness, and feeling of intoxication NOAEL for psychometric performance (however tests felt more difficult and strenuous)	4
300 mg/m^3 mean 88 ppm (range 50-150 ppm)	55 exposed, 31 internal controls, 190 external controls	work place	Increased rate of spontaneous abortion	105
150 mg/m^3 40 ppm	16 experimentally exposed subjects, serving as their own control	6 h	NOAEL for irritation of the eyes and nose, headache, dizziness, and feeling of intoxication	4
37,5 mg/m^3 10 ppm	16 experimentally exposed subjects, serving as their own control	6 h	LOAEL for deterioration in the perceived air quality and increased odour level	4

Table 5 includes the human studies, which are considered the most relevant for description of the important health effects identified in man. Additional studies exist which examine other endpoints for which the toxicological significance is less certain; these studies have not been included in the table.

Liquid toluene is irritating to skin and eyes in animals, while toluene vapours in concentrations at and above 100 ppm causes complaints of eye irritation in humans.

In the rat, a NOAEL for general systemic toxicity of 300 ppm for repeated exposure via inhalation was identified in a 2-year study. In another 2-year study higher exposure levels (600 ppm) resulted in nasal toxicity and increased incidence of stomach ulcers. For the dermal route, no systemic toxicity data have been found.

Toluene has been shown to affect the central nervous system and the inner ear.

In humans exposed under experimental conditions headache, dizziness, feeling of intoxication, irritation and sleepiness were recorded to occur with significantly increased frequency at exposure levels from 562 mg/m^3 (150 ppm) down to 375 mg/m^3 (100 ppm). At 150 mg/m^3 (40 ppm) and below the effects have not been recorded to occur with increased frequency. For these subjective symptoms a lowest observed adverse effect level (LOAEL) of 375 mg/m^3 (100 ppm) and a no observed adverse effect level (NOAEL) of 150 mg/m^3 (40 ppm) can be established.

Experimental chamber inhalation of 375 mg/m^3 (100 ppm) toluene for 6.5 hours, or inhalation of 281 mg/m^3 (75 ppm) and 562 mg/m^3 (150 ppm) by volunteers for 7 hours have resulted in significantly poorer results in a number of performance tests, indicating a LOAEL of 281 mg/m^3 (75 ppm) for these tests. A NOAEL of 150 mg/m^3 (40 ppm) for performance tests can be deducted from the study of Andersen et al.(4).

13. Previous evaluations by (inter)national bodies

The IPCS International Programme on Chemical Safety concluded that exposure of the general public and environment does not present any health and/or environmental hazard. However, the report further concluded that solvent abuse and long-term occupational exposure to toluene may be associated with permanent pathological changes, but did not mention which changes or at what exposure levels (62).

The Nordic Expert Group for Documentation of Occupational Exposure Limits concluded in 1989 that occupational exposure limits (OELs) for toluene should be based on acute effects on the nervous system, and that the fact that toluene rarely occurs alone, and that it possibly has an effect on reproduction and on the defence mechanism towards infection of mucous membranes should also be considered (66).

The IARC evaluation 1989 stated that there is inadequate evidence for the carcinogenicity of toluene in humans and in experimental animals. The overall

evaluation was that toluene is not classifiable as to its carcinogenicity to humans (Group 3) (60).

In a draft updating a previous evaluation on toluene by the U.S. Department of Health & Human Services the acute-duration and chronic-duration inhalation MRLs (Minimal risk levels) were based on CNS effects in humans. The draft is publicly available (158).

The Danish EPA has evaluated toluene (latest draft version May 2000) within the EU existing substances risk assessment programme. The conclusions of this draft are not yet available (May, 2000) but a copy of the draft can be obtained from the Danish EPA.

14. Evaluation of human health risks

14.1 Groups at extra risk

Exposure to noise may enhance the hearing loss induced by toluene. This has been shown to occur in the rat, and there are indications that man is also susceptible. Rat studies show that noise and toluene interact also when exposure is not simultaneous. Workers exposed to toluene in a noisy working environment, or who are exposed to noise at other occasions, are therefore considered to be at increased risk for developing hearing loss.

Toluene exposure is associated with an increased risk for spontaneous abortions. Women in fertile age are therefore a group at extra risk.

14.2 Assessment of health risks

A large database exists for the toxic effects of toluene in animals and man. Endpoints of concern include eye irritation, reproductive toxicity, ototoxicity, and neurotoxicity. The dose-response relation for eye irritation has been determined in experimental human exposure studies of good quality. There are several independent studies indicating increased risk of spontaneous abortion in women, and this is supported by evidence from animal studies. Ototoxicity of toluene is well documented in animals and two epidemiological studies indicate similar effects in man. The dose-response relation for acute neurotoxicity has been determined in experimental human exposure studies of good quality. Several epidemiological studies show a relation between long-term exposure and organic toxic encephalopathy, however, the dose-response is not well described.

14.3 Scientific basis for an occupational exposure limit

The major concerns for human health are reproductive toxicity, ototoxicity, and neurotoxicity. The LOAELs and NOAELs, if known, are shown in Table 5. The following may be considered for setting occupational exposure limits: Increased risk for spontaneous abortion has been identified in a group of women exposed to

50-150 ppm (average 88 ppm) toluene. For eye irritation, headache, and feeling of intoxication the LOAEL is 100 ppm and the NOAEL is 40 ppm. The LOAEL for deterioration in the perceived air quality and increased odour level is 10 ppm.

15. Research needs

There is a need for further investigation of the ototoxic effects of toluene in humans to allow determination of the time, dose-response relationship.

The study of mechanisms for the various toxicity endpoints is important. Also, the dose-response relationship for reproductive toxicity needs to be explored. CNS damage in laboratory animals should also be further investigated.

16. Summary

Østergaard Grete. *Toluene*. Arbete och Hälsa 2000;19:1-51.

The major route of toluene exposure is inhalation. Toluene is to a large extent metabolised in the liver and excreted in urine as hippuric acid.

Toluene has a low acute toxicity. Toluene vapours causes complaints of eye irritation, headache and dizziness. Toluene sniffing causes severe neurological abnormalities and brain atrophy, while it is possible that organic brain syndrome may develop in workers exposed to toluene for many years. Toluene may cause hearing loss in workers and the effect is enhanced if noise is present. Toluene abuse in pregnant women is associated with physical and neurological abnormalities in their foetuses. Lower birth weight and impairment of learning ability have been demonstrated in rats exposed in utero. An increased rate of spontaneous abortions in toluene-exposed female workers has been found.

The major concerns for human health are reproductive toxicity, ototoxicity, and neurotoxicity.

The rate of spontaneous abortion has been shown to be increased in women exposed to 50-150 ppm toluene (average 88 ppm). For eye irritation, headache, and feeling of intoxication the LOAEL is 100 ppm and the NOAEL is 40 ppm. The LOAEL for deterioration in the perceived air quality and increased odour level is 10 ppm.

Keywords: chronic toxic encephalopathy, irritation, neurotoxicity, occupational exposure limits, ototoxicity, toxicity, reproductive toxicity, toluene

17. Summary in Danish

Østergaard Grete. *Toluene*. Arbete och Hälsa 2000;19:1-51.

Toluene optages hovedsageligt ved indånding og udskilles hovedsageligt efter omsættelse i leveren som hippursyre i urinen.

Toluen har lav akut giftighed. Toluendampe giver anledning til øjenirritation, hovedpine og svimmelhed. Toluen-sniffing forårsager alvorlige neurologiske forstyrrelser og svind af hjernevæv, mens det er muligt, at organisk hjerneskade kan udvikles hos arbejdere efter mange års udsættelse. Toluen kan forårsage nedsat hørelse, og effekten forværres, hvis man også udsættes for støj. Toluen-misbrug hos gravide kvinder fører til fysiske og neurologiske skader hos børnene. Når rotter udsættes for toluen i fostertilstanden, finder man lavere fødselsvægt og nedsat indlæringsevne. Hos toluenudsatte kvindelige arbejdere er det påvist, at antallet af spontane aborter er forøget.

De største bekymringer for menneskets sundhet er reproduktionsskader, skader på hørelsen og skader på nervesystemet.

Forøget forekomst af spontan abort er påvist hos kvinder, der blev udsat for koncentrationer mellem 50 og 150 ppm (middelværdi 88 ppm).

For øjenirritation, hovedpine og følelse af giftpåvirkning er LOAEL 100 ppm og NOAEL 40 ppm. LOAEL for subjektiv oplevelse af nedsat luftkvalitet og øget lugt er 10 ppm.

Nøgleord: hygiejnisk grænseværdi, irritation, kronisk toksisk hjerneskade, malersyndrom, neurotoksicitet, ototoksicitet, reproduktionstoksicitet, toluen, toksicitet

18. References

1. Abbate C, Giorgianni C, Munaò F, Brecciaroli R. Neurotoxicity induced by exposure to toluene. *Int Arch Occup Environ Health* 1993;64:389-392.
2. Abou-El-Makarem MM, Millburn P, Smith RL, Williams RT. Biliary excretion of foreign compounds. Benzene and its derivatives in the rat. *Biochem J* 1967;105:1269-1274.
3. Amoore JE, Hautala E. Odor as an aid to chemical safety: Odor thresholds compared with threshold limit values and volatilities for 214 industrial chemicals in air and water dilution. *J Appl Toxicol* 1983;3:272-289.
4. Andersen I, Lundqvist GR, Mølhave L, Pedersen OF, Proctor DF, Vaeth M, Wyon DP. Human response to controlled levels of toluene in six-hour exposures. *Scand J Work Environ Health* 1983;9:405-418.
5. Antti-Poika M, Juntunen J, Matikainen E, Suoranta H, Hänninen H, Seppäläinen AM, Liira J. Occupational exposure to toluene: neurotoxic effects with special emphasis on drinking habits. *Int Arch Occup Environ Health* 1985;56:31-40.
6. Askergren A. Organic solvents and kidney function. *Adv Mod Environ Toxicol* 1982;2:157-172.
7. Bauchinger M, Schmid E, Dresp J, Kolin-Gerresheim J, Hauf R, Suhr E. Chromosome changes in lymphocytes after occupational exposure to toluene. *Mutat Res* 1982;102:439-445.
8. Benignus VA. Health effects of toluene: A review. *Neurotoxicology* 1981;2:567-588.
9. Bergman K. Whole-body autoradiography and allied tracer techniques in distribution and elimination studies of some organic solvents. *Scand J Work Environ Health* 1979;5, Suppl. 1:1-263.
10. Boey KW, Foo SC, Jeyaratnam J. Effects of occupational exposure to toluene: a neuropsychological study on workers in Singapore. *Ann Acad Med Singapore* 1997;26:184-187.
11. Bonnet P, Morele Y, Raoult G, Zissu D, Gradiski D. Détermination de la concentration léthale$_{50}$ des principaux hydrocarbures aromatiques chez le rat. *Arch Mal Prof* 1982;34:261-265.
12. Bonnet P, Raoult G, Gradiski D. Concentrations léthales$_{50}$ des principaux hydrocarbures aromatiques. *Arch Mal Prof* 1979;40:805-810.
13. Bos RP, Brouns RME, van Doorn R, Theuws JLG, Henderson PT. Non-mutagenicity of toluene, o-, m- and p-xylene, o-methylbenzylalcohol and o-methylbenzylsulfate in the Ames assay. *Mutat Res* 1981;88:273-279.
14. Braier L. Traitement des leucoses chroniques par le benzene et ses homologues. Le role des donneurs de méthyles. *Le Sang* 1953;24:603-612.
15. Browning E. *Toxicity and metabolism of industrial solvents.* Amsterdam: Elsevier Publishing Company, 1965.
16. Brugnone F, Perbellini L, Apostoli P, Locatelli M, Mariotto P. Decline of blood and alveolar toluene concentration following two accidental human poisonings. *Int Arch Occup Environ Health* 1983;53:157-165.
17. Bælum J, Andersen IB, Lundqvist GR, Mølhave L, Pedersen OF, Væth M, Wyon DP. Response of solvent-exposed printers and unexposed controls to six-hour toluene exposure. *Scand J Work Environ Health* 1985;11:271-280.
18. Bælum J, Lundqvist GR, Mølhave L, Andersen NT. Human response to varying concentrations of toluene. *Int Arch Occup Environ Health* 1990;62:65-71.

19. Cameron GR, Paterson JLH, De Saram GSW, Thomas JC. The toxicity of some methyl derivatives of benzene with special reference to pseudocumene and heavy coal tar naphtha. *J Pathol Bact* 1938;46:95-107.
20. Campo P, Lataye R, Cossec B, Placidi V. Toluene-induced hearing loss: a mid-frequency location of the cochlear lesions. *Neurotoxicol Teratol* 1997;19:129-140.
21. Carlsson A. Exposure to toluene. Uptake, distribution and elimination in man. *Scand J Work Environ Health* 1982;8:43-55.
22. Carlsson A, Lindqvist T. Exposure of animals and man to toluene. *Scand J Work Environ Health* 1977;3:135-143.
23. Carlsson A, Ljungquist E. Exposure to toluene. Concentration in subcutaneous adipose tissue. *Scand J Work Environ Health* 1982;8:56-62.
24. Casto BC. Detection of chemical carcinogens and mutagens in hamster cells by enhancement of adenovirus transformation. In: Mishra N, Dunkel V, Mehlman I, eds. *Advances in modern environmental toxicology.* Vol.1. Princeton NJ: Senate Press, 1981.
25. Chang MJW, Hsu KH, Chen YC, Hsieh LL, Luo JJ. Biological monitoring of urinary hippuric acid in a Taiwanese semiconductor company. International symposium on biological monitoring in occupational and environmental health. Finnish Institute of Occupational Health. 1996.
26. Cherry N, Johnston JD, Venables H, Waldron HA, Buck L, MacKay CJ. The effects of toluene and alcohol on psychomotor performance. *Ergonomics* 1983;26:1081-1087.
27. Cherry N, Venables H, Waldron HA. British studies on the neuropsychological effects of solvent exposure. *Scand J Work Environ Health* 1984;10, Suppl. 1:10-13.
28. Connor TH, Theiss JC, Hanna HA, Monteith DK, Matney TS. Genotoxicity of organic chemicals frequently found in the air of mobile homes. *Toxicol Lett* 1985;25:33-40.
29. Courtney KD, Andrews JE, Springer J, Menache M, Williams T, Dalley L, Graham JA. A perinatal study of toluene in CD-1 mice. *Fundam Appl Toxicol* 1986;6:145-154.
30. da Silva V, Malheiros LR, Paumgartten FJ, Sa-Rego Md, Riul TR, Golovattei MA. Developmental toxicity of in utero exposure to toluene on malnourished and well nourished rats. *Toxicology* 1990;64:155-168.
31. Danish EPA. Risk Assessment. Toluene. Draft report. *EU Existing Substances Risk Assessment Programme* 2000.
32. de-Ceaurriz JC, Micillino JC, Bonnet P, Guenier JP. Sensory irritation caused by various industrial airborne chemicals. *Toxicol Lett* 1981;9:137-143.
33. Echeverria D, Fine L, Langolf G, Schork A, Sampaio C. Acute neurobehavioural effects of toluene. *Br J Ind Med* 1989;46:483-495.
34. Fodor GG. *Schädliche Dämpfe*. Düsseldorf: VDI Verlag, 1972.
35. Foo SC, Jeyaratnam J, Koh D. Chronic neurobehavioural effects of toluene. *Br J Ind Med* 1990;47:480-484.
36. Fornazzari L, Wilkinson DA, Kapur BM, Carlen PL. Cerebellar, cortical and functional impairment in toluene abusers. *Acta Neurol Scand* 1983;67:319-329.
37. Forni A, Pacifico E, Limonta A. Chromosome studies in workers exposed to benzene or toluene or both. *Arch Environ Health* 1971;22:373-378.
38. Franchini I, Cavatorta A, Falzoi M, Lucertini S, Mutti A. Early indicators of renal damage in workers exposed to organic solvents. *Int Arch Occup Environ Health* 1983;52:1-9.
39. Freie Universität Berlin UBFIfT. *Feldstudie Toluol* (Tiefdruck). 1996.
40. Funes-Cravioto F, Zapata-Gayon C, Kolmodin-Hedman B, Lambert B, Lindsten J, Norberg E, Nordenskjöld M, Olin R, Swensson Å. Chromosome aberrations and sister-chromatid exchange in workers in chemical laboratories and a rotoprinting factory and in children of women laboratory workers. *Lancet* 1977;2:322-325.

41. Gad-El KM, Harper BL, Legator MS. Modifications in the myeloclastogenic effect of benzene in mice with toluene, phenobarbital, 3-methylcholanthrene, Aroclor 1254 and SKF-525A. *Mutat Res* 1984;135:225-243.
42. Gerarde HW. *Toxicology and biochemistry of aromatic hydrocarbons*. Amsterdam: Elsevier Publishing Company, 1960.
43. Gerner-Smidt P, Friedrich U. The mutagenic effect of benzene, toluene and xylene studied by the SCE technique. *Mutat Res* 1978;58:313-316.
44. Ghantous H, Danielsson BR. Placental transfer and distribution of toluene, xylene and benzene, and their metabolites during gestation in mice. *Biol Res Pregnancy Perinatol 1986*;7:98-105.
45. Gibson JE, Hardisty JF. Chronic toxicity and oncogenicity bioassay of inhaled toluene in Fischer-344 rats. *Fundam Appl Toxicol* 1983;3:315-319.
46. Guillot JP, Gonnet JF, Clement C, Caillard L, Truhaut R. Evaluation of the cutaneous-irritation potential of 56 compounds. *Food Chem Toxicol* 1982b;20:563-572.
47. Guillot JP, Gonnet JF, Clement C, Caillard L, Truhaut R. Evaluation of the ocular-irritation potential of 56 compounds. *Food Chem Toxicol* 1982a;20:573-582.
48. Gusev IS. The reflex action of microconcentrations of benzene, toluol, xylol and their comparative assessment (Russian, with summary in English). *Gig Sanit* 1965;30:6-11.
49. Haglund U, Lundberg I, Zech L. Chromosome aberrations and sister chromatid exchanges in Swedish paint industry workers. *Scand J Work Environ Health* 1980;6:291-298.
50. Hammer KD, Mayer N, Pfeiffer EH. Sister chromatid exchange in rotogravure printing plant workers. *Int Arch Occup Environ Health* 1998;71:138-142.
51. Hass U, Lund SP, Hougaard KS, Simonsen L. Developmental neurotoxicity after toluene inhalation exposure in rats. *Neurotoxicol Teratol* 1999;21:349-357.
52. Haworth S, Lawlor T, Mortelmans K, Speck W, Zeiger E. Salmonella mutagenicity test results for 250 chemicals. *Environ Mutagen* 1983;5, Suppl. 1:1-142.
53. Hougaard KS, Lund SP, Simonsen L. Effects of prenatal exposure to toluene on postnatal development and behaviour in rats. *Neurotoxicol Teratol* 1999;21:241-250.
54. Huang J, Asaeda N, Takeuchi Y, Shibata E, Hisanaga N, Ono Y, Kato K. Dose dependent effects of chronic exposure to toluene on neuronal and glial cell marker proteins in the central nervous system of rats. *Br J Ind Med* 1992;49:282-286.
55. Hudák A, Ungváry G. Embryotoxic effects of benzene and its methyl derivatives: toluene, xylene. *Toxicology* 1978;11:55-63.
56. Huff J. *Toxicology and carcinogenesis studies of toluene (Cas No. 108-88-3) in F344/N rats and B6C3F1 mice (Inhalation Studies)*. US Department of Health and Human Services. National Institute of Health, 1990.
57. Hughes TJ, Simmons DM, Monteith LG, Claxton LD. Vaporization technique to measure mutagenic activity of volatiles organic chemicals in the Ames/Salmonella assay. *Environ Mutagen* 1987;9:421-441.
58. Hydén D, Larsby B, Andersson H, Ödkvist LM, Liedgren SR, Tham R. Impairment of visuo-vestibular interaction in humans exposed to toluene. *ORL J Otorhinolaryngol Relat Spec* 1983;45:262-269.
59. Hänninen H, Antti-Poika M, Savolainen P. Psychological performance, toluene exposure and alcohol consumption in rotogravure printers. *Int Arch Occup Environ Health* 1987;59:475-483.
60. IARC. Re-evaluation of some organic chemicals, hydrazine and hydrogen peroxide (Part two). In: *IARC monographs on the evaluation of carcinogenic risks to humans.* Lyon: International Agency for Research on Cancer, 1999.
61. Ikeda M, Othsuji H. Phenobarbital-induced protection against toxicity of toluene and benzene in the rat. *Toxicol Appl Pharmacol* 1971;20:30-43.

62. IPCS. *Environmental Health Criteria 52. Toluene.* World Health Organization, Genveva, 1985, 146 p.

63. Iregren A. Effects on psychological test performance of workers exposed to a single solvent (toluene)--a comparison with effects of exposure to a mixture of organic solvents. *Neurobehav Toxicol Teratol* 1982;4:695-701.

64. Iregren A, Akerstedt T, Anshelm OB, Gamberale F. Experimental exposure to toluene in combination with ethanol intake. Psychophysiological functions. *Scand J Work Environ Health* 1986;12:128-136.

65. Jagannath DR, Matheson D, Brusick D. *Mutagenicity evaluation of toluene*. Litton Bionetics Inc., Kensington, Maryland, 1978.

66. Jelnes JE. Toluene. In: Heimbürger G, Beije B, Lundberg P, eds. *Criteria documents from the Nordic Expert Group 1989*. Arbete och Hälsa 1989; 37:7-57, National Institute of Occupational Health, Solna.

67. Jensen AA and Slorach SA. *Chemical contaminants in human milk*. Boca Raton: CRC Press, 1991.

68. Johnson AC, Canlon B. Toluene exposure affects the functional activity of the outer hair cells. *Hear Res* 1994;72:189-196.

69. Johnson AC, Juntunen L, Nylen P, Borg E, Hoglund G. Effect of interaction between noise and toluene on auditory function in the rat. *Acta Otolaryngol (Stockh)* 1988;105:56-63.

70. Jones HE, Balster RL. Neurobehavioral consequences of intermittent prenatal exposure to high concentrations of toluene. *Neurotoxicol Teratol* 1997;19:305-313.

71. Juntunen J, Matikainen E, Antti PM, Suoranta H, Valle M. Nervous system effects of long-term occupational exposure to toluene. *Acta Neurol Scand* 1985;72:512-517.

72. Karacic V, Skender L, Bosner-Cucancic B, Bogadi-Sare A. Possible genotoxicity in low level benzene exposure. *Am J Ind Med* 1995;27:379-388.

73. Kimura ET, Ebert DM, Dodge PW. Acute toxicity and limits of solvent residue for sixteen organic solvents. *Toxicol Appl Pharmacol* 1971;19:699-704.

74. Kishi R, Harabuchi I, Ikeda T, Yokota H, Miyake H. Neurobehavioural effects and pharmacokinetics of toluene in rats and their relevance to man. *Br J Ind Med* 1988;45:396-408.

75. Klimisch HJ, Hellwig J, Hofmann A. Studies on the prenatal toxicity of toluene in rabbits following inhalation exposure and proposal of a pregnancy guidance value. *Arch Toxicol* 1992;66:373-381.

76. Knoop F, Gerhrke M. Über die Oxydation von Essigsäure, Aceton und Toluol. I. Über die Oxydation von Essigsäure und Aceton mit Hydroperoxyd. II. Über die Oxydation des Toluols im Tierkörper. *Hoppe Seylers Z Physiol Chem* 1925;146:63-71.

77. Koga K, Ohmiya Y. Potentiation of toluene toxicity by hepatic enzyme inhibition in mice. *J Toxicol Sci* 1978;3:25-30.

78. Korbo L, Ladefoged O, Lam HR, Ostergaard G, West MJ, Arlien SP. Neuronal loss in hippocampus in rats exposed to toluene. *Neurotoxicology* 1996;17:359-366.

79. Kostas J, Hotchin J. Behavioral effects of low-level perinatal exposure to toluene in mice. *Neurobehav Toxicol Teratol* 1981;3:467-469.

80. Ladefoged O, Strange P, Moller A, Lam HR, Ostergaard G, Larsen JJ, Arlien SP. Irreversible effects in rats of toluene (inhalation) exposure for six months. *Pharmacol Toxicol* 1991;68:384-390.

81. Lagorio S, Tagesson C, Forastiere F, Iavarone I, Axelson O, Carere A. Exposure to benzene and urinary concentrations of 8-hydroxydeoxyguanosine, a biological marker of oxidative damage to DNA. *Occup Environ Med* 1994;51:739-743.

82. Larsen F, Leira HL. Organic brain syndrome and long-term exposure to toluene: a clinical, psychiatric study of vocationally active printing workers. *J Occup Med* 1988;30:875-878.

83. Lataye R, Campo P. Combined effects of a simultaneous exposure to noise and toluene on hearing function. *Neurotoxicol Teratol* 1997;19:373-382.

84. Lauwerys R. *Human biological monitoring of industrial chemicals series. Toluene.* Industrial health and safety. Ispra, 1983.

85. Lazar RB, Ho SU, Melen O, Daghestani AN. Multifocal central nervous system damage caused by toluene abuse. *Neurology* 1983;33:1337-1340.

86. Lee BK, Lee SH, Lee KM, Cho KS, Ahn KD, Kim SB, Ukai H, Nakatsuka H, Watanabe T, Ikeda M. Dose-dependent increase in subjective symptom prevalence among toluene-exposed workers. *Ind Health* 1988;26:11-23.

87. Lindquist T. *Fördelningskoefficienterna blod/luft och vatten/luft för några vanliga lösningsmedel* (in Swedish with English summary). Arbete och Hälsa 1977;8:1-5. National Institute of Occupational Health, Solna.

88. Lundberg I, Håkansson M, Gustavsson P. *Relativ leverskadande effekt av 14 organiska lösningmedel vid intraperitoneal injektion på råtta* (in Swedish with English summary). *Arbete och Hälsa* 1983;22:1-20. National Institute of Occupational Health, Solna.

89. Löf A, Johanson G. Toxicokinetics of organic solvents: A review of modifying factors. *Crit Rev Toxicol* 1998;28:571-650.

90. Löf A, Wallen M, Wigaeus Hjelm E. Influence of paracetamol and acetylsalicylic acid on the toxicokinetics of toluene. *Pharmacol Toxicol* 1990;66:138-141.

91. Löf A, Wigaeus Hjelm E, Colmsjo A, Lundmark BO, Norstrom A, Sato A. Toxicokinetics of toluene and urinary excretion of hippuric acid after human exposure to 2H8-toluene. *Br J Ind Med* 1993;50:55-59.

92. Matsushita T, Arimatsu Y, Ueda A, Satoh K, Nomura S. Hematological and neuro-muscular response of workers exposed to low concentration of toluene vapor. *Ind Health* 1975;13:115-121.

93. McCarrol NE, Keech BH, Piper CE. A microsuspension adaptation of the Bacillus subtilis 'rec' assay. *Environ Mutagen* 1981;3:607-616.

94. McCarrol NE, Piper CE, Keech BH. An E. coli microsuspension assay for the detection of DNA damage induced by direct-acting agents and promutagens. *Environ Mutagen* 1981;3:429-444.

95. Mohtashamipur E, Norpoth K, Woelke U, Huber P. Effects of ethylbenzene, toluene, and xylene on the induction of micronuclei in bone marrow polychromatic erythrocytes of mice. *Arch Toxicol* 1985;58:106-109.

96. Morata TC, Dunn DE, Kretschmer LW, Lemasters GK, Keith RW. Effects of occupational exposure to organic solvents and noise on hearing. *Scand J Work Environ Health* 1993;19:245-254.

97. Morata TC, Fiorini AC, Fischer FM, Colacioppo S, Wallingford KM, Krieg EF, Dunn DE, Gozzoli L, Padrao MA, Cesar CL. Toluene-induced hearing loss among rotogravure printing workers. *Scand J Work Environ Health* 1997;23:289-298.

98. Muller J, Greff G. Relation between the toxicity of molecules of industrial value and their physico-chemical properties: test of upper airway irritation applied to 4 chemical groups. *Food Chem Toxicol* 1984;22:661-664.

99. Muttray A, Wolters V, Mayer PO, Schicketanz KH, Konietzko J. Effect of subacute occupational exposure to toluene on color vision. *Int J Occup Med Environ Health* 1995;8:339-345.

100. Mäki-Paakkanen J, Husgafvel-Pursiainen K, Kalliomäki P-L, Tuominen J, Sorsa M. Toluene-exposed workers and chromosome aberrations. *J Toxicol Environ Health* 1980;6:775-781.

101. Mørck HI, Winkel P, Gyntelberg F. *Helbredseffekter af toluenudsættelse* (in Danish with English summary). Arbejdsmiljøfondet, København, 1985.

102. Nakamura S, Oda Y, Shimada T, Oki I, Sugimoto K. SOS-inducing activity of chemical carcinogens and mutagens in Salmonella typhimurium TA1535/pSK 1002: examination with 151 chemicals. *Mutat Res* 1987;192:239-246.

103. Nestmann ER, Lee EGH, Matula TI, Douglas GR, Mueller JC. Mutagenicity of constituents identified in pulp and paper mill effluents using the Salmonella/mammalian-microsome assay. *Mutat Res* 1980;79:203-212.

104. Ng TP, Foo SC, Yoong T. Menstrual function in workers exposed to toluene. *Br J Ind Med* 1992;49:799-803.

105. Ng TP, Foo SC, Yoong T. Risk of spontaneous abortion in workers exposed to toluene. *Br J Ind Med* 1992;49:804-808.

106. Nielsen GD, Alarie Y. Sensory irritation, pulmonary irritation, and respiratory stimulation by airborne benzene and alkylbenzenes: prediction of safe industrial exposure levels and correlation with their thermodynamic properties. *Toxicol Appl Pharmacol* 1982;65:459-477.

107. Nielsen HK, Krusell L, Bælum J, Lundqvist G, Omland Ø, Væth M, Husted SE, Mogensen CE, Geday E. Renal effects of acute exposure to toluene. A controlled clinical trial. *Acta Med Scand* 1985;218:317-321.

108. Nise G, Attewell R, Skerfving S, Ørbæk P. Elimination of toluene from venous blood and adipose tissue after occupational exposure. *Br J Ind Med* 1989;46:407-411.

109. Nise G, Högstedt B, Bratt I, Skerfving S. Cytogenetic effects in rotogravure workers exposed to toluene (and benzene). *Mutat Res* 1991;261:217-223.

110. Nomiyama K, Nomiyama H. Respiratory retention, uptake and excretion of organic solvents in man. Benzene, toluene, n-hexane, trichloroethylene, acetone, ethyl acetate and ethyl alcohol. *Int Arch Arbeitsmed* 1974;32:75-83.

111. Nylén P, Hagman M, Johnson AC. Function of the auditory and visual systems, and of peripheral nerve, in rats after long-term combined exposure to n-hexane and methylated benzene derivatives. I. *Pharmacol Toxicol* 1994;74:116-123.

112. Nylén P, Hagman M, Johnson AC. Function of the auditory system, the visual system, and peripheral nerve and long-term combined exposure to toluene and ethanol in rats. *Pharmacol Toxicol* 1995;76:107-111.

113. Ono A, Sekita K, Ogawa Y, Hirose A, Suzuki S, Saito M, Naito K, Kaneko T, Furuya T, Kawashima K, Yasuhara K, Matsumoto K, Tanaka S, Inoue T, Kurokawa Y. Reproductive and developmental toxicity studies of toluene. II. Effects of inhalation exposure on fertility in rats. *J Environ Pathol Toxicol Oncol* 1996;15:9-20.

114. Ono A, Sekita K, Ohno K, Hirose A, Ogawa Y, Saito M, Naito K, Kaneko T, Furuya T, Matsumoto K, Tanaka S, Kurokawa Y. Reproductive and developmental toxicity of toluene I. Teratogenicity study of inhalation exposure in pregnant rats. *J Toxicol Sci* 1995;20:109-134.

115. Pearson MA, Hoyme HE, Seaver LH, Rimeza ME. Toluene embryopathy: Delineation of the phenotype and comparison with fetal alcohol syndrome. *Pediatrics* 1994;93:211-215.

116. Pelclová D, Rössner P, Picková J. Chromosome aberrations in rotogravure printing plant workers. *Mutat Res* 1990;245:299-303.

117. Piotrowski J. Quantitative estimate of the absorption of toluene in people (in Polish with English summary). *Med Pr* 1967;18:213-223.

118. Pitarque M, Vaglenov A, Nosko M, Hirvonen A, Norrpa H, Creus A, Marcos R. Evaluation of DNA damage by the Comet assay in shoe workers exposed to toluene and other organic solvents. *Mutat Res* 1999;441:115-127.

119. Plappert U, Barthel E, Seidel HJ. Reduction of benzene toxicity by toluene. *Environ Mol Mutagen* 1994;24:283-292.

120. Plenge-Bönig A, Karmaus W. Exposure to toluene in the printing industry is associated with subfecundity in women but not in men. *Occup Environ Med* 1999;56:443-448.

121. Popp W, Vahrenholz C, Yaman S, Müller C, Müller G, Schmeiding W, Norpoth K, Fahnert R. Investigation of the frequency of DNA strand breakage and cross-linking and of sister

chromatid exchange frequency in the lymphocytes of female workers exposed to benzene and toluene. *Carcinogenesis* 1992;13:57-61.

122. Pozzani UC, Weil CS, Carpenter CP. The toxicological basis of threshold limit values: 5. The experimental inhalation of vapor mixtures by rats, with notes upon the relationship between single dose inhalation and single dose oral data. *Am Ind Hyg Assoc J* 1959;20:364-369.
123. Pryor GT, Dickinson J, Howd RA, Rebert CS. Neurobehavioral effects of subchronic exposure of weanling rats to toluene or hexane. *Neurobehav Toxicol Teratol* 1983;5:47-52.
124. Pryor GT, Dickinson J, Howd RA, Rebert CS. Transient cognitive deficits and high-frequency hearing loss in weanling rats exposed to toluene. *Neurobehav Toxicol Teratol* 1983;5:53-57.
125. Pryor GT, Rebert CS, Dickinson J, Feeney EM. Factors affecting toluene-induced ototoxicity in rats. *Neurobehav Toxicol Teratol* 1984;6:223-238.
126. Pyykkö K, Tähti H, Vapaatalo H. Toluene concentrations in various tissues of rats after inhalation and oral administration. *Arch Toxicol* 1977;38:169-176.
127. Rebert CS, Sorenson SS, Howd RA, Pryor GT. Toluene-induced hearing loss in rats evidenced by the brainstem auditory-evoked response. *Neurobehav Toxicol Teratol* 1983;5:59-62.
128. Reisin E, Teicher A, Jaffe R, Eliahou HE. Myoglobinuria and renal failure in toluene poisoning. *Br J Ind Med* 1975;32:163-168.
129. Richer CL, Chakrabarti S, Senécal-Quevillon M, Duhr MA, Zhang XX, Tardif R. Cytogenetic effects of low-level exposure to toluene, xylene, and their mixture on human blood lymphocytes. *Int Arch Occup Environ Health* 1993;64:581-585.
130. Riihimäki V, Pfäffli P. Percutaneous absorption of solvent vapors in man. *Scand J Work Environ Health* 1978;4:73-85.
131. Rodrigue-Arnaiz R, Villalobos-Pietrini R. Genetic effects of thinner, benzene and toluene in Drosophila melanogaster. 1. Sex chromosome loss and non-dis-junction. *Contam Ambiental* 1985a;1:35-43.
132. Rodrigue-Arnaiz R, Villalobos-Pietrini R. Genetic effects of thinner, benzene and toluene in Drosophila melanogaster. 2. Sex linked recessive lethal mutations and translocations II-III. *Contam Ambiental* 1985b;1:45-49.
133. Roh J, Moon YH, Kirr K-Y. The cytogenetic effects of benzene and toluene on bone marrow cells in rats. *Yonsei Medical Journal* 1987;28:297-309.
134. Russ G, Clarkson AR, Woodroffe AJ, Seymour AE, Cheng IKP. Renal failure from glue sniffing. *Med J Aust* 1981;2:121-123.
135. Ruth JH. Odor thresholds and irritation levels of several chemical substances: A review. *Am Ind Hyg Assoc J* 1986;47:142-151.
136. Römmelt H, Kessel R, Pfaller A. Rückschlüsse auf die Arbeitsplatzbelastung durch die Bestimmung von Lösungsmittelkonzentration im Vollblut. *Verh Dtsch Ges Arbeitsmed* 1982;22:575-578.
137. Sato A, Fujwara Y, Hirosawa K. Solubility of benzene, toluene and m-xylene in blood (in Japanese with English summary). *Jap J Ind Health* 1972;14:3-8.
138. Sato A, Nakajima T. Partition coefficients of some aromatic hydrocarbons and ketones in water, blood and oil. *Br J Ind Med* 1979;36:231-234.
139. Sato A, Nakajima T. Differences following skin or inhalation exposure in the absorption and excretion kinetics of trichloroethylene and toluene. *Br J Ind Med* 1978;35:43-49.
140. Sato A, Nakajima T, Fujwara Y, Hirosawa K. Pharmacokinetics of benzene and toluene. *Int Arch Arbeitsmed* 1974;33:169-182.
141. Sherwood RJ. Ostwald solubility coefficients of some industrially important substances. *Br J Ind Med* 1976;33:106-107.

142. Sina JF, Bean CL, Dysart GR, Taylor VI, Bradley BO. Evaluation of the alkaline elution/rat hepatocyte as a predictor of carcinogenic/mutagenic potential. *Mutat Res* 1983;113:357-391.

143. Slomianka L, Edelfors S, Ravn-Jonsen A, Rungby J, Danscher G, West MJ. The effect of low-level toluene exposure on the developing hippocampal region of the rat: Histological evidence and volumetric findings. *Toxicology* 1990;62:189-202.

144. Slomianka L, Rungby J, Edelfors S, Ravn-Jonsen A. Late postnatal growth in the dentate area of the rat hippocampus compensates for volumetric changes caused by early postnatal toluene exposure. *Toxicology* 1992;94:203-208.

145. Smith JN, Smithies RH, Williams RT. Studies in detoxication. 55. The metabolism of alkylbenzenes. (a) Glucuronic acid excretion following the administration of alkylbenzenes. (b) Elimination of toluene in the expired air of rabbits. *Biochem J* 1954;56:317-320.

146. Smyth HF, Carpenter CP, Weil CS, Pozzani UC, Striegel JA, Nycum JS. Range-finding toxicity data: List VII. *Am Ind Hyg Assoc J* 1969;30:470-476.

147. Snyder RD, Matheson DW. Nick translation – a new assay for monitoring DNA damage and repair in cultured human fibroblasts. *Environ Mutagen* 1985;7:267-279.

148. Spanggord RJ, Mortelmans KE, Griffin AF, Simmon VF. Mutagenicity in Salmonella typhimurium and structure-activity relationships of wastewater components emanating from the manufacture of trinitrotoluene. *Environ Mutagen* 1982;4:163-179.

149. Sugai S, Murata K, Kitagaki T, Tomita I. Studies on the eye irritation caused by chemicals in rabbits - 1. A quantitative structure-activity relationships approach to primary eye irritation of chemicals in rabbits. *J Toxicol Sci* 1990;15:245-262.

150. Sullivan MJ, Rarey KE, Conolly RB. Ototoxicity of toluene in rats. *Neurotoxicol Teratol* 1989;10:525-530.

151. Svensson BG, Erfurth EM, Nise G, Nilsson A, Skerfving S. Hormone status in occupational toluene exposure. *Am J Ind Med* 1992;22:99-107.

152. Svensson BG, Nise G, Englander V, Attewell R, Skerfving S, Möller T. Deaths and tumours among rotogravure printers exposed to toluene. *Br J Ind Med* 1990;47:372-379.

153. Svensson BG, Nise G, Erfurth EM, Olsson H. Neuroendocrine effects in printing workers exposed to toluene. *Br J Ind Med* 1992;49:402-408.

154. Svirbely JL, Dunn RC, Von Oettingen WF. The acute toxicity of vapors of certain solvents containing appreciable amounts of benzene and toluene. *J Ind Hyg Toxicol* 1943;25:366-373.

155. Taskinen H, Kyyrönen P, Hemminki K, Hoikkala M, Lajunen K, Lindbohm M-L. Laboratory work and pregnancy outcome. *J Occup Med* 1994;36:311-319.

156. Thiel R, Chahoud I. Postnatal development and behaviour of Wistar rats after prenatal toluene exposure. *Arch Toxicol, 71: 258-265* 1997;71:258-265.

157. Tsuruta H. Percutaneous absorption of organic solvents. III. On the penetration rates of hydrophobic solvents through the excised rat skin. *Ind Health* 1982;20:335-345.

158. U.S. Department of Health & Human Services. Public Health Service. Agency for Toxic Substances and Disease Registry (ATSDR). *Toxicological profile for toluene (Update*). Draft for public comment. 1998.

159. Ulfvarson U, Övrum P. *Fördelning av lösningsmedel mellan blod och luft. I. Bestämning av fördelningskoefficienten mellan blod och luft för några lättflyktiga lösningsmedel* (in Swedish with English summary). Arbete och Hälsa 1976;7:1-7. Arbetarskyddsverket, Stockholm, 1976.

160. Ungváry G, Mányai S, Tátrai E, Szeberényi S, Cseh RJ, Molnár J, Folly G. Effect of toluene inhalation on the liver of rats - dependence on sex, dose and exposure time. *J Hyg Epidemiol Microbiol Immunol* 1980;24:242-252.

161. Ungváry G, Tátrai E, Szeberényi S, Rodics K, Lörincz M, Barcza G. Effect of toluene exposure on the liver under different experimental conditions. *Exp Mol Pathol* 1982;36:347-360.

162. Veulemans H, Masschelein R. Experimental human exposure to toluene. I. Factors influencing the individual respiratory uptake and elimination. *Int Arch Occup Environ Health* 1978a;42:91-103.

163. Veulemans H, Masschelein R. Experimental human exposure to toluene. II. Toluene in venous blood during and after exposure. *Int Arch Occup Environ Health* 1978b;42:105-117.

164. Vrca A, Bozicevic D, Bozikov V, Fuchs R, Malinar M. Brain stem evoked potentials and visual evoked potentials in relation to the length of occupational exposure to low levels of toluene. *Acta Med Croatica* 1997;51:215-219.

165. Vrca A, Bozicevic D, Karacic V, Fuchs R, Prpic-Majic D, Malinar M. Visual evoked potentials in individuals exposed to long-term low concentrations of toluene. *Arch Toxicol* 1995;69:337-340.

166. Vrca A, Karacic V, Bozicevic D, Fuchs R, Malinar M. Cognitive evoked potentials VEP P300 in persons occupationally exposed to low concentrations of toluene. *Arh Hig Rada Toksikol* 1997;48:277-285.

167. Wiebelt H, Becker N, Holzmeier S. *Kohortenstudie zur Mortalität in einer toluolexponierten Berufsgruppe (Tiefdrucker) und einer Vergleichsgruppe aus der papierverarbeitenden Industrie (Hygieneartikel).* Abschlussbericht. Deutsches Krebsforschungszentrum, Abteilung Epidemiologie, Heidelberg, 1996.

168. Williams RT. Detoxication mechanisms. *The metabolism and detoxication of drugs, toxic substances and other organic compounds*. London: Chapman & Hall Ltd., 1959.

169. Winneke G, Krämer U, Kastka J. Zur Beeinflussung psychomotorischer Leistungen durch Alkohol und durch verschiedene Lösungsmitteldämpfe. In: Horváth M, ed. *Adverse effects of environmental chemical and psychotropic drugs*. Vol. 2. Amsterdam: Elsevier Scientific Publishing Company, 1976.

170. Winston S, Matsuhita T. Permanent loss of chromosome initiation in toluene-treated Bacillus subtilis cells. *J Bacteriol* 1975;123:921-927.

171. Withey RJ, Hall JW. The joint toxic action of perchloroethylene with benzene or toluene in rats. *Toxicology* 1975;4:5-15.

172. Woiwode W, Drysch K. Experimental exposure to toluene: further consideration of cresol formation in man. *Br J Ind Med* 1981;38:194-197.

173. Woiwode W, Wodarz R, Drysch K, Weichardt H. Metabolism of toluene in man: Gas-chromatographic determination of o-, m- and p-cresol in urine. *Arch Toxicol* 1979;43:93-98.

174. Wolf MA, Rowe VK, McCollister DD, Hollingsworth RL, Oyen F. Toxicological studies of certain alkylated benzenes and benzene. *American Medical Association Archives of Industrial Health* 1956;14:387-398.

175. Zahlsen K, Eide I, Nilsen AM, Nilsen OG. Inhalation kinetics of C6 to C10 aliphatic, aromatic and naphthenic hydrocarbons in rat after repeated exposures. *Pharmacol Toxicol* 1992;71:144-149.

176. Zarani F, Papazafiri P, Kappas A. Induction of micronuclei in human lymphocytes by organic solvents in vitro. *J Environ Pathol Toxicol Oncol* 1999;18:21-28.

177. Ørbæk P, Nise G. Neurasthenic complaints and psychometric function of toluene-exposed rotogravure printers. *Am J Ind Med* 1989;16:67-77.

178. Åstrand I. Uptake of solvents in the blood and tissues of man. A review. *Scand J Work Environ Health* 1975;1:199-218.

179. Åstrand I, Ehrner-Samuel H, Kilbom Å, Övrum P. Toluene exposure I. Concentration in alveolar air and blood at rest and during exercise. *Work Environ Health* 1972;9:119-130.

19. Data bases used in search for literature

In the search for literature the following data bases were used:

-Medline
-Toxline
-HSDB

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Appendix 1.

Occupational exposure limits for toluene in air.

Country	ppm	mg/m^3	Comments	Year	Ref
Denmark	25	94	Skin uptake	1996	1
Finland	50	190	Skin uptake	1998	2
	100	380	15 min short term	1998	2
Germany	50	190	Skin uptake	2000	3
Iceland	25	94	Skin uptake	1999	4
Netherlands	40	150		2000	5
Norway	25	94	Skin uptake	1996	6
Sweden	50	200	Skin uptake	2000	7
	100	400	15 min short term	2000	7
USA (ACGIH)	50		Skin uptake	2000	8
(NIOSH)	100	375		2000	9
	150	560	15 min short term	2000	9
(OSHA)	200			2000	9
	300		Ceiling value	2000	9
	500		10 min short term	2000	9

References

1. *Grænsverdier for stoffer og materialer.* København: Arbejdstilsynet, 1997 (At-anvisning Nr. 3.1.0.2).
2. HTP-arvot 1996. Tampere: Työministeriö, 1996 (Turvallisuustiedote 25).
3. *MAK- und BAT-Werte-Liste 2000.* Weinheim: Wiley-VCH Verlag, 2000.
4. Mengunarmörk og aðgerðir til að draga úr mengun á vinnustöðum. Vinnueftirlit ríksins, 1999.
5. *Nationale MAC-lijst 2000.* Den Haag: Sdu Uitgevers 1999. ISBN 90-12-08835 6.
6. *Administrative normer for forurensning i arbeidsatmosfære.* Veiledning til arbeidsmiljøloven. Oslo: Direktoratet for Arbeidstilsynet, 1996 (Bestillingsnr. 361).
7. *Hygieniska gränsvärden och åtgärder mot luftföroreningar.* Stockholm: Arbetarskyddsstyrelsen, 2000 (AFS 2000:3) ISBN 91-7930-357-9.
8. *2000 TLVs and BEIs.* Cincinnati, Ohio: American Conference of Governmental Industrial Hygienists, 2000. ISBN 1-882417-36-4.
9. *NIOSH Pocket Guide to Chemical Hazards.* Washington: U.S. Department of Health and Human Services, 2000.