HAZARD ASSESSMENT REPORT

3,3’-Dichloro-4,4’-diaminodiphenylmethane

CAS No. 101-14-4

Chemicals Evaluation and Research Institute (CERI), Japan

This report is prepared by CERI in collaboration with National Institute of Technology and Evaluation (NITE) under the sponsorship of New Energy and Industrial Technology Development Organization (NEDO).
Preface to the English Version of the Hazard Assessment Reports

For six years from April 2001 to March 2007, Chemicals Evaluation and Research Institute (CERI/Japan) was engaged in a project named “Chemical Risk Assessment and Development of Risk Assessment Methods” under "Comprehensive Chemical Substance Assessment and Management Program" funded by New Energy and Industrial Technology Development Organization (NEDO/Japan). Under this project, about 150 chemical substances were selected among those designated as Class-I Chemicals in the Law for Pollutant Release and Transfer Register and Promotion of Chemical Management (hereafter PRTR Law). The selection criteria of these chemicals were their priorities for risk assessment based on their production levels and environmental/human health concerns.

CERI developed the hazard assessment reports of these selected chemical substances based on the review and evaluation of the environmental and human health hazard data obtained from the existing evaluation documents released by the regulatory agencies and international organizations as well as those from the published scientific literatures. The data review and compilation of the reports were conducted according to the guidelines and the guidance manual developed for this project. The proposed hazard assessment reports by CERI were reviewed by the experts in the relevant scientific fields from both inside and outside this project for accuracy, relevance and completeness. The final reports were published in Japanese after going through the deliberation by the “Council on Chemical Substances” under the Ministry of Economy, Trade and Industry (METI/Japan), which is responsible for regulation of chemical substances in Japan.

This project was the first attempt in Japan to develop comprehensive hazard assessments of chemical substances for application in risk assessment. In order to share the outcomes of the project globally, CERI independently selected the following seven chemical substances and developed the English version of the hazard assessment reports:

1. Acetaldehyde
2. Chlorobenzene
3. Hydrazine
4. N,N-Dimethylformamide
5. Poly(oxyethylene)nonylphenylether
6. 3,3’-Dichloro-4,4’-diaminodiphenylmethane
7. Dimethyl-2,2-dichlorovinyl phosphate (Dichlorvos)

We hope that the hazard assessment reports from our project contribute to the risk assessment and management of chemical substances globally, and appreciate your feedback.

1) Details of the PRTR Law, the list of designated chemical substances, and release data in Japan are available on Internet at: http://www.prtr.nite.go.jp/index-e.html.

Also, the initial risk assessment reports in Japanese developed in this project which include calculations of margin of exposure based on the result of hazard assessment and exposure assessment, are available on Internet at: http://www.safe.nite.go.jp/risk/riskhykdl01.html.
Summary

3,3’-Dichloro-4,4’-diaminodiphenylmethane (MBOCA) is a colorless crystal or light brown pellet having a melting point of 110°C and a vapor pressure of 0.17 Pa at 60°C. It has water solubility of 13.9 mg/L at 24°C and is soluble in organic solvents including dichloromethane, acetonitrile and acetone. MBOCA is mainly used as a hardener of urethane resin for waterproof, flooring and all-weather pavement materials. Domestic production of MBOCA was 4,000 tons per year for 5 years from 1997 to 2001 in Japan.

Considering the uses of MBOCA and annual emission data for fiscal year 2001 in Japan (the 2001 PRTR data), the main release route is through the use of MBOCA or products containing MBOCA. As the scenario of MBOCA releases in Japan, it has been estimated that 201 kg was annually released into air and 30 kg into water.

MBOCA released into the aquatic environment is adsorbed to suspended solids in water and transferred to sludge. It is assumed that MBOCA is rarely volatilized from water into the air. However, in a specific condition of assimilation of activated sludge, MBOCA can be eliminated by biodegradation. Low bioaccumulation is suggested in aquatic organisms.

Many studies have been conducted to assess toxic effects of MBOCA on organisms in the environment using indices including mortality, immobilization and growth inhibition. In a growth inhibition study of MBOCA in freshwater alga, the 96-hr EC₅₀ was 1.82 mg/L in biomass for the alga. The NOEC for the alga was 0.313 mg/L in biomass and 2.5 mg/L in growth rate. The acute toxicity of MBOCA to invertebrates is reported in freshwater water flea. The 48-hr EC₅₀ (immobilization) was 0.25 mg/L. The long-term toxicity of MBOCA is reported in a reproductivity study of the water flea. The 21-day NOEC was 0.0375 mg/L with the endpoints of effects on reproduction and parent lethality. The acute toxicity of MBOCA to fish is reported in Japanese killifish. The 96-hr LC₅₀ is 0.657 mg/L. No reports on long-term toxicity of MBOCA to fish were obtained in this investigation.

The lowest value of toxicity in aquatic organisms is 0.0375 mg/L as the 21-day NOEC for reproduction and parent lethality in crustacean water flea.

In an oral administration study of MBOCA to rats, MBOCA is distributed in the liver, adipose tissue, kidney and small intestine at 48 hours after administration. MBOCA is metabolized by cytochrome P450 to form N-hydroxy-MBOCA in humans, rats and guinea pigs, but o-hydroxy-MBOCA in dogs. These metabolites are further metabolized into glucuronocojugates and sulfoconjugates and excreted in urine. Unchanged MBOCA was detected in the urine of humans and rats to lesser extent. Over 60% of given dose was excreted in feces, 20 to 40% in
urine by 48 hours after administration. MBOCA was also excreted in bile.

In human studies, two accidental cases have been reported. A person who was exposed to melted MBOCA in the face complained conjunctivitis, pain in the eyes and face and nausea and showed transient renal dysfunction. Another person who received melted MBOCA on the upper body, arms and legs had moderate inflammation in the arm but showed no methemoglobinemia, hematuria or proteinuria. In this case, DNA adduct of N-hydroxy-MBOCA was observed in the urothelial cells collected over time from the urine until 98 hours after exposure. In an epidemiological study for the workers who were engaged in MBOCA production, the possibility that MBOCA induced bladder tumors in humans was suggested, although there was no sufficient evidence.

In experimental animals, for the acute toxicity of MBOCA, the oral LD₅₀ values ranged from 640 to 880 mg/kg in mice, 750 to 2,100 mg/kg in rats and 400 mg/kg in guinea pigs. The percutaneous LD₅₀ was over 5,000 mg/kg in rabbits. As acute toxicity symptoms of MBOCA, ataxia and cyanosis were observed in rats and rabbits.

MBOCA exhibited very slight irritation to the skin of guinea pigs and slight irritation to the conjunctiva of rabbits. MBOCA exhibited no skin sensitization in guinea pigs.

The oral (gavage) repeated administration of MBOCA for ten days caused cyanosis, depression in body weight gain, methemoglobinemia, pallor, weakness and polyuria and death. Percutaneous administration of MBOCA to rabbits for 2 weeks resulted in cyanosis, pallor, slight cyanosis and hematuria in the first week. In the second week, a rabbit showed cyanosis only. However, no appropriate data to establish the NOAEL were obtained in this investigation.

No reports on reproductive and developmental toxicity of MBOCA were obtained in this investigation.

In genotoxicity studies, MBOCA showed positive responses in reverse mutation assays using bacteria, and in gene mutation, chromosomal aberration and DNA damage tests using mammalian cultured cells in in vitro studies. In addition, MBOCA showed positive responses in cell transformation assays using cultured cells. MBOCA induced somatic mutation, chromosomal aberration, increases in SCE of the peripheral lymphocytes and DNA adduct of N-hydroxy-MBOCA in the urothelial cells in experimental animals in in vivo studies. From the overall evaluation of these data, MBOCA is considered to be genotoxic.

In carcinogenicity studies, oral administration of MBOCA induced hepatocellular carcinoma in mice, lung tumor, mammary adenocarcinoma, Zymbal gland carcinoma, hepatocellular carcinoma and haemangiosarcoma in rats and bladder carcinoma in dogs. Therefore, MBOCA is considered to be carcinogenic in experimental animals. MBOCA has been categorized as Group 2A (the agent is possibly carcinogenic to humans) by the IARC.
## Contents

1. Identity of the substance
   1.1 Chemical name
   1.2 Class reference number in Chemical Substance Control Law
   1.3 PRTR number (Law for PRTR and Promotion of Chemical Management)
   1.4 CAS registry number
   1.5 Structural formula
   1.6 Molecular formula
   1.7 Molecular weight

2. General Information
   2.1 Synonyms
   2.2 Purity
   2.3 Impurities
   2.4 Additives/Stabilizers
   2.5 Current regulations in Japan

3. Physico-chemical properties

4. Sources of release to the environment
   4.1 Production and import
   4.2 Uses
   4.3 Releases
     4.3.1 Releases under PRTR system
     4.3.2 Releases from other PRTR
   4.4 Estimated routes of releases

5. Environment fate
   5.1 Stability in the atmosphere
   5.2 Stability in water
     5.2.1 Abiotic degradation
     5.2.2 Biodegradation
   5.2.3 Removal in sewage treatment
   5.3 Behavior in the aquatic environment
   5.4 Bioaccumulation
6. Effects on organisms in the environment ................................................................. 7
   6.1 Effects on aquatic organisms ............................................................................. 7
      6.1.1 Microorganisms ....................................................................................... 7
      6.1.2 Algae ........................................................................................................ 7
      6.1.3 Invertebrates ......................................................................................... 7
      6.1.4 Fish ......................................................................................................... 8
      6.1.5 Other aquatic organisms ......................................................................... 8
   6.2 Effects on terrestrial organisms ......................................................................... 8
      6.2.1 Microorganisms ....................................................................................... 8
      6.2.2 Plants ..................................................................................................... 9
      6.2.3 Animals .................................................................................................. 9
   6.3 Summary of effects on organisms in the environment ..................................... 9

7. Effects on human health ....................................................................................... 9
   7.1 Kinetics and metabolism .................................................................................. 9
   7.2 Epidemiological studies and case reports ....................................................... 12
   7.3 Studies in experimental animals and in vitro studies ...................................... 13
      7.3.1 Acute toxicity ......................................................................................... 13
      7.3.2 Irritation and corrosion ......................................................................... 13
      7.3.3 Sensitization ......................................................................................... 14
      7.3.4 Repeated dose toxicity ......................................................................... 14
      7.3.5 Reproductive and developmental toxicity ............................................. 14
      7.3.6 Genotoxicity ......................................................................................... 14
      7.3.7 Carcinogenicity ..................................................................................... 17
   7.4 Summary of effects on human health ............................................................... 21

References ................................................................................................................ 23
1. Identity of the substance

1.1 Chemical name
   : 3,3’-Dichloro-4,4’-diaminodiphenylmethane

1.2 Class reference number in Chemical Substance Control Law\(^1\)
   : 4-95, 4-96, 4-275

1.3 PRTR\(^2\) number (Law for PRTR and Promotion of Chemical Management)
   : 1-120

1.4 CAS registry number
   : 101-14-4

1.5 Structural formula
   ![Chemical Structure](image)

1.6 Molecular formula
   : C\(_{13}\)H\(_{12}\)Cl\(_2\)N\(_2\)

1.7 Molecular weight
   : 267.16

2. General Information

2.1 Synonyms
   4, 4’-Methylenebis (chloroaniline), Bis (4-amino-3-chlorophenyl) methane
   4, 4’-Methylenebis(o-chloroaniline), MBOCA

2.2 Purity
   >98\% (Commercial products) (CERI/Japan, 2002a)

2.3 Impurities
   o-chloroaniline (Commercial products) (CERI/Japan, 2002a)

2.4 Additives/Stabilizers
   No additives and stabilizers (Commercial products) (CERI/Japan, 2002a)

---

\(^1\) The Low Concerning the Evaluation of Chemical Substances and Regulation of Their Manufacture, etc., Japan. Provisional translation is available on Internet at: http://www.safe.nite.go.jp/english/kasinn/kaiseikasinhou.html

\(^2\) Pollutant Release and Transfer Register
2.5 **Current regulations in Japan**\(^3\)

- Law for PRTR and Promotion of Chemical Management: Class I designated chemical substance
- Law Concerning The Examination And Regulation Of Manufacture, Etc. Of Chemical Substances: Designated chemical substance (Type II monitoring chemical substance)
- Industrial Safety and Health Law: Specified chemical substance, Group-2 substance, Harmful substance whose name is to be indicated, Hazardous substance to be notified in terms of whose name, Administrative Control Level 0.005 mg/m\(^3\)

3. **Physico-chemical properties**

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appearance</td>
<td>Colourless crystals or light brown pellets</td>
</tr>
<tr>
<td>Melting point</td>
<td>110°C</td>
</tr>
<tr>
<td>Boiling point</td>
<td>Not applicable for crystal (The substance decomposes on heating above 200°C)</td>
</tr>
<tr>
<td>Flash point</td>
<td>No data</td>
</tr>
<tr>
<td>Ignition point</td>
<td>No data</td>
</tr>
<tr>
<td>Explosion limit</td>
<td>No data</td>
</tr>
<tr>
<td>Density</td>
<td>1.44 g/cm(^3)</td>
</tr>
<tr>
<td>Vapor density</td>
<td>9.21 (air = 1)</td>
</tr>
<tr>
<td>Vapor pressure</td>
<td>0.17 Pa (60°C)</td>
</tr>
<tr>
<td>Partition coefficient</td>
<td>[\log Kow (n-octanol/water) = 3.91 \text{ (measured)}, 3.47 \text{ (estimated)}]</td>
</tr>
<tr>
<td>Dissociation constant</td>
<td>No data</td>
</tr>
<tr>
<td>Mass spectrum</td>
<td>Main mass fragments: m/z 231 (base peak= 1.0), 266 (0.46), 140 (0.36)</td>
</tr>
<tr>
<td>Soil adsorption coefficient:</td>
<td>Koc = 1.4 \times 10^4 \text{ (estimated)}</td>
</tr>
<tr>
<td>Solubility</td>
<td>Water solubility: 13.9 mg/L (24°C) Soluble in dichloromethane, acetonitrile and acetone.</td>
</tr>
<tr>
<td>Henry's constant</td>
<td>(4.11 \times 10^{-6} \text{ Pa} \cdot \text{m}^3/\text{mol} (4.06 \times 10^{-11} \text{ atm} \cdot \text{m}^3/\text{mol})) (25°C, estimated)</td>
</tr>
</tbody>
</table>

\(^3\) As this document covers basic information on Japanese regulations (unofficial translations), you should confirm the details using it.
Conversion factor: 
(Air, 20°C) 1 ppm = 11.11 mg/m³, 
1 mg/m³ = 0.090 ppm

4. Sources of release to the environment

4.1 Production and import

The production and import of 3,3’-dichloro-4,4’-diaminodiphenylmethane (MBOCA) in fiscal year 2001 was 1,389 tons (METI/Japan, 2003). The production level stated here corresponds to the shipment level excluding self consumption at MBOCA manufacturing sites.

In another report, MBOCA production was 4,000 tons per year for 5 years from 1997 to 2001 in Japan (NITE/Japan, 2003).

4.2 Uses

All MBOCA is used as a hardening agent of urethane resin for waterproofing materials, flooring and all-weather type pavement materials (NITE/Japan, 2003).

4.3 Releases

4.3.1 Releases under PRTR system

According to “Total Release and Transfers for Fiscal Year 2001 (hereafter the 2001 PRTR Data)” under the PRTR system (METI/Japan and MOE/Japan, 2003a), 201 kg of MBOCA was released into the air, 30 kg into public water, 40 tons was transferred as waste from the business institutions required to report their releases and transfer in one year. No MBOCA was reported to have been released into the land and sewers. In addition, it is estimated that 8 tons of MBOCA was released from the business institutions in the business categories designated under the PRTR system but exempted from notification. No estimation was made for the amounts of releases from the business categories outside the scope of the PRTR system and those from households and those from mobile sources.

a. Release and transfer from the business categories within the scope of PRTR system

The amounts of releases into the environmental media (air, water and land) and transfer by the designated business categories summarized from the 2001 PRTR Data are shown in Table 4-1. METI/Japan and MOE/Japan (2003a) do not provide the amounts of releases by environmental media for the estimations of releases from the business institutions exempted from notification. The ratio for each environmental medium of the releases estimated for the business institutions exempted for notification is calculated based on the assumption that ratios of releases into the air, water and land were the same as those obtained by notification (NITE/Japan, 2004).
Table 4-1  Releases and transfer of 3,3’-dichloro-4,4’-diaminodiphenylmethane to environmental media by business categories (tons/year)

<table>
<thead>
<tr>
<th>Business Category</th>
<th>By Notification</th>
<th>Notification Exempted</th>
<th>Total amount of releases by notification and by estimation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Release</td>
<td>Transfer</td>
<td>(estimated)(^1)</td>
</tr>
<tr>
<td></td>
<td>Air  Water  Land</td>
<td>Sewer  Wastes  Air  Water  Land</td>
<td>Total release  Ratio (%)</td>
</tr>
<tr>
<td>Rubber products</td>
<td>&lt;0.5 0 0</td>
<td>0 12 3 1 0</td>
<td>4 48</td>
</tr>
<tr>
<td>Plastic products</td>
<td>0 0 0</td>
<td>0 &lt;0.5 1 0</td>
<td>1 10</td>
</tr>
<tr>
<td>Fabricated metal products</td>
<td>0 0 0</td>
<td>0 5 1 &lt;0.5 0</td>
<td>1 9</td>
</tr>
<tr>
<td>Other Industries</td>
<td>- - -</td>
<td>- - &lt;0.5 &lt;0.5 0</td>
<td>&lt;0.5 4</td>
</tr>
<tr>
<td>Chemical and allied products</td>
<td>&lt;0.5 &lt;0.5</td>
<td>0 23 - -</td>
<td>&lt;0.5 3</td>
</tr>
<tr>
<td>Ceramic, stone and clay products</td>
<td>- - -</td>
<td>- - &lt;0.5 &lt;0.5 0</td>
<td>&lt;0.5 2</td>
</tr>
<tr>
<td>General machinery</td>
<td>- - -</td>
<td>- - &lt;0.5 &lt;0.5 0</td>
<td>&lt;0.5 1</td>
</tr>
<tr>
<td>Others (^2)</td>
<td>- - -</td>
<td>- - 2 &lt;0.5 0</td>
<td>2 23</td>
</tr>
<tr>
<td>Total</td>
<td>&lt;0.5 &lt;0.5 0</td>
<td>40 7 1 0</td>
<td>8 100</td>
</tr>
</tbody>
</table>

(NITE/Japan, 2004)

1) Based on the assumption that ratios of releases into the air, water and land were the same as those of the releases obtained by notification, the amounts of releases from the business institutions exempted from notification were estimated.

2) "Others" indicates the total release in the business categories other than the above.

- : Not notified or estimated

The release and transfer of less than 0.5 tons was mentioned as “<0.5” without exception.

Based on the production volume and the emission factor in manufacturing sites of MBOCA in 2001 (Japan Chemical Industry Association, 2002), the releases of MBOCA is not considered to occur during the manufacturing process (NITE/Japan, 2004). Therefore, based on the 2001 PRTR Data, the releases of MBOCA from the business categories within the scope of PRTR system are considered not to occur during the manufacturing process but in use of products containing MBOCA.

b. Releases from the non-designated business categories, households and mobile sources

In the 2001 PRTR Data, the amounts of MBOCA releases from the non-designated business categories, households and mobile sources are outside the scope of estimation required under the PRTR system (METI/Japan and MOE/Japan, 2003b).

4.3.2 Releases from other PRTR

Reports on MBOCA release sources outside the scope of the 2001 PRTR Data were not obtained in this investigation.
4.4 Estimated routes of releases

Considering the information on the uses of MBOCA and the 2001 PRTR data, the main releases are considered to occur during the use of either MBOCA or products containing MBOCA.

As the scenario of MBOCA releases, it is estimated that 201 kg of MBOCA was released annually into air, and 30 kg into water in Japan. Releases into the environment after processing of wastes at waste disposal facilities are not considered for estimation of the amounts transferred as wastes and that transferred into sewers.

5. Environment fate

5.1 Stability in the atmosphere

Since the melting point of 3,3’-dichloro-4,4’-diaminodiphenylmethane (MBOCA) is 110°C (see the Chapter 3), it is assumed that MBOCA is released into air as dust. MBOCA has a low water solubility of 13.9 mg/L (24°C, see the Chapter 3) and a high soil adsorption coefficient (1.4×10⁴, see the Chapter 3). Therefore, MBOCA itself or adsorbed on the surface of air dust is considered to founder.

a. Reaction with OH radical

The reaction rate constant of MBOCA with OH radical is $7.8 \times 10^{-11}$ cm³/molecule-sec (25°C, estimated value) in the tropospheric air (SRC: AopWin, 2003). On the assumption of OH radical level of $5 \times 10^5$ to $1 \times 10^6$ molecule/cm³, the half-life was calculated to be 3 to 5 hours.

b. Reaction with ozone

No reports were obtained on reaction of MBOCA with ozone in this investigation.

c. Reaction with nitrate radical

No reports were obtained on reaction of MBOCA with nitrate radical in this investigation.

d. Direct degradation by sunlight

As MBOCA absorbs light at 290 nm and above, it is possible that MBOCA is degraded directly by sunlight in the air (U.S.NLM:HSDB, 2003).

5.2 Stability in water

5.2.1 Abiotic degradation

As MBOCA absorbs light at 290 nm and above, it is assumed that MBOCA is degraded by sunlight in the surface water (U.S.NLM:HSDB, 2003), but actual degradation rate is unknown. MBOCA has no chemical bonds that are subject to hydrolysis, which it is not hydrolyzed in the aquatic environment.
5.2.2 Biodegradation

MBOCA is ranked as a persistent substance, based on the result of the aerobic biodegradation study required under the Chemical Substance Control Law. The study result indicated that the degradation rate of MBOCA was 0% in biochemical oxygen demand (BOD) determination under the conditions of 100 mg/L of test substance concentration, 30 mg/L of activated sludge concentration and 4 weeks of test period (MITI/Japan, 1983).

However, MBOCA is biodegraded at low concentrations in some conditions. It has been reported that MBOCA was not degraded in a static 1-week incubation, but that under an incubation with activated sludge which was fed continuously for 1 week, MBOCA was degraded from an initial concentration of 2.02 mg/L to 0.09 mg/L (95%) within 24 hours (Tabak et al., 1981). These results suggest that microorganisms in activated sludge acquired metabolic capability to degrade MBOCA by acclimatization.

No reports on anaerobic biodegradation of MBOCA were obtained in this investigation.

5.2.3 Removal in sewage treatment

It has been reported that MBOCA was degraded to concentrations below the detection limit by ozone treatment within 5 minutes and removed, and that 90% of MBOCA was eliminated by activated carbon adsorption system with 21 to 35 mg/L of activated carbon (U.S. EPA, 1979).

5.3 Behavior in the aquatic environment

Since MBOCA has a high soil adsorption coefficient Koc of 14,000 (see the Chapter 3) and amino groups of MBOCA are considered to bind strongly to carboxyl groups of humic materials, it is assumed that MBOCA is easily adsorbed to suspended solids in water and sediments. On the other hand, MBOCA in water is hardly emitted into air by volatilization, because MBOCA has a low water solubility of 13.9 mg/L (24°C), a low vapor pressure of 0.17 Pa at 60°C and, as a result, low Henry's constant of $4.11 \times 10^{-6}$ Pa·m$^3$/mol at 25°C (see the Chapter 3).

Based on the information described above and in Section 5.2, it is assumed that MBOCA released into the aquatic environment is adsorbed to suspended solids in water and transferred to sludge. It is assumed MBOCA is rarely volatilized from water into air. However, in specific conditions including acclimatization of the microorganisms, MBOCA can be eliminated by biodegradation.

5.4 Bioaccumulation

MBOCA is ranked as no or low bioaccumulative substance, based on the result of an 8-week bioaccumulation study in carp required under the Chemical Substance Control Law, Japan. The study results indicated that the bioaccumulation factors of MBOCA were 130 to 398 and 114 to 232 at 50 and 5 μg/L of MBOCA concentration in water, respectively (MITI/Japan, 1983).
6. Effects on organisms in the environment

6.1 Effects on aquatic organisms

6.1.1 Microorganisms

No reports on toxicity of 3,3’-dichloro-4,4’-diaminodiphenylmethane (MBOCA) for microorganisms were obtained in this investigation.

6.1.2 Algae

The toxicity studies of MBOCA to algae are summarized in Table 6-1.

According to the OECD test guideline, the 96-hr EC₅₀ and NOEC of MBOCA for growth inhibition in freshwater green alga in biomass estimated from the area under the growth curve were 1.82 and 0.313 mg/L, respectively, and over 5.00 mg/L and 2.50 mg/L in growth rate (MITI/Japan, 1991).

No reports on toxicity of MBOCA to marine species were obtained in this investigation.

| Table 6-1 Toxicity of 3,3’-dichloro-4,4’-diaminodiphenylmethane for algae |
|-----------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Species                      | Method/Condition | Temperature (°C) | Endpoint          | Concentration (mg/L) | Reference |
| Selenastrum capricornutum¹  | OECD            | 23±2            | 96-hr EC₅₀        | 1.82              | MITI/Japan, 1991 |
|                             | Static          |                 | Growth inhibition | 1.49              |                |
|                             | Solvent²        |                 | biomass (area)³   | >5.00             |                |
|                             |                 |                 | (cell number)⁴   | 0.313             |                |
|                             |                 |                 | Growth rate       | 1.25              |                |
|                             |                 |                 | biomass (area)⁵   | 2.50              |                |
|                             |                 |                 | (cell number)     | (n)               |                |
|                             |                 |                 | Growth rate       |                   |                |

(n): Nominal concentration
1) Current scientific name: Pseudokirchneriella subcapitata, 2) Dimethyl sulfoxide, 20-fold concentration of MBOCA nominal concentration, 3) Estimated from the area under growth, 4) Estimated from the present volume (cell number)

6.1.3 Invertebrates

The toxicity studies of MBOCA to invertebrates are summarized in Table 6-2.

The 48-hr EC₅₀ for immobilization in freshwater crustacea water flea Daphnia magna was 0.250 mg/L (MITI/Japan, 1991).

As the long-term toxicity of MBOCA, the 21-day NOEC in Daphnia magna was 0.0375 mg/L with the endpoints of effect on reproduction and parent lethality (MITI/Japan, 1993).

No reports on toxicity of MBOCA to marine species were obtained in this investigation.
Table 6-2  Toxicity of 3,3’-dichloro-4,4’-diaminodiphenylmethane to invertebrates

<table>
<thead>
<tr>
<th>Species</th>
<th>Growth Stage</th>
<th>Method/Condition</th>
<th>Temperature (°C)</th>
<th>Hardness (mg CaCO₃/L)</th>
<th>pH</th>
<th>Endpoint</th>
<th>Concentration (mg/L)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Freshwater species</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Daphnia magna</em> (crustacea)</td>
<td>&lt;24 hours</td>
<td>OECD 202 Static Solvent 1</td>
<td>20±1</td>
<td>108</td>
<td>7.00-7.40</td>
<td>24-hr EC₅₀</td>
<td>0.736 (a, n)</td>
<td>MITI/Japan, 1991</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>48-hr EC₅₀</td>
<td>0.250 (a, n)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Immobilization</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Daphnia magna</em> (crustacea)</td>
<td>&lt;24 hours</td>
<td>OECD 202 Semi-static Solvent 1</td>
<td>20±1</td>
<td>110</td>
<td>7.96-8.01</td>
<td>21-day LOEC</td>
<td>0.0750 (a, n)</td>
<td>MITI/Japan, 1993</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>21-day NOEC</td>
<td>0.0375 (a, n)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Reproduction, parent lethality</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(a, n): The measured concentrations of test substance were within ±20% of the nominal concentrations, and thus, the nominal concentrations are shown in this table.
1) Dimethyl sulfoxide was used as solvent at 20-fold concentration of MBOCA’s nominal concentration.

6.1.4 Fish

The toxicity studies of MBOCA to fish are summarized in Table 6-3.

The 96-hr LC₅₀ of MBOCA in Japanese killifish according to the OECD test guideline was 0.657 mg/L (MITI/Japan, 1991).

No reports on long-term toxicity to freshwater species and on toxicity to marine species were obtained in this investigation.

Table 6-3  Toxicity of 3,3’-Dichloro-4,4’-diaminodiphenylmethane for fish

<table>
<thead>
<tr>
<th>Species</th>
<th>Growth Stage</th>
<th>Method/Condition</th>
<th>Temperature (°C)</th>
<th>Hardness (mg CaCO₃/L)</th>
<th>pH</th>
<th>Hardness</th>
<th>Concentration (mg/L)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Freshwater species</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Oryzias latipes</em> (Japanese killifish)</td>
<td>2±1 cm</td>
<td>OECD 203 Flow-through Solvent 1</td>
<td>24±1</td>
<td>108</td>
<td>8.06-8.11</td>
<td>48-hr LC₅₀</td>
<td>1.24 (a, n)</td>
<td>MITI/Japan, 1991</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>96-hr LC₅₀</td>
<td></td>
</tr>
</tbody>
</table>

(a, n): The measured concentrations of test substance were within ±20% of the nominal concentrations, and thus, the nominal concentrations are shown in this table.
1) Dimethyl sulfoxide was used as solvent at 50-fold concentration of MBOCA’s nominal concentration.

6.1.5 Other aquatic organisms

No reports on toxicity of MBOCA to other aquatic organisms (e.g., amphibians) were obtained in this investigation.

6.2 Effects on terrestrial organisms

6.2.1 Microorganisms

No reports on toxicity of MBOCA to terrestrial microorganisms (soil bacteria and fungi, etc.) were
obtained in this investigation.

6.2.2 Plants

No reports on toxicity of MBOCA to plants were obtained in this investigation.

6.2.3 Animals

No reports on toxicity of MBOCA to animals were obtained in this investigation.

6.3 Summary of effects on organisms in the environment

On the acute toxicity of MBOCA to algae, the 96-hr EC$_{50}$ for growth inhibition was 1.82 mg/L (biomass) in freshwater green alga. The 96-hr NOECs were 0.313 mg/L (biomass) and 2.5 mg/L (growth rate).

The acute toxicity of MBOCA to invertebrates was reported in freshwater crustacean water flea and the 48-hr EC$_{50}$ (immobilization) was 0.25 mg/L. As the long-term toxicity of MBOCA, the 21-day NOEC for reproduction and parent lethality was reported to be 0.0375 mg/L in the water flea.

The acute toxicity of MBOCA to fish has been reported in Japanese killifish and the 96-hr LC$_{50}$ was 0.657 mg/L. No reports on long-term toxicity of MBOCA to fish were obtained in this investigation.

No reports on toxicity of MBOCA to terrestrial organisms were obtained in this investigation.

Based on the data summarized above, the lowest value of acute toxicity in aquatic organisms is the 48-hr EC$_{50}$ (immobilization) of 0.25 mg/L in freshwater crustacean water flea. Although formal classification criteria is not used in this investigation, it can be considered that the acute toxicity values of MBOCA to aquatic organisms is corresponding to the GHS acute toxicity hazard category I (very toxic). The long-term NOECs in algae and crustacea are 0.313 and 0.0375 mg/L, respectively.

The lowest value of toxicity in aquatic organisms is 0.0375 mg/L as the 21-day NOEC for reproduction and parent lethality in crustacea water flea.

7. Effects on human health

7.1 Kinetics and metabolism

Metabolic pathway of 3,3’-dichloro-4,4’-diaminodiphenylmethane (MBOCA) is shown in Figure 7-1.

a. Absorption/Distribution

Following an intraperitoneal administration of $^{14}$C-MBOCA in rats at a single dose of 0.49 mg/kg, radioactivity was detected in the small intestine, liver, adipose tissue, kidney, skin and adrenal gland at high levels within 1 hour after administration. The radioactivity was transiently detected in the small intestine, adipose tissue and skin (Tobes et al., 1983).

In female LAC:Porton rats, [${^{14}}$C-CH$_3$]-MBOCA was intraperitoneally injected at doses of 1, 13 and
100 mg/kg and a oral dose of 10 mg/kg, the radioactivity 48 hours after administration was the highest in the liver, followed by the adipose tissue, kidney and small intestine (Farmer et al., 1981).

In male Beagle dogs, $^{14}$C-MBOCA was applied to the shaved skin (25cm$^2$) at a dose of 10 mg (in 0.5 mL acetone solvent). Radioactivity was not detected in the blood 24 hours after administration, but of radioactivity administered, 90% was recovered from the applied site. Radioactivity was detected in the liver, kidney and adipose tissue at high levels. After intravenous injection, radioactivity was eliminated from the blood rapidly (half-life: 0.70 hour), while radioactivity was detected in the liver, kidney, adipose tissue and lung at high levels (Manis et al., 1984).

b. Metabolism

In an in vitro metabolism study of methylene or amino-labeled $^{14}$C-MBOCA with human liver microsomes, MBOCA is oxidatively metabolized into $N$-hydroxy-MBOCA, $o$-hydroxy-MBOCA and methylene-hydroxy-MBOCA. In metabolism of MBOCA with human, rat, guinea pig and dog liver microsomes, the major metabolite was $N$-hydroxy-MBOCA in humans, rats and guinea pigs, but $o$-hydroxy-MBOCA in dogs (Morton et al., 1988). It has been confirmed that MBOCA is metabolized mainly by cytochrome P450 3A4 in humans and P450 2B 1 and 2B2 in rats (Butler et al., 1989; Yun et al., 1992).

From analogy of metabolism of other aromatic amines, the major pathways were considered to be oxidation and acetylation at N-site, oxidation at C-site and glucuronate and sulfate conjugation. In dogs, no acetylation at N-site was found but sulfate conjugation was found at O-site of 5-OH (Manis and Braselton, 1984).

In a 4-day oral administration (gavage) study of $^{14}$C-MBOCA in male SD rats at a dose of 50 mg/kg/day, unchanged MBOCA that was recovered from the urine in 36 hours after the completion of administration was 0.2% or less and, glucuronocojugate and sulfoconjugate were detected as metabolites. The major metabolite in the bile was mono-$N$-glucuronocojugate (Morton et al., 1988).

The major metabolite in the urine of dogs was sulfate conjugates of $o$-hydroxy-MBOCA and similar metabolites were detected in the liver and kidney (Manis and Braselton, 1986).

The major metabolite in the urine of humans was $N$-glucuronocojugate (2 to 3 times of unchanged MBOCA), and $N$-acetyl-MBOCA was 1% to 9% of unchanged MBOCA. No thioether was detected in the urine (Cocker et al., 1990; Edwards and Priestly, 1992).

In an oral administration study of methylene-labeled $^{14}$C-MBOCA in male SD rats at a single dose of 75 mg/kg, DNA adduct formation was the highest in the liver, followed by the bladder and lymphocyte in order. After repeated oral administration for 28 days at 7.5 mg/kg, covalent bonding with globin was linearly increased with the administration period and the tissue concentration was the highest in the liver, followed by the kidney and lung in order (Cheever et al., 1988, 1990).

c. Excretion

In human case, a person was exposed to melted MBOCA in the face. The urine MBOCA concentration was 3,600 μg/L at 5 hours after exposure. The concentration was reduced to 30 to 60 μg/L
24 hours after exposure (Hosein and Van Roosmalen, 1978).

In female LAC:Porton rats, [\(^{14}\)C-CH\(_2\)]-MBOCA was intraperitonealy administered at doses of 1, 13 and 100 mg/kg and a oral dose of 10 mg/kg. In 48 hours after administration, 60% to 69% of radioactivity administered was excreted in the feces. In the urine, 23% to 41% of radioactivity was excreted and the percentage of unchanged MBOCA was 1% to 2% and at least 9 metabolites were identified (Farmer et al., 1981).

In an intravenous administration study of \(^{14}\)C-MBOCA in female SD rats at a single dose of 0.49 mg/kg, 21% and 73.4% of given dose were excreted in the urine and feces in 48 hours after administration, respectively (Tobes et al., 1983).

In male Beagle dogs, \(^{14}\)C-MBOCA was applied to the shaved skin (25cm\(^2\)) at a dose of 10 mg (in 0.5 mL acetone solvent). 1.3% (unchanged MBOCA: 0.4%) and 0.62% (all metabolites) of radioactivity administered were excreted in the urine and bile respectively in 24 hours after administration. After intravenous injection, 46% (unchanged MBOCA: 0.54%) and 32% of radioactivity administered were excreted in the urine and bile, respectively, by 24 hours after administration (Manis et al., 1984).

In summary, radiolabeled MBOCA administered orally in rats was rapidly absorbed and the radioactivity was distributed in the liver, adipose tissue, kidney and small intestine 48 hours after administration. MBOCA is metabolized into \(N\)-hydroxy-MBOCA, \(o\)-hydroxy-MBOCA and methylene-hydroxy-MBOCA. The major metabolite was \(N\)-hydroxy-MBOCA in humans, rats and guinea pigs, but \(o\)-hydroxy-MBOCA in dogs. MBOCA is further metabolized into glucuronococonjugates and sulfoconjugates, and excreted in the urine or feces. Glucuronococonjugates and sulfoconjugates were excreted in the urine of rats. The main metabolite in the urine of dogs was sulfoconjugate of \(o\)-hydroxy-MBOCA. The main metabolite in the urine of humans was \(N\)-glucuronococonjugate. The main metabolite in the bile of rats was mono-\(N\)-glucuronococonjugate. In rats, over 60% of administered dose was excreted in the feces, and 20% to 40% in the urine by 48 hours after administration.
7.2 Epidemiological studies and case reports

a. Acute effects

It was reported that a person who was exposed to melted MBOCA in the face complained of conjunctivitis, pain in the eyes and face, nausea and showed transient renal dysfunction (an increase in urine protein within 11 hours after exposure) (Hosein and Van Roosmalen, 1978).

A worker (male aged 30 years) who was sprayed with a significant volume of melted MBOCA to the upper body, arms and legs had moderate inflammation in the arm, but no abnormal values were found in renal and hepatic function tests. No methemoglobinemia, hematuria nor proteinuria was observed (Osorio et al., 1990).

In the peripheral lymphocytes of laboratory workers and manufacturing operators in a polyurethane plant using MBOCA as hardener, the incidence of sister chromatid exchange (SCE) was significantly increased. The urine MBOCA concentration of manufacturing operators at the end of work was 38 μmol/mol creatinine (Edwards and Priestly, 1992).

In the urothelial cells collected with time from the urine of a worker (male aged 30 years) who was sprayed with a significant volume of melted MBOCA to the upper body, arms and legs, DNA adduct of N-hydroxy-MBOCA was detected until 98 hours after exposure (Kaderlik et al., 1993).

b. Chronic effects

No reports on chronic effects of MBOCA in humans were obtained in this investigation.

c. Carcinogenicity
In a carcinogenicity study of MBOCA in 31 male workers of a MBOCA production plant from 6 months to 16 years (1971), bladder carcinoma were not observed with urinary cytology survey (Linch et al., 1971).

Of the workers at a MBOCA production plant in the U.K., 13 persons developed bladder cancers, but the exposure status was unknown (Cartwright, 1983).

In 552 workers who were engaged in MBOCA production from 1968 to 1981 (interview: 452; cytology: 385), 3 workers (aged 28, 29 and 44 years) who were exposed to high concentrations of MBOCA developed bladder cancers. The urinary cytology survey could not be conducted in the control group, and, therefore, the expected values were not estimated. However, considering the co-exposure of other chemicals and the onset of cancer (the incidence of bladder cancer was extremely rare in the young), it was suggested that observed incidences of bladder cancer were due to MBOCA (Ward et al., 1988, 1990).

7.3 Studies in experimental animals and in vitro studies

7.3.1 Acute toxicity

Acute toxicity studies of MBOCA to experimental animals are summarized in Table 7-1 (E.I. DuPont, 1963, 1964, 1965; Salamone, 1981; U.S. NIOSH, 2002).

The oral LD₅₀ values ranged from 640 to 880 mg/kg in mice, 750 to 2,100 mg/kg in rats and 400 mg/kg in guinea pigs. The percutaneous LD₅₀ was over 5,000 mg/kg in rabbits and the intraperitoneal LD₅₀ was 64 mg/kg in mice.

With oral administration of MBOCA in mice, rats and rabbits, ataxia and cyanosis were observed (U.S. NIOSH, 2002).

In an intraperitoneal study of MBOCA (purity: 90%) in male rats at single doses of 0.4 to 100 mg/kg, epoxide hydratase, ethoxyresorufin o-deethylase, ethoxycoumarin o-deethylase, and glutathione S-transferase activities were increased (Wu et al., 1989).

In an intraperitoneal study of MBOCA in male SD rats at a single dose of 75 mg/kg, ornithine decarboxylase was significantly induced, which continued until 42 hours after administration (Savage et al., 1992).

7.3.2 Irritation and corrosion

In a skin irritation study of MBOCA in guinea pigs, slight irritation was observed. In an eye irritation study in rabbits, mild irritation to the conjunctiva was shown (E.I. DuPont, 1963).
7.3.3 Sensitization
In guinea pigs, no dermal sensitization of MBOCA was observed (E.I. DuPont, 1963).

7.3.4 Repeated dose toxicity
Studies on repeated dose toxicity of MBOCA to experimental animals are summarized in Table 7-2.

In an oral administration (gavage) study, rats were given MBOCA at doses of 0, 200 and 1,000 mg/kg/day for 10 days. Mild cyanosis, suppression in body weight gain and methemoglobinemia were found at 200 mg/kg/day. At 1,000 mg/kg/day, cyanosis, pallor, weakness and polyuria and dead animals were found (Linch et al., 1971).

In a 2-week percutaneous administration study of MBOCA in 4 rabbits at a dose of 2,250 mg/kg/day, pallor, mild cyanosis (2/4) and hematuria (3/4) were observed in the first week. In the second week, only one rabbit showed cyanosis (E.I. DuPont, 1964).

Table 7-2  Repeated dose toxicity of 3,3’-dichloro-4,4’-diaminodiphenylmethane

<table>
<thead>
<tr>
<th>Species</th>
<th>Route</th>
<th>Period</th>
<th>Dose</th>
<th>Results</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rat (species, sex and age unknown) 6 animals/group</td>
<td>Oral gavage</td>
<td>Continuous 10 days</td>
<td>0, 200, 1,000 mg/kg/day</td>
<td>200 mg/kg/day mild cyanosis, suppression in body weight gain, methemoglobinemia 1,000 mg/kg/day cyanosis, pallor, weakness, polyuria, death</td>
<td>Linch et al., 1971</td>
</tr>
<tr>
<td>Rabbit (strain, sex and age not specified) 4 animals</td>
<td>Percutaneous</td>
<td>2 weeks</td>
<td>0, 2,250 mg/kg/day</td>
<td>1st week pallor, mild cyanosis (2/4), hematuria (3/4) 2nd week cyanosis (1/4)</td>
<td>E.I. du Pont, 1964</td>
</tr>
</tbody>
</table>

7.3.5 Reproductive and developmental toxicity
No reports on reproductive and developmental toxicity of MBOCA to experimental animals were obtained in this investigation.

7.3.6 Genotoxicity
Studies on genotoxicity of MBOCA are summarized in Table 7-3 and the summary of these data is shown in Table 7-4.

a. In vitro studies:
MBOCA showed positive responses in a mutation study with Salmonella typhimurium (TA100 and TA98) without metabolic activation. N-hydroxy-MBOCA, a metabolite of MBOCA, showed positive
responses in TA98 and TA100 strains without metabolic activation, while o-hydroxy-MBOCA, mononitroso-MBOCA (4-amino-2,2'-dichloro-4'-nitrosodiphenyl-methane) and dinitroso-MBOCA (o-hydroxy-di(3-chloro-4-nitrosophenyl)methane) showed no positive responses in any strains (Kuslikis et al, 1991).

MBOCA showed positive responses in reverse mutation for *Escherichia coli* with metabolic activation (Matsushima et al., 1981). No positive reverse mutation was observed in yeast (Mehta and von Borstel, 1981). MBOCA showed positive responses in mutation for mouse lymphoma cells L5178Y (tk locus) (Mitchell et al., 1988; Myhr and Caspary, 1988).

MBOCA induced an increase of aneuploidy in yeast (Parry and Sharp, 1981), but did not induce chromosomal aberration in Chinese hamster ovary (CHO) cells (Galloway et al., 1985; Perry and Thompson, 1981) and human cultured leukocytes (Ho et al., 1979).

MBOCA induced λ prophage in *Escherichia coli* carrying the prophage (Thomson, 1981) and showed positive responses in a rec-assay of *Bacillus subtilis* (Kada, 1981). MBOCA increased unscheduled DNA synthesis (UDS) in mouse, rat and hamster primary-cultured hepatocytes (McQueen et al., 1981; Mori et al., 1988; Williams et al., 1982).

MBOCA induced an increase in sister chromatid exchange (SCE) in CHO cells (Galloway at al., 1985; Perry and Thomson, 1981) but not in human cultured lymphocytes (Ho et al., 1979).

MBOCA induced cell transformation in cultured mammalian cells of Syrian hamster kidney BHK cells (Daniel and Dehnel, 1981; Styles, 1981), rat fetal RLV cells (Dunkel et al., 1981), and mouse BALB/c 3T3 cells (Dunkel et al., 1981).

b. *In vivo* studies:

In a somatic mutation study (wing spot test) (Kugler-Steigmeier et al., 1989) and a sex-linked recessive lethal test for *Drosophila melanogaster*, MBOCA showed positive responses (Donner et al., 1983).

In a micronucleus test, MBOCA was administered intraperitoneally in mice twice at 32 mg/kg. The frequency of micronucleus in the bone marrow cells was increased (Salamone, 1981).

In an SCE test, MBOCA was administered intraperitoneally in rats 6 times at 125 mg/kg. The frequency of SCE in the lymphocytes was increased (Edwards and Priestly, 1992).

In a protein adduct formation study, MBOCA was administered intraperitoneally in male SD rats at doses of 0.5 to 50 mg/kg and administered subcutaneously in guinea pigs at doses of 4 to 400 mg/kg. In both cases, the amounts of hemoglobin adduct formation were increased dose-dependently (Chen et al., 1991).

In a DNA adduct formation study, [14C-CH2]-MBOCA was orally administered in rats at a single dose of 25.4 mg/kg. DNA adducts were detected in the liver, lung and kidney after 24 hours of administration (Segerback and Kadlubar, 1992).

Based on the data summarized above, in *in vitro* studies, MBOCA showed positive responses in reverse mutation assays using bacteria, and mutation, chromosomal aberration and DNA damage tests.
using cultured cells. Also, chromosomal aberration and SCE tests using human cultured cells exhibited negative responses. MBOCA showed positive responses in a cell transformation assay using cultured cells. In *in vivo* studies, MBOCA induced chromosomal aberration, DNA damage and increases in SCE of the peripheral lymphocytes and DNA adduct of \(N\)-hydroxy-MBOCA in the urothelial cells in experimental animals. From the overall evaluation of these data, MBOCA is considered to be genotoxic.

### Table 7-3 Genotoxicity of 3,3′-dichloro-4,4′-diaminodiphenylmethane

<table>
<thead>
<tr>
<th>Test system</th>
<th>Species (Organisms) /Strain</th>
<th>Experimental condition</th>
<th>Conc/Dose</th>
<th>Result</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>in vitro</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reverse mutation</td>
<td>Salmonella typhimurium TA98, TA100</td>
<td>ND</td>
<td>ND</td>
<td>+</td>
<td>ND Kuslikis et al., 1991</td>
</tr>
<tr>
<td></td>
<td><em>Escherichia coli</em> (WP2 uvr)</td>
<td>ND</td>
<td>ND</td>
<td>-</td>
<td>+ Matsushima et al., 1981</td>
</tr>
<tr>
<td></td>
<td>Saccharomyces cerevisiae</td>
<td>ND</td>
<td>ND</td>
<td>-</td>
<td>ND Mehta &amp; von Borstel, 1981</td>
</tr>
<tr>
<td></td>
<td>Mouse lymphoma L5178Y cells</td>
<td>ND</td>
<td>ND</td>
<td>+</td>
<td>ND Mitchell et al., 1988; Myhr &amp; Caspary, 1988</td>
</tr>
<tr>
<td></td>
<td><em>(tk locus)</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chromosomal aberration</td>
<td>Saccharomyces cerevisiae</td>
<td>ND</td>
<td>ND</td>
<td>+</td>
<td>ND aneuploidy Parry &amp; Sharp, 1981</td>
</tr>
<tr>
<td></td>
<td>CHO cells (^1)</td>
<td>ND</td>
<td>ND</td>
<td>-</td>
<td>ND Galloway et al., 1985; Perry &amp; Thompson, 1981</td>
</tr>
<tr>
<td></td>
<td>Human leukocytes</td>
<td>ND</td>
<td>ND</td>
<td>-</td>
<td>ND Ho et al., 1979</td>
</tr>
<tr>
<td>DNA damage</td>
<td><em>E. coli</em> prophage (\lambda)</td>
<td>ND</td>
<td>1-20 mg/mL</td>
<td>+</td>
<td>ND prophage induction Thomson, 1981</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>rec-assay</td>
<td><em>B. subtilis</em></td>
<td>ND</td>
<td>0-1,000 µg/plate</td>
<td>+</td>
<td>- Kada, 1981</td>
</tr>
<tr>
<td>Unscheduled DNA synthesis (UDS)</td>
<td>Primary-cultured hepatocytes Mouse, rat, hamster</td>
<td>ND</td>
<td>ND</td>
<td>+</td>
<td>ND McQueen et al., 1981; Mori et al., 1988; Williams et al., 1982</td>
</tr>
<tr>
<td>Sister chromatid exchange (SCE)</td>
<td>CHO cells (^1)</td>
<td>ND</td>
<td>ND</td>
<td>+</td>
<td>ND Galloway et al., 1985; Perry &amp; Thomson, 1981</td>
</tr>
<tr>
<td>Sister chromatid exchange (SCE)</td>
<td>Human leukocytes</td>
<td>ND</td>
<td>ND</td>
<td>-</td>
<td>ND Ho et al., 1979</td>
</tr>
<tr>
<td></td>
<td>Fischer rat embryo RLV cells</td>
<td>ND</td>
<td>ND</td>
<td>+</td>
<td>Dunkel et al., 1981</td>
</tr>
<tr>
<td></td>
<td>mouse BALB/c 3T3 cells</td>
<td>ND</td>
<td>ND</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td><strong>in vivo</strong></td>
<td><em>Drosophila melanogaster</em></td>
<td>ND</td>
<td>ND</td>
<td>+</td>
<td>Kugler-Steigmeier et al., 1989</td>
</tr>
<tr>
<td>Somatic mutation (wing spot test)</td>
<td><em>Drosophila melanogaster</em></td>
<td>ND</td>
<td>ND</td>
<td>+</td>
<td>Donner et al., 1983</td>
</tr>
<tr>
<td>Sex-linked recessive lethal (SLRL-test)</td>
<td>Mouse bone marrow cells</td>
<td>Intraperitoneal injection twice 32 mg/kg</td>
<td>+</td>
<td>Salamone, 1981</td>
<td></td>
</tr>
<tr>
<td>Test system</td>
<td>Species (Organisms) /Strain</td>
<td>Experimental condition</td>
<td>Conc/Dose</td>
<td>Result -S9 +S9</td>
<td>Reference</td>
</tr>
<tr>
<td>-------------</td>
<td>-----------------------------</td>
<td>------------------------</td>
<td>-----------</td>
<td>----------------</td>
<td>-----------</td>
</tr>
<tr>
<td>SCE</td>
<td>Rat lymphocytes</td>
<td>Intraperitoneal injection</td>
<td>125 mg/kg</td>
<td>+</td>
<td>Edwards &amp; Priestly, 1992</td>
</tr>
<tr>
<td>DNA adduct formation</td>
<td>SD male rat hemoglobin</td>
<td>Intraperitoneal injection</td>
<td>0.5-50 mg/kg</td>
<td>+</td>
<td>Chen et al., 1991</td>
</tr>
<tr>
<td></td>
<td>guinea pig hemoglobin</td>
<td>subcutaneous injection</td>
<td>4-400 mg/kg</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>DNA adduct formation</td>
<td>Rat liver, kidney, lung</td>
<td>Oral single</td>
<td>25.4 mg/kg</td>
<td>+</td>
<td>Segerback &amp; Kladlubar, 1992</td>
</tr>
</tbody>
</table>

ND: No data available, - : Negative, +: Positive
1) CHO cells: Chinese hamster ovary cells.

Table 7-4  Genotoxicity of 3,3'-dichloro-4,4'-diaminodiphenylmethane (Summary)

<table>
<thead>
<tr>
<th></th>
<th>Mutation</th>
<th>Chromosomal aberration</th>
<th>DNA damage</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>bacteria</td>
<td>+</td>
<td>ND</td>
<td>-</td>
<td>ND</td>
</tr>
<tr>
<td>mold / yeast / plant</td>
<td>-</td>
<td>+</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>insects</td>
<td>+</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>culture cells</td>
<td>+</td>
<td>–, +</td>
<td>+</td>
<td>+ cell transformation</td>
</tr>
<tr>
<td>manmals (in vivo)</td>
<td>ND</td>
<td>+</td>
<td>+</td>
<td>ND</td>
</tr>
<tr>
<td>human</td>
<td>ND</td>
<td>–</td>
<td>–</td>
<td>ND</td>
</tr>
</tbody>
</table>

+: positive, –: negative, ND: No data available

7.3.7 Carcinogenicity

Studies on carcinogenicity of MBOCA are summarized in Table 7-5.

In an 18-month carcinogenicity study of MBOCA hydrochloride, male and female ICR mice were fed diets containing 0, 1,000 and 2,000 ppm of MBOCA hydrochloride. A significant increase in the incidence of hepatomas was found in females (control: 0/20, 0.1%: 9/21, 0.2%: 7/14) (Russfield et al., 1975).

In a 71-week carcinogenicity study of MBOCA, male and female Wistar rats were fed a protein-deficient diet (details unknown) containing 0 and 1,000 ppm (total dose: 27 g/kg) of MBOCA. Significant increases in the incidences of hepatomas and lung tumor (mainly carcinoma) were found in males and females. Although no statistical significance was observed, pleural mesothelioma, hepatocellular adenoma and carcinoma
were also found. In a low-protein (protein content: 7%) fed groups of the same study, significant differences in the incidences of hepatocellular adenoma and carcinoma were found in males (Stula et al., 1975).

In an 18-month carcinogenicity study of MBOCA (industrial chemical grade), male SD rats were fed standard protein diets (protein content: 27%) containing 0, 250, 500 and 1,000 ppm of MBOCA. Significant increases were found in the incidences of lung tumours, mammary adenocarcinomas, Zymbal gland carcinomas and hepatocellular carcinomas. In the groups which were fed protein deficient diets (protein content: 7%) containing 0, 125, 250 and 500 ppm of MBOCA in the same study, the incidences of these tumors and haemangiosarcoma were also increased (Kommineni et al., 1979).

In a carcinogenicity study of MBOCA (purity: 90% and less), female Beagle dogs were orally (gavage) administered MBOCA at 0, 100 mg/animal/day for 6 weeks (3 days/week) and thereafter for 9 years (5 days/week). Transitional-cell carcinomas of the urinary bladder were found in 4 of 5 animals, and one of them developed also urethral transitional-cell carcinomas and adenocarcinomas (Stula et al., 1977).

In an 88-week carcinogenicity study, MBOCA was subcutaneously injected as a suspension in physiological saline to male and female Wistar rats at doses of 0, 500, 1,000 mg/kg once a week (total dose: 25 g/kg bw). The incidences of hepatocellular carcinoma and lung adenocarcinoma were significantly increased (Steinhoff and Grundmann, 1971). This report, however, is a brief communication and the details are unknown.

In a tumor initiating study of MBOCA, SENCAR mice were dermally applied with MBOCA of 0, 0.1, 1, 10, 100, 200 mg/animal once and then 0.002 mg of 12-o-tetradecanoyl-phorbol-13-acetate (TPA) was applied to the skin twice a week for 26 weeks. No incidence of skin papilloma was observed (Nesnow et al., 1985).

Based on the data summarized above, oral administration of MBOCA developed hepatocellular carcinoma in mice, lung, liver, mammary and Zymbal gland carcinoma and angiosarcoma in rats and bladder carcinoma in dogs. Therefore, MBOCA is considered to be carcinogenic in experimental animals.

The evaluation of carcinogenicity of MBOCA by the international and national organizations is shown in Table 7-6. The IARC has categorized MBOCA as Group 2A (the agent is possibly carcinogenic to humans). The ACGIH has categorized MBOCA as A2 (suspected human carcinogen).

### Table 7-5  Carcinogenicity of 3,3’-dichloro-4,4’-diaminodiphenylmethane

<table>
<thead>
<tr>
<th>Species sex/number of animals</th>
<th>Method</th>
<th>Period</th>
<th>Dose</th>
<th>Results (male)</th>
<th>Results (female)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mouse ICR (6-8 weeks male and)</td>
<td>Oral feeding</td>
<td>18 months</td>
<td>0 ppm</td>
<td>3/18</td>
<td>0/20</td>
<td>Russfield et al., 1975</td>
</tr>
<tr>
<td></td>
<td></td>
<td>sacrificed 24</td>
<td>1,000 ppm</td>
<td>3/13</td>
<td>9/21*</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2,000 ppm</td>
<td>4/20</td>
<td>7/14*</td>
<td></td>
</tr>
<tr>
<td>Species</td>
<td>Method</td>
<td>Period</td>
<td>Dose</td>
<td>Results</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>---------</td>
<td>--------</td>
<td>--------</td>
<td>------</td>
<td>---------</td>
<td>-----------</td>
<td></td>
</tr>
<tr>
<td>female 25 animals/group</td>
<td>Oral feeding Low-protein diet</td>
<td>500 days (71 weeks) sacrificed 104 weeks after</td>
<td>0, 1,000 ppm</td>
<td>Hepatomas (male) (female) 0 ppm 0/25 0/25 1,000 ppm 22/25* 8/25** <em>: p&lt;0.001 <em><em>: p&lt;0.002 Lung tumor (male) (female) 0 ppm 0/25 0/25 1,000 ppm 8/25</em> 5/25</em></em> *: p&lt;0.001 **: p&lt;0.025</td>
<td>Grundmann &amp; Steinhoff, 1970</td>
<td></td>
</tr>
<tr>
<td>Rat Wistar 14 weeks male and female 25 animals/group</td>
<td>Oral feeding</td>
<td>18 months sacrificed 24 months after</td>
<td>0, 500, 1,000 ppm</td>
<td>Hepatoma (male) 0 ppm 0/22 500 ppm 1/22 1,000 ppm 4/19* Evaluation could not be conducted due to the small number of animals.</td>
<td>Russfield et al., 1975</td>
<td></td>
</tr>
<tr>
<td>Rat SD 6-8 weeks male 25 animals/group</td>
<td>Oral feeding</td>
<td>Lifetime (standard diet) mean/g/548-628 days (Protein deficient diet) 16 months</td>
<td>0, 1,000 ppm</td>
<td>Lung adenocarcinoma (ppm) (male) (female) 0 0/44 0/44 0/21 1/21 1,000 21/44* 27/44* 5/21* 6/21* Lung adenoma 0 1/44 1/44 1/21 1/21 1,000 14/44* 11/44* 8/21* 14/21* Pleural mesothelioma 0 0/44 0/44 0/21 0/21 1,000 4/44 2/44 1/21 0/21 Hepatocellular adenoma 0 0/44 0/44 0/21 0/21 1,000 3/44 2/44 5/21* 2/21 Hepatocellular carcinoma (male) (female) (male) (female) 0 0/44 0/44 0/21 0/21 1,000 3/44 3/44 11/21* 1/21 *: p&lt;0.05, **: p&lt;0.025</td>
<td>Stula et al., 1975</td>
<td></td>
</tr>
<tr>
<td>Rat SD 5 weeks Male 50-100 animals/group</td>
<td>Oral feeding</td>
<td>(standard diet)</td>
<td>(ppm) (Protein deficient diet)</td>
<td>Lung adenocarcinoma (male) 0 0/100 0/100 125 ND 3/100 250 14/100*** 7/75** 500 20/75*** 8/50***</td>
<td>Kommineni et al., 1979</td>
<td></td>
</tr>
<tr>
<td>Species sex/number of animals</td>
<td>Method</td>
<td>Period</td>
<td>Dose</td>
<td>Results</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>-------------------------------</td>
<td>--------</td>
<td>--------</td>
<td>------</td>
<td>---------</td>
<td>-----------</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1,000</td>
<td>31/50 ***</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0</td>
<td>1/100</td>
<td>0/100</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>125</td>
<td>ND</td>
<td>6/100 **</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>250</td>
<td>23/100 ***</td>
<td>11/75 ***</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>500</td>
<td>28/75 ***</td>
<td>13/50 ***</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1,000</td>
<td>35/50 ***</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0</td>
<td>1/100</td>
<td>0/100</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>125</td>
<td>ND</td>
<td>1/100</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>250</td>
<td>5/100</td>
<td>3/75</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>500</td>
<td>8/75 **</td>
<td>3/50 *</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1,000</td>
<td>14/50 ***</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0</td>
<td>1/100</td>
<td>0/100</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>125</td>
<td>ND</td>
<td>0/100</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>250</td>
<td>8/100 *</td>
<td>4/75 *</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>500</td>
<td>5/75</td>
<td>6/50 ***</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1,000</td>
<td>11/50 ***</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0</td>
<td>0/100</td>
<td>0/100</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>125</td>
<td>ND</td>
<td>0/100</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>250</td>
<td>3/100</td>
<td>0/75</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>500</td>
<td>3/75</td>
<td>9/50 ***</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1,000</td>
<td>18/50 ***</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0</td>
<td>2/100</td>
<td>1/100</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>125</td>
<td>ND</td>
<td>2/100</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>250</td>
<td>4/100</td>
<td>4/75</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>500</td>
<td>3/75</td>
<td>4/50 *</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1,000</td>
<td>0/50</td>
<td>ND</td>
<td></td>
</tr>
</tbody>
</table>

*: p<0.05, **: p<0.01, ***: p<0.001
ND: No data available

Bladder transitional- cell carcinoma (4/5)
One of them developed also urethral transitional- cell carcinoma and adenocarcinoma.

Stula et al., 1977
Table 7-6  Evaluation of carcinogenicity of 3,3’-dichloro-4,4’-diaminodiphenylmethane by the international and national organizations

<table>
<thead>
<tr>
<th>Organization/Source</th>
<th>Classification</th>
<th>Classification criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>IARC (2002)</td>
<td>Group 2A</td>
<td>The agent is probably carcinogenic to humans.</td>
</tr>
</tbody>
</table>

7.4 Summary of effects on human health

Regarding kinetics and metabolism of MBOCA, radiolabeled MBOCA administered orally in rats was rapidly absorbed and the radioactivity was distributed in the liver, adipose tissue, kidney and small intestine 48 hours after administration. MBOCA is metabolized into N-hydroxy-MBOCA, o-hydroxy-MBOCA and methylene-hydroxy-MBOCA. The major metabolite was N-hydroxy-MBOCA in humans, rats and guinea pigs, but o-hydroxy-MBOCA in dogs. MBOCA is further metabolized into glucuronocojugates and sulfoconjugates, and excreted in the urine or feces. Glucuronocojugates and sulfoconjugates were excreted in the urine of rats. The main metabolite in the urine of dogs was sulfoconjugate of o-hydroxy-MBOCA. The main metabolite in the urine of humans was N-glucuronocojugate. The main metabolite in the bile of rats was mono-N-glucuronocojugate. In rats, over 60% of administered dose was excreted in the feces, and 20% to 40% in the urine by 48 hours after administration.

In human studies, it has been reported that a person who was exposed to melted MBOCA in the face complained conjunctivitis, pain in the eyes and face, nausea and showed transient renal dysfunction and that another person who received melted MBOCA to the upper body, arms and legs had moderate inflammation in the arm but no abnormal values in renal and hepatic function tests and showed no methemoglobinemia, hematuria or proteinuria. In an investigation in the workers who were engaged in MBOCA production, the possibility that MBOCA induced bladder tumors in humans was suggested, although there was no sufficient evidence.

In experimental animals, MBOCA exhibits acute toxicity symptoms such as ataxia and cyanosis in mice, rats and rabbits after oral administration. The oral LD_{50} values of acute toxicity studies in various experimental animals ranged from 640 to 2,100 mg/kg in mice and rats.

MBOCA causes slight skin irritation in guinea pigs and mild eye irritation in rabbits, but MBOCA has no dermal sensitization in guinea pigs.

Repeated dose administration of MBOCA causes cyanosis, suppression in body weight gain, methemoglobinemia, pallor, weakness and polyuria in rats. Mild cyanosis and hematuria were found in rabbits after percutaneous administration. However, no appropriate data to establish a NOAEL were
obtained, because of short-term studies.

No reports on reproductive and developmental effects of MBOCA were obtained in this investigation.

Regarding genotoxicity of MBOCA, in in vitro studies, MBOCA showed positive responses in reverse mutation assays using bacteria, and mutation, chromosomal aberration and DNA damage tests using cultured cells. Also, chromosomal aberration and SCE tests using human cultured cells exhibited negative responses. MBOCA showed positive responses in a cell transformation assay using cultured cells. In in vivo studies, MBOCA induced chromosomal aberration, DNA damage and increases in SCE of the peripheral lymphocytes and DNA adduct of N-hydroxy-MBOCA in the urothelial cells in experimental animals. From the overall evaluation of these data, MBOCA is considered to be genotoxic.

Oral administration of MBOCA developed hepatocellular carcinoma in mice, lung, liver, mammary and Zymbal gland carcinoma and angiosarcoma in rats and bladder carcinoma in dogs. Therefore, MBOCA is considered to be carcinogenic in experimental animals. MBOCA has been categorized as Group 2A (the agent is possibly carcinogenic to humans) by the IARC.
References

ACGIH, American Conference of Governmental Industrial Hygienists (2001) Documentation of the threshold limit values and biological exposure indices, 7th ed. Cincinnati, OH.
ACGIH, American Conference of Governmental Industrial Hygienists (2002) TLVs and BEIs.
ATSDR, Agency for Toxic Substances and Disease Registry (1994) Toxicological profile for 4,4'-Methylenebis(2-chloroaniline) MBOCA, Atranta, GA.

1) The literature search was conducted in April 2002, 2003 with the databases including CAS online, HSDB, IRIS, RTECS, TOXLINE etc.


149-171.


Manis, M.O. and Braselton, W.E., Jr. (1986) Metabolism of 4,4'-methylenebis(2-chloroaniline) by canine liver and kidney slices. Drug Metab. Dispos., 14, 166-174. (as cited in IARC, 1993)


METI/Japan and MOE/Japan, Ministry of Economy, Trade and Industry, Japan and Ministry of the Environment, Japan (2003b) Summary of Estimation Methods of Unreported Amount Emitted on the Basis of Japan PRTR Law. (on the website:


Steinhoff, D. and Grundmann, E. (1971) Carcinogenic effect of 3,3'-dichloro-4,4'-diaminodiphenylmethane in rats. Naturwissenschaften, 58, 578. (in German)


ABBREVIATIONS

ACGIH : American Conference of Governmental Industrial Hygienists
ADH : alcohol dehydrogenase
ALDH : aldehyde dehydrogenase
ALP : alkaline phosphatase
ALT : alanine aminotransferase
ASAT : aspartate aminotransferase
AST : aspartate aminotransferase
ATSDR : Agency for Toxic Substances and Disease Registry
BCF : Bioconcentration Factor
BHK : Syrian hamster kidney culture cells
BOD : Biological Oxygen Demand
BUN : blood urea nitrogen
CAS : Chemical Abstract Services
CAS Online : Chemical Abstract Services Online
CEPA : Commonwealth Environment Protection Agency
CERHR : Center for the Evaluation of Risks to Human Reproduction
CERI : Chemicals Evaluation and Research Institute, Japan
CHL : Chinese hamster lung cells
CHO : Chinese hamster ovary cells
CICAD : Concise International Chemical Assessment Document
Cmax : the maximum concentration of a compound in the blood, etc.
COD : Chemical Oxygen Demand
CPK : Creatinine phosphokinase
DDT : dichlorodiphenyltrichloroethane
DOC : Dissolved Organic Carbon
EA : Environment Agency of Japan
EC : European Communities
EC10 : Effect Concentration measured as 10% effect
EC50 : median Effect Concentration
ECB : European Chemicals Bureau
ECETOC : European Centre for Ecotoxicology and Toxicology of Chemicals
EEC : European Economic Communities
EHC : Environmental Health Criteria
EHI : Estimated Human Intake
EPA : Environmental Protection Agency (USA)
EU : European Union
EUSES : Europen Union System for the Evaluation of Substances
FAD : flavin adenine dinucleotide
FAO : Food and Agriculture Organisation of the United Nations
GABA : g-aminobutyric acid
GC : gas chromatography
GGT : gamma-glutamyl transpeptidase
GLP : Good Laboratory Practice
hr : hour
HSDB : Hazardous Substances Data Bank
IARC : International Agency for Research on Cancer
IC : Industrial Category
IC50 : median Immobilisation Concentration or median Inhibitory Concentration
ILO : International Labour Organisation
IPCS : International Programme on Chemical Safety
IRIS : Integrated Risk Information System
IUCLID : International Uniform Chemical Information Database (existing substances)
Koc : Soil adsorption coefficient Koc
Kow : octanol/water partition coefficient
LC50 : median Lethal Concentration
v/v : volume per volume ratio
w : week
w/w : weight per weight ratio
WHO : World Health Organization
γ-GTP : γ-glutamyl transpeptidase
δALS : δ-aminolevulinic acid synthetase