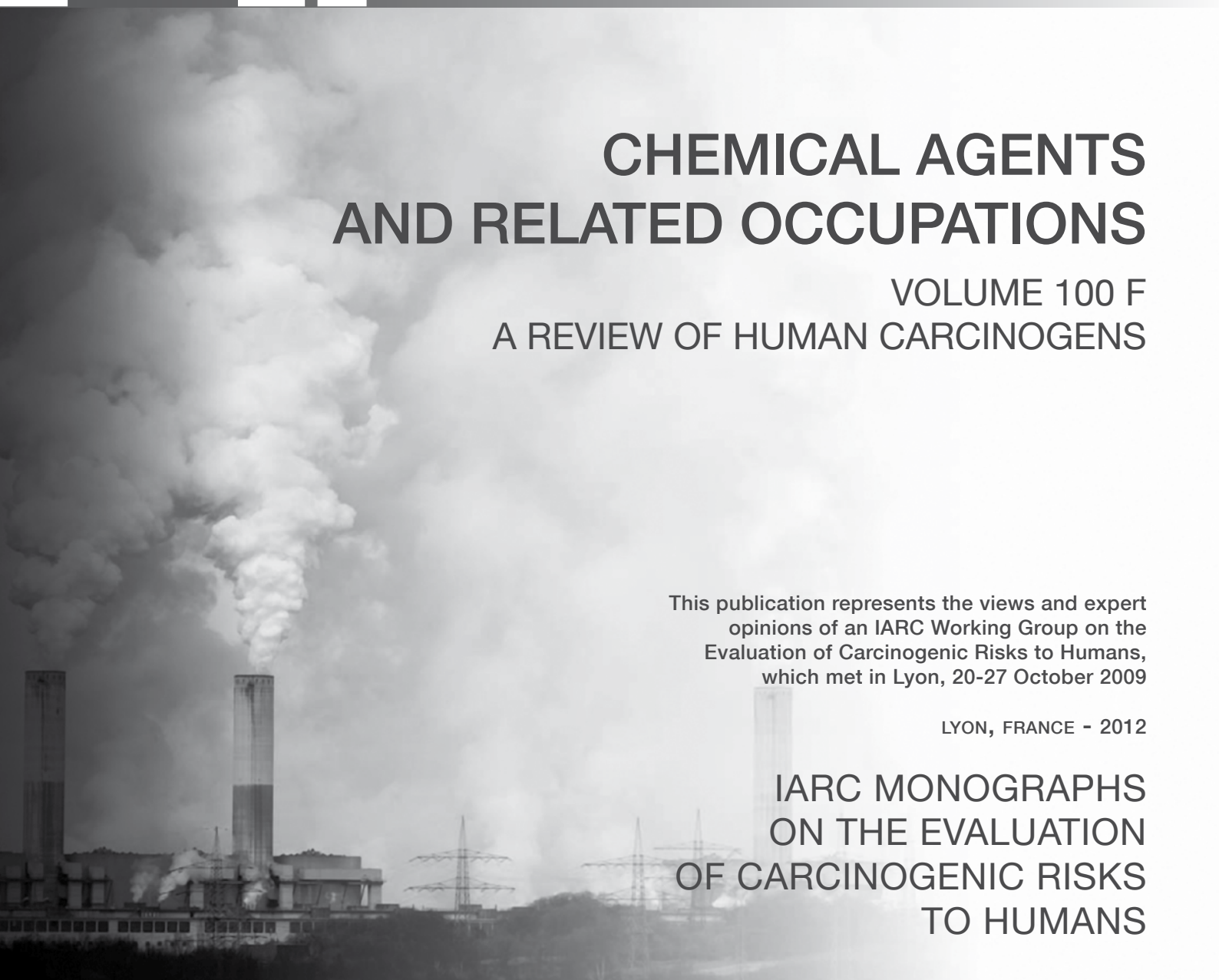
IARC MONOGRAPHS



CHEMICAL AGENTS AND RELATED OCCUPATIONS

VOLUME 100 F
A REVIEW OF HUMAN CARCINOGENS

This publication represents the views and expert opinions of an IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, which met in Lyon, 20-27 October 2009

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IARC MONOGRAPHS ON THE EVALUATION OF CARCINOGENIC RISKS TO HUMANS

International Agency for Research on Cancer
World Health Organization

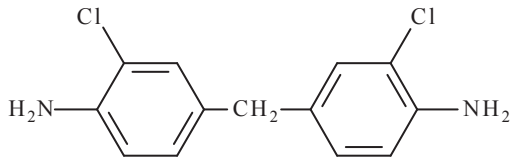
4,4′-METHYLENEBIS(2-CHLOROBENZENAMINE)

4,4′-Methylenebis(2-chlorobenzenamine) (MOCA) was considered by previous IARC Working Groups in 1973, 1992, and 2008 (IARC, 1974, 1987, 2010). Since that time new data have become available, which have been incorporated in this *Monograph,* and taken into consideration in the present evaluation.

1. Exposure Data

1.1 Identification of the agent

From IARC (2010) unless indicated otherwise
Chem. Abstr. Serv. Reg. No.: 101-14-4
Chem. Abstr. Serv. Name: 4,4′-Methylenebis(2-chlorobenzenamine)
Synonym: this compound is commonly known as methylenebis(*ortho*-chloroaniline), MOCA



$C_{13}H_{12}Cl_2N_2$
Relative molecular mass: 267.15
Description: Colourless to yellow or light-brown crystalline solid with a faint amine-like odour
Solubility: Slightly soluble in water; soluble in dilute acids, ether, alcohol (O'Neil, 2006)

1.2 Uses

MOCA is used primarily as a curing agent for polyurethane pre-polymers in the manufacture of castable urethane rubber products (e.g. shock-absorption pads and conveyor belting). In the laboratory, MOCA is used as a model compound for studying carcinogens (NTP, 2005; O'Neil, 2006; IARC, 2010).

1.3 Human exposure

1.3.1 Occupational exposure

Occupational exposure to MOCA can occur during its production and use in the polyurethane industry. Workers can be exposed to MOCA when it is processed in the form of a liquid emulsion, as solid pellets with dust, or as solid pellets without dust. In most cases, dermal absorption after contact with contaminated surfaces is the most important occupational exposure route, with inhalation and ingestion representing minor exposure pathways (IARC, 1993).

CAREX (CARcinogen EXposure) is an international information system on occupational

exposure to known and suspected carcinogens, based on data collected in the European Union (EU) from 1990 to 1993. The CAREX database provides selected exposure data and documented estimates of the number of exposed workers by country, carcinogen, and industry (Kauppinen *et al.*, 2000). Table 1.1 presents the results for MOCA by industry in the EU (CAREX, 1999).

An estimated 10000 workers were exposed to MOCA in industrialized countries in 1972 (Rappaport & Morales, 1979; Will *et al.*, 1981). In 1979, an estimated 1400 workers in the United States of America (USA) were directly exposed and 7400 indirectly exposed by working in polyurethane-manufacturing processes involving MOCA (Ward *et al.*, 1987). More recently, the Health and Safety Executive estimated that in 2005–06 approximately 300 workers in the United Kingdom were directly exposed to MOCA during polyurethane-elastomer production and over 1000 workers were indirectly exposed (e.g. office staff) (HSE, 2007; Cocker *et al.*, 2009).

(a) Exposure measurements

MOCA levels in air, blood and urine and in surface-wipe samples have been reported for workers employed in the production and use of this chemical in several countries. Different analytical methods have been applied, which complicates comparison of reported MOCA levels (IARC, 2010). Surface wipes have been used mainly to give an indication of potential for dermal exposure to MOCA by anyone working in the area. As measurement of airborne MOCA alone is considered ineffective in the assessment of worker exposure (Robert *et al.*, 1999), post-shift measurement in urine is the most employed method to assess exposure. The concentration of MOCA in urine reflects recent exposure, since the biological half-life of this compound is approximately 23 hours (Osorio *et al.*, 1990). In some studies urinary concentrations of acetyl-MOCA have been determined in addition to those of MOCA, showing that *N*-acetyl-MOCA is a minor urinary metabolite compared with the elimination of the parent amine (Cocker *et al.*, 1988; Shih *et al.*, 2007).

An alternative to measuring MOCA in urine is to determine haemoglobin-MOCA adducts in blood. These adducts are stable for the lifespan of haemoglobin, which in humans is about 120 days (Vaughan & Kenyon, 1996).

(b) MOCA production

Air concentrations of MOCA have been reported from two production plants. In a study from the USA (Linch *et al.*, 1971), the airborne concentration of MOCA was below the detection limit. In a study from Taiwan, China (Chen *et al.*, 2005), the highest concentrations in air (0.41 mg/m^3) were recorded during the purification of MOCA.

Measurements of MOCA concentrations in the urine of production workers from France, Taiwan (China), and the USA were reviewed recently (IARC, 2010). In workers without gloves or protective clothing, concentrations ranged up to several thousand μg/L; the values were much lower when proper protection had been used.

(c) Polyurethane-production workers

Measurements of MOCA concentrations in the urine of polyurethane-production workers from Australia, Canada, France, Germany, Japan, the United Kingdom and the USA were reviewed recently (IARC, 2010). The use of protective equipment and the application of safety procedures reduced the values from several hundred μg/L to as low as 1–10 μg/L.

1.3.2 Non-occupational exposure

The general population can be exposed to MOCA in areas that have been contaminated with MOCA (Keeslar, 1986) or through consumption of certain types of plant (e.g. root crops) grown in contaminated soil (ATSDR, 1994). Immediate family members of workers exposed to MOCA

Table 1.1 Estimated numbers of workers exposed to MOCA in the European Union

Industry, occupational activity	
Manufacture of plastic products not elsewhere classified	1390
Manufacture of rubber products	1360
Manufacture of industrial chemicals	100
Manufacture of miscellaneous products from petroleum and coal	10
Research and scientific institutes	430
TOTAL	3300

From: CAREX (1999)

were reported to have concentrations of up to 15 µg/L in their urine (Keeslar, 1986).

In 1979, extensive environmental contamination with MOCA was discovered on several hundred hectares of land surrounding a MOCA plant in Adrian, MI, USA. Concentrations of up to several mg/kg were found in gardens and community-recreation areas. MOCA was also found in the urine of young children living in the contaminated area (Keeslar, 1986). Of 12 selected children, aged 2 to 16 years, six were found to have detectable concentrations of MOCA in their urine, ranging from 0.3–1.0 ppb (µg/L). These six children were all under the age of six years. Contact with contaminated soil during playing and going barefoot were considered the most likely routes of exposure. The general adult population living in the contaminated area had no detectable MOCA concentrations in urine (IARC, 2010).

2. Cancer in Humans

Bladder-cytology surveys have identified bladder-cancer cases in workers exposed to MOCA in Michigan, USA (Ward *et al.*, 1988, 1990), New Jersey, USA (Mason & Vogler, 1990; Mason *et al.*, 1992), and Taiwan (China) (Chen *et al.*, 2005), but expected numbers were not calculated, so risks for bladder cancer cannot be evaluated. Dost *et al.* (2009) reported on a cohort of 308 male MOCA-production workers in the United Kingdom and found one bladder-cancer death in the period 1979–2007, with 0.18 deaths expected (SMR 5.6; 95%CI: 0.14–31.2), based on the United Kingdom mortality rates.

No adequate epidemiological studies were available to the Working Group to evaluate an association between MOCA and bladder-cancer risk.

3. Cancer in Experimental Animals

Studies on the carcinogenicity of MOCA in mice, rats, and dogs after oral administration, subcutaneous injection or dermal application have been reviewed in previous *IARC Monographs* (IARC, 1974, 1987, 1993, 2010). Results of adequately conducted carcinogenicity studies are summarized in Table 3.1. There have been no additional carcinogenicity studies in animals reported since the most recent evaluation (IARC, 2010).

MOCA was tested for carcinogenicity by oral administration (in the feed or in a gelatin capsule) in one experiment in mice, five experiments in rats and one experiment in dogs; by subcutaneous injection in one experiment in rats; and as an initiator or as a promoter in three experiments in mice, following dermal application.

Following its oral administration (feed) to female mice and male rats, MOCA increased the incidence of hepatomas (Russfield *et al.*, 1975). Oral administration (feed) to male and female

Table 3.1 Carcinogenicity studies of 4,4′-methylenebis(2-chloroaniline) in experimental animals

Species, strain (sex) Duration Reference	Route Dosing regimen, Animals/group at start	Incidence of tumours	Significance	Comments
Mouse, HaM/ICR (M, F) ~24 mo Russfield *et al.* (1975)	Feed Groups of mice were fed diets containing 0, 1000, or 2000 ppm MOCA as the hydrochloride salt for 18 mo. 25/group/sex	Haemangiomas or haemangiosarcomas (combined) M–0/18, 3/13, 8/20 F–1/20, 0/21, 6/14 Hepatomas: M–3/18, 3/13, 4/20 F–0/20, 9/21*, 7/14*	*$P < 0.01$, Fisher exact test	Purity, 97% Authors stated that the incidence of vascular tumours in the high-dose groups was comparable with that in historical controls of the same strain. [The Working Group noted that these vascular tumours were probably not treatment-related]
Rat, Wistar (M, F) Lifetime Grundmann & Steinhoff (1970)	Feed Groups of rats were fed 0 or 1000 ppm MOCA in a protein-deficient diet for 500 d (total dose 27 g/kg bw). 25/group/sex	Hepatomas: M–0/25, 22/25* F–0/25, 18/25* Lung tumours: M–0/25, 8/25** F–0/25, 5/25***	*[$P < 0.001$ Fisher exact test] **[$P = 0.002$] ***[$P = 0.025$]	Purity NR Mean survival times of treated males and females were 565 d and 535 d, respectively, and mean survival of male and female controls was 730 d. Lung tumours were mainly carcinomas.
Rat, Charles River CD1 (M) ~24 mo Russfield *et al.* (1975)	Feed Groups of rats were fed diets containing 0, 500, or 1000 ppm MOCA as the hydrochloride salt for 18 mo 25/group	Hepatomas: 0/22, 1/22, 4/19	[$P < 0.05$, Cochran-Armitage trend test]	Purity, 97%
Rat, Charles River CD (M, F) 2 yr Stula *et al.* (1975)	Feed Groups of rats were fed 0 or 1000 ppm MOCA in a standard diet for up to two yr. 50/group/sex	Lung adenocarcinomas: M–0/44, 21/44* F–0/44, 27/44* Lung adenomatosis: M–1/44, 14/44* F–1/44, 11/44* Hepatocellular carcinomas: M–0/44, 3/44 F–0/44, 3/44 Hepatocellular adenomas: M–0/44, 3/44 F–0/44, 2/44 Pleural mesotheliomas: M–0/44, 4/44 F–0/44, 2/44	*$P < 0.05$, χ^2-test	Purity NR Lung adenomatosis considered as pre-neoplastic or early neoplastic lesion

Table 3.1 (continued)

Species, strain (sex) Duration Reference	Route Dosing regimen, Animals/group at start	Incidence of tumours	Significance	Comments
Rat, Charles River CD (M, F) 16 mo Stula *et al.* (1975)	Feed Groups of rats were fed 0 or 1000 ppm MOCA in a low-protein diet for up to 16 mo. 25/group/sex	Lung adenocarcinomas: M–0/21, 5/21* F–0/21, 6/21* Lung adenomatosis: M–1/21, 8/21* F–1/21, 14/21* Hepatocellular carcinomas: M–0/21, 11/21* F–0/21, 1/21 Hepatocellular adenomas: M–0/21, 5/21* F–0/21, 2/21 Mammary gland adenocarcinomas: F–0/21, 6/21*	*$P < 0.05$, χ^2-test	Purity NR Lung adenomatosis considered as pre-neoplastic or early neoplastic lesion
Rat, Charles River CD (M) 24 mo Kommineni *et al.* (1979)	Feed Groups of rats were fed a 'protein-adequate' diet (Group A) containing 0, 250, 500, or 1000 ppm MOCA or a 'protein-deficient' diet (Group B) containing 0, 125, 250, and 500 ppm MOCA for 18 mo, then kept on these same diets without MOCA. 50, 75 or 100/group	Lung adenocarcinomas: A–0/100, 14/100*, 20/75*, 31/50* B–0/100, 3/100, 7/75**, 8/50* All lung tumours: A–1/100, 23/100*, 28/75*, 35/50* B–0/100, 6/100**, 11/75*, 13/50* Mammary gland adenocarcinomas: A–1/100, 5/100, 8/75**, 14/50* B–0/100, 1/100, 3/75, 3/50*** Zymbal gland carcinomas: A–1/100, 8/100***, 5/75, 11/50* B–0/100, 0/100, 4/75***, 6/50* Hepatocellular carcinomas: A–0/100, 3/100, 3/75, 18/50* B–0/100, 0/100, 0/75, 9/50* Haemangiosarcomas: A–2/100, 4/100, 3/75, 0/50 B–1/100, 2/100, 4/75, 4/50***	* $P < 0.001$ (two-tailed test) **$P < 0.01$ (two-tailed test) ***$P < 0.05$ (two-tailed test)	Industrial grade, purity NR

Table 3.1 (continued)

Species, strain (sex) Duration Reference	Route Dosing regimen, Animals/group at start	Incidence of tumours	Significance	Comments
Dog, Beagle (F) 9 yr Stula *et al.* (1978)	Oral administration A group of one-yr-old dogs was given 100 mg MOCA in gelatin capsules 3 × /wk for 6 wk and then 5 × /wk for up to 9 yr. A group of dogs served as untreated controls. 6/group	Urinary bladder carcinomas: 0/6, 4/5	[$P < 0.05$]	~90% pure One treated dog died prematurely of infection. A transitional-cell carcinoma/adenocarcinoma of the urethra developed in the one treated dog that did not develop a bladder carcinoma
Rat, Wistar (M, F) Lifetime Steinhoff & Grundmann (1971)	Subcutaneous injection Groups of rats were given subcutaneous injections of MOCA (suspension in saline) at doses of 500 or 1000 mg/kg bw, either once a wk or at longer time intervals during 620 d (total dose, 25 g/kg bw). A group of rats served as untreated controls. 17 or 25 (controls)/group/sex	Hepatocellular carcinomas: 0/50, 9/34* Lung cancers: 1/50, 7/34**	*[$P \leq 0.0042$, Fisher exact test] **[$P \leq 0.016$, Fisher exact test]	94% pure Age NR Study inadequately described in a short communication. Lung cancers in treated rats were six adenocarcinomas and one carcinoma.

bw, body weight; d, day or days; F, female; M, male; mo, month or months; NR, not reported; wk, week or weeks; yr, year or years

rats increased the incidence of hepatomas and lung tumours (Grundmann & Steinhoff, 1970). Oral administration (feed) to rats of both sexes caused an increased incidence of lung and mammary gland adenocarcinoma, and hepatocellular carcinoma in two studies (Stula *et al.*, 1975, Kommineni *et al.*, 1979). MOCA also caused haemangiosarcomas and Zymbal gland carcinomas in male rats in one of these studies (Kommineni *et al.*, 1979). Oral administration of MOCA in a gelatin capsule caused carcinomas of the urinary bladder in female dogs (Stula *et al.*, 1978). Subcutaneous injection of MOCA produced an increased incidence in hepatocellular carcinoma and lung cancer in rats (Steinhoff & Grundmann, 1971). After dermal application, MOCA was neither an initiator nor a promoter in the two experiments in mice (Nesnow *et al.*, 1985; Rozinova *et al.*, 1998).

4. Other Relevant Data

A general Section on "Aromatic amines: metabolism, genotoxicity, and cancer susceptibility" appears as Section 4.1 in the *Monograph* on 4-aminobiphenyl in this volume.

Studies on the metabolism, genotoxicity, and animal carcinogenicity of MOCA indicate that this substance acts similarly to other aromatic amines that are known to cause cancer of the urinary bladder in humans.

CYP2A6 or CYP3A4 catalyse *N*-oxidation of MOCA (Butler *et al.*, 1989; Yun *et al.*, 1992) to *N*-hydroxy-MOCA, which can bind to DNA or haemoglobin, or can be further activated to an *N*-sulfate ester by liver sulfotransferases (Chou *et al.*, 1995). Also prostaglandin H synthase (Wiese *et al.*, 2001) and myeloperoxidase (Culp *et al.*, 1997) may catalyse the binding of MOCA to DNA. In exfoliated urothelial cells from MOCA-exposed workers, the predominant DNA adduct was *N*-(deoxyadenosin-8-yl)-4-amino-3-chlorobenzyl alcohol (Kaderlik *et al.*, 1993). The same adduct was found in the liver, lung and kidney of rats exposed to MOCA (Silk *et al.*, 1989). In rat liver the adduct *N*-(deoxyadenosin-8-yl)-4-amino-3-chlorotoluene was also detected. MOCA-DNA adducts were found in the liver and bladder of exposed dogs. Metabolites in urine and blood and haemoglobin adducts have been detected in workers in the polyurethane elastomer industry (Vaughan & Kenyon, 1996). In contrast to the situation with benzidine, very low levels of *N*-acetylated metabolites were observed in urine. Because human liver can also catalyse the *N*-acetylation of MOCA, these low urinary levels may reflect an efficient de-acetylation pathway (Lakshmi *et al.*, 1995).

MOCA is a multiorgan carcinogen in experimental animals: it induces bladder tumours in dogs, liver tumours in rats and mice, and haemangiosarcomas, lung, and mammary gland tumours in rats. Particularly compelling data on the genotoxicity of MOCA include the higher micronucleus frequencies measured in exfoliated bladder epithelial cells and in peripheral lymphocytes of exposed workers (Murray & Edwards, 1999). MOCA and *N*-hydroxy-MOCA are mutagenic in *S. typhimurium* (Bridges *et al.*, 1981; Kuslikis *et al.*, 1991). In addition, MOCA induced mutations at the *HPRT* locus in human lymphoblastoid cells, it stimulated prophage induction in *E. coli*, and caused aneuploidy in *S. cerevisiae*, unscheduled DNA synthesis in cultured mouse hepatocytes, transformation in several mammalian cell cultures, and sister chromatid exchange in lymphocytes of rats treated *in vivo*, and in cultured Chinese hamster ovary cells.

5. Evaluation

There is *inadequate evidence* in humans for the carcinogenicity of 4,4′-methylenebis(2-chlorobenzenamine).

There is *sufficient evidence* in experimental animals for the carcinogenicity of 4,4′-methylenebis(2-chlorobenzenamine).

There is strong mechanistic evidence indicating that the carcinogenicity of 4,4′-methylenebis(2-chlorobenzenamine) involves a genotoxic mechanism of action that includes metabolic activation, formation of DNA adducts, and induction of mutagenic and clastogenic effects in humans. Metabolic activation to DNA-reactive intermediates occurs by multiple pathways including *N*-oxidation in the liver, *O*-acetylation in the bladder, and peroxidative activation in the mammary gland and other organs.

4,4′-Methylenebis(2-chlorobenzenamine) is *carcinogenic to humans (Group 1).*

In making the overall evaluation, the Working Group considered that:

The genotoxicity of 4,4′-methylenebis(2-chlorobenzenamine) is well documented and its toxicological profile is similar to that of *ortho*-toluidine, thus indicating a common mode of action. 4,4′-Methylenebis(2-chlorobenzenamine) has been shown to interact with DNA to form adducts in urothelial cells, and with haemoglobin to form adducts in the blood of workers exposed to this compound. It has also been shown to cause the formation of sister chromatid exchange and micronuclei in urothelial cells and lymphocytes of exposed workers.

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